ROTATOR CUFF CALCIFIC TENDINITIS

Another entity of rotator cuff problems

Bart Willem Oudelaar

ROTATOR CUFF CALCIFIC TENDINITIS

Another entity of rotator cuff problems

Bart Willem Oudelaar

ISBN: 978-94-6458-410-3
Lay-out & cover design: Publiss | www.publiss.nl
Printing: Ridderprint | www.ridderprint.nl

The publication of this thesis was financially supported by: Nederlandse Orthopaedische Vereniging, Anna Fonds|NOREF and Chipsoft.

Rotator Cuff Calcific Tendinitis

Another entity of rotator cuff problems

Proefschrift

ter verkrijging van

de graad van doctor aan de Universiteit Leiden,

op gezag van rector magnificus prof.dr.ir. H. Bijl,

volgens besluit van het college voor promoties

te verdedigen op dinsdag 22 november 2022

klokke 16.15 uur

door

Bart Willem Oudelaar

geboren te Naarden

in 1986

Promotiecommissie

Promotor	prof. dr. R.G.H.H. Nelissen	
Co-promotores	dr. A.J.H. Vochteloo	
	dr. R. Huis in 't Veld	Universiteit Twente
Leden promotiecommissie	prof. dr. G. Kloppenburg	
	prof. dr. I.B. Schipper	
	prof. dr. D. Eygendaal	Erasmus MC
	dr. E.R.A. van Arkel	Haaglanden MC
	dr. P.B. de Witte	

Table of contents

Chapter 1

General introduction and outline of the thesis

The incidence of patients who present with shoulder pain in general practice is high. Shoulder pain is the third most common musculoskeletal reason to consult in primary care with a lifetime prevalence of up to 67% and approximately 1% of adults are likely to consult with new shoulder pain annually[1,2]. As shoulder pain often affects patients of working age, it creates a large economic burden for society[3,4]

Rotator cuff calcific tendinitis

Rotator cuff calcific tendinitis (RCCT) is a frequently diagnosed cause of shoulder pain with a reported prevalence of 7% to 54% in patients with shoulder pain[5-8]. RCCT is characterized by the presence of carbonate hydroxyapatite deposits in the rotator cuff tendons. The pathogenesis of this condition is still not fully understood. Several hypotheses have been proposed such as degenerative changes, repetitive trauma, tenocyte necrosis, reactive and endochondral ossification[7, 9-12]. More recent research suggests that calcific tendinitis should be considered as a failed cell-mediated healing process in which tendon stem cells play a principal role. In the presence of altered local conditions, such as excessive mechanical loading and the accumulation of microinjuries, tendon stem cells could differentiate into chondrocytes or osteoblasts instead of tenocytes. The activity of these non-tenocytes results in chondrometaplasia and ossification which leads to the formation of calcific deposits within the tendon structure[13].

RCCT mainly affects patients of working age (30-60 years old), is more common in women (affected 1.5-2 times more often than men) and is bilateral in 10%–25% of patients. It is suggested that RCCT is more common in patients whose occupation requires internal rotation and slight abduction of the arm, such as desk and production line workers. The condition is also found more often in patients with insulin-dependent diabetes and thyroid disorders[13].

The natural course of the disease is self-limiting and can be divided into three subsequent stages: precalcific, calcific, and postcalcific. The calcific stage can be further divided into the formative, resting, and reabsorption phase. Pain is the main clinical feature of symptomatic RCCT. Pain usually increases during the reabsorption phase probably due to an inflammatory response, which ultimately will lead to resorption of the calcific deposit. Other symptoms of RCCT could be restriction of joint mobility and loss of strength[14-16].

Calcific deposits are usually visible on plain radiographs and can, according to Gärtner and Heyer, be classified into three types: 1) well circumscribed and dense, 2) soft counter/dense or sharp/transparent, and 3) translucent and cloudy appearance without clear circumscription (figure 1)[17]. Ultrasound examination of the shoulder can further aid the diagnosis and detect associated conditions such as bursitis, rotator cuff tears and long head of the biceps pathology[18,19].

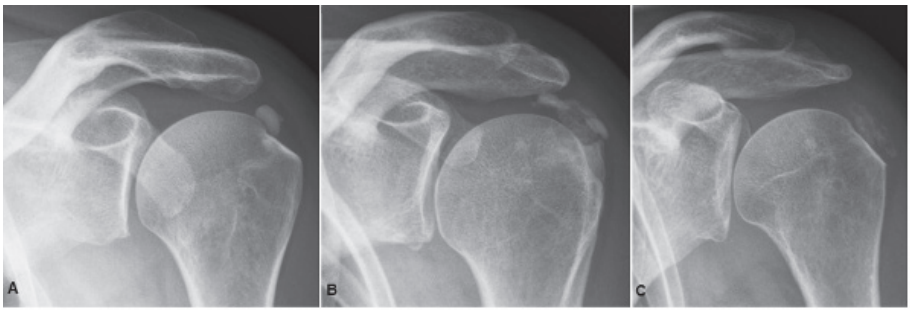

Figure 1: Gärtner and Heyer classification of calcific deposits. (A) type I calcific deposit: dense with a well-defined border; (B) type II calcific deposit: dense with an indistinct border or transparent with a well-defined border; (C) type III calcific deposit: translucent and cloudy appearance without clear circumscription.

Not all calcific deposits in rotator cuff tendons are symptomatic. In asymptomatic populations, calcific deposits were found in 3 to up to 20% of the population. Larger calcific deposits (>1.5 cm in length) seem to have the highest chance of becoming symptomatic while some authors state that larger calcific deposits will always become symptomatic in time[20-23].

Although RCCT is believed to be a self-limiting disease, treatment is warranted for symptomatic patients with a prolonged duration of symptoms, as spontaneous resorption of the calcium deposit may take years. Initial treatment of RCCT includes conservative therapies such as non-steroidal anti-inflammatory drugs (NSAID's), physiotherapy (stimulating shoulder depressors) and subacromial injections with corticosteroids (SAI). Success rates of these conservative measures range from 70–90%[8 ,15, 24-26]. Negative prognostic factors for the outcome of conservative treatment are bilateral calcific deposits, localization of the deposit near the anterior portion of the acromion, medial (subacromial) extension and a high volume of calcific deposits. Gärtner and Heyer type III calcific deposits and lack of sonographic sound

extinction were identified as positive prognostic factors[25]. When conservative measures fail, other treatment modalities such as extracorporeal shockwave therapy (ESWT) and needle aspiration of calcific deposits (NACD) are advocated[27-29]. Comparative studies between these treatment modalities are scarce but NACD seems to be more effective in restoration of function and pain relief in the short term[30,31].

Needle aspiration of calcific deposits (NACD)

NACD was introduced in 1937 using fluoroscopic guidance[32]. Farin et al. were the first to describe the outcome of ultrasound-guided NACD[33]. During this procedure a needle is introduced into the calcific deposit after which a small amount of fluid is injected in the calcific deposit. If necessary, the calcific deposit can be repeatedly perforated after which the calcific remains can removed by aspiration. Some authors advocate the use of a second needle for aspiration[34]. Studies on the efficacy of NACD for RCCT show good mid-term and long-term results but are limited to relatively small sample sizes[33, 35-43]. In a large prospective study, Serafini et al. reported the outcome of NACD in 219 patients and compared it to a control group of 68 patients who refused to undergo NACD for unreported reasons. They found significantly better results in the NACD group at one, three- and 12-months follow-up, but at five- and ten-years follow-up no more significant differences were found between groups[42]. In a large randomized controlled study by De Witte et al., NACD was compared with SAI and patients were reviewed after one and five years. Results of this study showed significantly superior results for NACD at one-year follow-up, but at five-year follow-up differences between groups were absent. However, during the course of these studies 36% (9/25) of the patients in the SAI group underwent additional NACD during the first year of follow-up and over half the patients in the SAI group (13/25) required additional NACD during the five-year follow-up. The authors therefore concluded that NACD is associated with faster improvement and a lower number of patients requiring additional treatment[44,45].

Despite these promising reports, up to 30% of patients experience persisting or recurrent symptoms after NACD[33, 35-43]. At long term follow-up this percentage even increases: 42% of patients with RCCT had a severely impaired shoulder function (i.e. WORC score $<$ 60 points) in a study with a mean follow-up of 14 years[46]. Although it is unclear whether the impaired shoulder function in the long term is

due to persisting or recurrent RCCT, or due to other shoulder pathology, this might indicate that the calcium deposit as such is just one (small) part of a more complex, and perhaps degenerative, shoulder disease.

Regarding prognostic factors for the outcome of NACD, type I calcific deposits, according to the Gärtner and Heyer classification, are believed to affect the outcome of NACD negatively[17]. Female gender, dominant arm involvement, bilateral disease, prolonged duration of symptoms and presence of multiple calcifications are associated with inferior shoulder function in patients with RCCT[46]. No studies aimed at identifying prognostic factors for the outcome of NACD have, however, been conducted. Even more, large studies on the effectiveness of NACD are lacking, as well as studies investigating novel therapies for the treatment of RCCT.

Platelet-rich plasma (PRP)

A possible novel treatment for RCCT could be platelet-rich plasma (PRP). PRP is a small volume of autologous blood plasma that has been enriched with blood-derived platelets. PRP is considered to have beneficial effects on many healing processes as a result of the growth factors contained in the platelet alpha-granules. Several studies show favorable outcomes of PRP in the treatment of tendinopathies such as lateral epicondylitis and patellar tendon tendinitis[47-50]. The role of PRP in the treatment of rotator cuff pathology is more controversial. In the conservative treatment of rotator cuff disease, such as partial rotator cuff tears and tendinopathy, conflicting results have been published on the efficacy of PRP[51-59]. However, in comparison with corticosteroid injections, PRP seems to give better results at short-term in patients with partial rotator cuff tears[58,59]. The use of PRP in the treatment of RCCT has never been investigated.

Aim of this thesis

The aim of this thesis is to evaluate and optimize the outcome of the treatment of rotator cuff calcific tendinitis (RCCT). In order to do so, the clinical outcome of needle aspiration of calcific deposits (NACD) and prognostic factors for the outcome are evaluated in two cohorts: a retrospective and prospective cohort of patients with symptomatic RCCT. Furthermore, the efficacy of platelet-rich plasma (PRP) in RCCT is investigated in a randomized controlled trial.

Outline of the thesis

First, the outcome of NACD in the treatment of RCCT is evaluated and prognostic factors for the effectiveness of NACD are identified. To do so, a cohort study on the outcome of NACD in 431 patients with symptomatic RCCT is conducted (**chapter 2)**. In **chapter 3**, factors associated with successful NACD and factors associated with the need for multiple NACD procedures are evaluated in a retrospective cohort study. This study is followed up by a prospective cohort study to further identify prognostic factors for the effectiveness of NACD (**chapter 4**).

Secondly, the efficacy of the use of PRP in the treatment of RCCT is investigated. In **chapter 5,** the differences in concentrations of blood components between the different available PRP separation systems and techniques are evaluated in a review of literature. Finally, in **chapter 6**, the efficacy of the adjuvant application of platelet-rich plasma for the treatment of RCCT is evaluated in a randomized controlled trial.

A summary of the main results of the studies in this thesis and a general discussion including future perspectives is provided in **chapter 7**.

References

1. Luime JJ, Koes BW, Hendriksen IJ, Burdorf A, Verhagen AP, Miedema HS, Verhaar JA. Prevalence and incidence of shoulder pain in the general population; a systematic review. Scand J Rheumatol. 2004;33(2):73-81.
2. Urwin M, Symmons D, Allison T, Brammah T, Busby H, Roxby M, Simmons A, Williams G. Estimating the burden of musculoskeletal disorders in the community: the comparative prevalence of symptoms at different anatomical sites, and the relation to social deprivation. Ann Rheum Dis. 1998;57(11):649-55.
3. Kuijpers T, van Tulder MW, van der Heijden GJ, Bouter LM, van der Windt DA. Costs of shoulder pain in primary care consulters: a prospective cohort study in The Netherlands. BMC Musculoskelet Disord. 2006;7:83.
4. Marks D, Comans T, Bisset L, Thomas M, Scuffham PA. Shoulder pain cost-of-illness in patients referred for public orthopaedic care in Australia. Aust Health Rev. 2019;43(5):540-548.
5. Welfling J, Kahn MF, Desroy M, Paologgi JB, Seze SD. Calcification of the shoulder. The disease of multiple tendinous calcifications. Rev Rheumatology 1965;32:325–334
6. Uhthoff HK, Sarkar K. Calcifying tendinitis. Baillieres Clin Rheumatol. 1989;3:567-581.
7. Speed CA, Hazleman BL. Calcific tendinitis of the shoulder. N Engl J Med 1999;20;340(20):1582-4.
8. Diehl P, Gerdesmeyer L, Gollwitzer H, Sauer W, Tischer T. Calcific tendinitis of the shoulder. Orthopade 2011;40(8):733-46.
9. Uhthoff HK. Calcifying tendinitis, an active cell-mediated calcification. Virchows Arch A Pathol Anat Histol. 1975;366(1):51-8.
10. Hamada J, Ono W, Tamai K, Saotome K, Hoshino T. Analysis of calcium deposits in calcific periarthritis. J Rheumatol. 2001;28(4):809-13.
11. Schulz CU, Maier M, Glaser C, Anetzberger H, Müller-Gerbl M. Pathologic glenohumeral stress distribution in calcific tendinosis of the supraspinatus. Z Orthop Ihre Grenzgeb. 2006;144(3):311-5.
12. Siegal DS, Wu JS, Newman JS, Del Cura JL, Hochman MG. Calcific tendinitis: a pictorial review. Can Assoc Radiol J. 2009;60(5):263-72.
13. Sansone V, Maiorano E, Galluzzo A, Pascale V. Calcific tendinopathy of the shoulder: clinical perspectives into the mechanisms, pathogenesis, and treatment. Orthop Res Rev. 2018;10:63-72.
14. Uhthoff HK, Loehr JW. Calcific Tendinopathy of the Rotator Cuff: Pathogenesis, Diagnosis, and Management. J Am Acad Orthop Surg. 1997;5(4):183-191.
15. Gosens T, Hofstee DJ. Calcifying tendinitis of the shoulder: advances in imaging and management. Curr Rheumatol Rep. 2009;11(2):129-34.
16. Uhthoff HK. Anatomopathology of calcifying tendinitis of the cuff. In: Gazielly DF, Gleyze P, Thomas T. The Cuff. Paris: Elsevier; 1997. pp. 144–147.
17. Gärtner J, Heyer A. Calcific tendinitis of the shoulder. Orthopade. 1995;24(3):284–302.
18. Farin PU, Jaroma H. Sonographic findings of rotator cuff calcifications. J Ultrasound Med. 1995;14(1):7–14.

19. Papatheodorou A, Ellinas P, Takis F, Tsanis A, Maris I, Batakis N. US of the shoulder: rotator cuff and non-rotator cuff disorders. Radiographics. 2006;26(1):23
20. Bosworth BM. Calcium deposits in the shoulder and subacromial bursitis: a survey of 12,122 shoulders. J Am Med Assoc. 1941;116:2477–2482.
21. LeGoff B, Berthelot JM, Guillot P, Glémarec J, Maugars Y. Assessment of calcific tendonitis of rotator cuff by ultrasonography: comparison between symptomatic and asymptomatic shoulders. Joint Bone Spine. 2010;77(3):258–263.
22. Sansone V, Consonni O, Maiorano E, Meroni R, Goddi A. Calcific tendinopathy of the rotator cuff: the correlation between pain and imaging features in symptomatic and asymptomatic female shoulders. Skeletal Radiol. 2016;45(1):49–55.
23. Louwerens JK, Sierevelt IN, van Hove RP, van den Bekerom MP, van Noort A. Prevalence of calcific deposits within the rotator cuff tendons in adults with and without subacromial pain syndrome: clinical and radiologic analysis of 1219 patients. J Shoulder Elbow Surg. 2015;24(10):1588-93.
24. Cho NS, Lee BG, Rhee YG. Radiologic course of the calcific deposits in calcific tendinitis of the shoulder: does the initial radiologic aspect affect the final results? J Shoulder Elbow Surg. 2010;19(2):267-72.
25. Ogon P, Suedkamp NP, Jaeger M, Izadpanah K, Koestler W, Maier D. Prognostic factors in nonoperative therapy for chronic symptomatic calcific tendinitis of the shoulder. Arthritis Rheum. 2009;60(10):2978-84.
26. Wolk T, Wittenberg RH. Calcifying subacromial syndrome--clinical and ultrasound outcome of non-surgical therapy. Z Orthop Ihre Grenzgeb. 1997;135(5):451-7.
27. Lam F, Bhatia D, van Rooyen K, de Beer JF. Modern management of calcifying tendinitis of the shoulder. Curr Orthop. 2006;20:446-452.
28. Louwerens JK, Veltman ES, van NA, van den Bekerom MP. The effectiveness of high-energy extracorporeal shockwave therapy versus ultrasound-guided needling versus arthroscopic surgery in the management of chronic calcific rotator cuff tendinopathy: a systematic review. Arthroscopy. 2016;32:165-175.
29. Merolla G, Singh S, Paladini P, Porcellini G (2016) Calcific tendinitis of the rotator cuff: state of the art in diagnosis and treatment. J Orthop Traumatol. 17(1):7-14.
30. Kim YS, Lee HJ, Kim YV, Kong CG. Which method is more effective in treatment of calcific tendinitis in the shoulder? Prospective randomized comparison between ultrasound-guided needling and extracorporeal shock wave therapy. J Shoulder Elbow Surg. 2014;23: 1640-1646.
31. Louwerens JKG, Sierevelt IN, Kramer ET, Boonstra R, van den Bekerom MPJ, van Royen BJ, Eygendaal D, van Noort A. Comparing Ultrasound-Guided Needling Combined With a Subacromial Corticosteroid Injection Versus High-Energy Extracorporeal Shockwave Therapy for Calcific Tendinitis of the Rotator Cuff: A Randomized Controlled Trial. Arthroscopy. 2020;36(7):1823-1833.e1.
32. Patterson RL, Darrach W. Treatment of acute bursitis by needle irrigation. J Bone Joint Surg Am. 1937;19:993-1002.
33. Farin PU, Rasanen H, Jaroma H, Harju A. Rotator cuff calcifications: treatment with ultrasound-guided percutaneous needle aspiration and lavage. Skeletal Radiol. 1996;25(6):551-4.

34. Orlandi D, Mauri G, Lacelli F, Corazza A, Messina C, Silvestri E, Serafini G, Sconfienza LM. Rotator Cuff Calcific Tendinopathy: Randomized Comparison of US-guided Percutaneous Treatments by Using One or Two Needles. Radiology. 2017;285(2):518-527.
35. Aina R, Cardinal E, Bureau NJ, Aubin B, Brassard P. Calcific shoulder tendinitis: treatment with modified US-guided fine-needle technique. Radiology. 2001;221(2):455-61.
36. De Conti G, Marchioro U, Dorigo A, Boscolo N, Vio S, Trevisan M, et al. Percutaneous ultrasound-guided treatment of shoulder tendon calcifications: Clinical and radiological follow-up at 6 months. J Ultrasound. 2010;13(4):188-98.
37. Del Cura JL, Torre I, Zabala R, Legorburu A. Sonographically guided percutaneous needle lavage in calcific tendinitis of the shoulder: short- and long-term results. AJR Am J Roentgenol. 2007;189(3):W128-34.
38. Fusaro I, Orsini S, Diani S, Saffioti G, Zaccarelli L, Galletti S. Functional results in calcific tendinitis of the shoulder treated with rehabilitation after ultrasonic-guided approach. Musculoskelet Surg. 2011;95 Suppl 1:S31-6.
39. Galletti S, Magnani M, Rotini R, Mignani G, Affinito D, Pelotti P, et al. The echo-guided treatment of calcific tendinitis of the shoulder. Chir Organi Mov. 2004;89(4):319-23.
40. Giacomoni P, Siliotto R. Echo-guided percutaneous treatment of chronic calcific tendinitis of the shoulder. Radiol Med. 1999;98(5):386-90.
41. Lin JT, Adler RS, Bracilovic A, Cooper G, Sofka C, Lutz GE. Clinical outcomes of ultrasound-guided aspiration and lavage in calcific tendinosis of the shoulder. HSS J. 2007;3(1):99-105.
42. Serafini G, Sconfienza LM, Lacelli F, Silvestri E, Aliprandi A, Sardanelli F. Rotator cuff calcific tendonitis: short-term and 10-year outcomes after two-needle us-guided percutaneous treatment--nonrandomized controlled trial. Radiology. 2009;252(1):157-64.
43. Yoo JC, Koh KH, Park WH, Park JC, Kim SM, Yoon YC. The outcome of ultrasound-guided needle decompression and steroid injection in calcific tendinitis. J Shoulder Elbow Surg. 2010;19(4):596-600.
44. de Witte PB, Selten JW, Navas A, et al. Calcific tendinitis of the rotator cuff: a randomized controlled trial of ultrasound-guided needling and lavage versus subacromial corticosteroids. Am J Sports Med. 2013;41:1665-1673.
45. de Witte PB, Kolk A, Overes F, Nelissen RGHH, Reijnierse M. Rotator Cuff Calcific Tendinitis: Ultrasound-Guided Needling and Lavage Versus Subacromial Corticosteroids: Five-Year Outcomes of a Randomized Controlled Trial. Am J Sports Med. 2017;45(14):3305-3314.
46. de Witte PB, van Adrichem RA, Selten JW, Nagels J, Reijnierse M, Nelissen RG (2016) Radiological and clinical predictors of long-term outcome in rotator cuff calcific tendinitis. Eur Radiol. 26(10):3401-11.
47. Balasubramaniam U, Dissanayake R, Annabell L. Efficacy of platelet-rich plasma injections in pain associated with chronic tendinopathy: A systematic review. Phys Sportsmed. 2015;43(3):253-61.
48. Chen X, Jones IA, Park C, Vangsness CT Jr. The Efficacy of Platelet-Rich Plasma on Tendon and Ligament Healing: A Systematic Review and Meta-analysis With Bias Assessment. Am J Sports Med. 2018;46(8):2020-2032.
49. Dupley L, Charalambous CP. Platelet-Rich Plasma Injections as a Treatment for Refractory Patellar Tendinosis: A Meta-Analysis of Randomised Trials. Knee Surg Relat Res. 2017;29(3):165-171. doi: 10.5792/ksrr.16.055.

50. Filardo G, Di Matteo B, Kon E, Merli G, Marcacci M. Platelet-rich plasma in tendon-related disorders: results and indications. Knee Surg Sports Traumatol Arthrosc. 2018;26(7):1984 1999.

51. Barreto RB, Azevedo AR, Gois MC, Freire MRM, Silva DS, Cardoso JC. Platelet-Rich Plasma and Corticosteroid in the Treatment of Rotator Cuff Impingement Syndrome: Randomized Clinical Trial. Rev Bras Ortop (Sao Paulo). 2019;54(6):636-643.

52. Ilhanli I, Guder N, Gul M. Platelet-Rich Plasma Treatment With Physical Therapy in Chronic Partial Supraspinatus Tears. Iran Red Crescent Med J. 2015;17(9):e23732.

53. Kesikburun S, Tan AK, Yilmaz B, Yaşar E, Yazicioğlu K. Platelet-rich plasma injections in the treatment of chronic rotator cuff tendinopathy: a randomized controlled trial with 1-year follow-up. Am J Sports Med. 2013;41(11):2609-16.

54. Kim SJ, Yeo SM, Noh SJ, et al. Effect of platelet-rich plasma on the degenerative rotator cuff tendinopathy according to the compositions. J Orthop Surg Res. 2019;14(1):408.

55. Pasin T, Ataoğlu S, Pasin Ö, Ankarali H. Comparison of the Effectiveness of Platelet-Rich Plasma, Corticosteroid, and Physical Therapy in Subacromial Impingement Syndrome. Arch Rheumatol. 2019;34(3):308-316.

56. Rha DW, Park GY, Kim YK, Kim MT, Lee SC. Comparison of the therapeutic effects of ultrasound-guided platelet-rich plasma injection and dry needling in rotator cuff disease: a randomized controlled trial. Clin Rehabil. 2013;27(2):113-22.

57. Schwitzguebel AJ, Kolo FC, Tirefort J, Kourhani A, Nowak A, Gremeaux V, Saffarini M, Lädermann A. Efficacy of Platelet-Rich Plasma for the Treatment of Interstitial Supraspinatus Tears: A Double-Blinded, Randomized Controlled Trial. Am J Sports Med. 2019;47(8):1885-1892.

58. Shams A, El-Sayed M, Gamal O, Ewes W. Subacromial injection of autologous platelet-rich plasma versus corticosteroid for the treatment of symptomatic partial rotator cuff tears. Eur J Orthop Surg Traumatol. 2016;26(8):837-842.

59. von Wehren L, Blanke F, Todorov A, Heisterbach P, Sailer J, Majewski M. The effect of subacromial injections of autologous conditioned plasma versus cortisone for the treatment of symptomatic partial rotator cuff tears. Knee Surg Sports Traumatol Arthrosc. 2016;24(12):3787-3792.

Chapter 2

Needle aspiration of calcific deposits (NACD) for calcific tendinitis is safe and effective: six-month follow-up of clinical results and complications in a series of 431 patients

Bart W. Oudelaar
Relinde Schepers-Bok
Edwin M. Ooms
Rianne Huis In 't Veld
Anne J.H. Vochteloo

Eur J Radiol. 2016;85:689-94

Abstract

Background

Although needle aspiration of calcific deposits (NACD) has proven to be an effective treatment for calcific tendinitis of the rotator cuff (CTRC) in patients who are resistant to conservative treatment, little is known about the effectiveness of NACD in terms of complete relief of symptoms and the effectiveness of repeated NACD procedures. Furthermore, analyses of complications of the procedure in large series are scarce.

Methods

431 consecutive patients with symptomatic CTRC treated by NACD were included in this retrospective cohort study. Short-term effects were assessed at two weeks post-treatment by using an 11-point numeric rating scale (NRS). The six months outcome was determined on a dichotomous symptom scale (symptom free or persistence of symptoms). NACD procedures performed within six months of a previous NACD procedure were considered repeated procedures. All complications that occurred within six months of the NACD procedure were registered.

Results

At two weeks post-treatment, a significant improvement of pain scores was noted (mean reduction of NRS: 4.4 points; $p<0.001$). 74% of patients had complete relief of symptoms at six months post-treatment. 143 (33.2%) patients required multiple treatments. These repeated procedures were equally effective as the primary procedure. Complications of the NACD procedure were seen in 31 (7.2%) patients: 21 patients (4.9%) developed a subacromial bursitis, seven patients (1.6%) a frozen shoulder and three patients (0.7%) developed a septic bursitis.

Conclusion

Needle aspiration of calcific deposits (NACD) is an effective treatment for calcific tendinitis of the rotator cuff in the majority of patients. Approximately one third of the patients will require multiple treatments, which were equally effective as the primary procedure. Based on this, patients should not be withheld a second or even a third treatment in case of persistent symptoms. Furthermore, NACD has a low complication rate, the risk of infection should, however, always be accounted for.

Introduction

Calcific tendinitis of the rotator cuff (CTRC) is a frequently diagnosed condition characterized by deposits of calcium hydroxyapatite in tendons of the rotator cuff. It is the most common ultrasound-diagnosed shoulder disorder in general practice and accounts for approximately 7% of all shoulder complaints[1, 2].

Initial treatment is preferably conservative, e.g. non-steroidal anti-inflammatory drugs (NSAIDs), physiotherapy and/or subacromial steroid injections, with reported success rates ranging from 70 to 90%[3-7]. Patients not responding to conservative treatment are often treated by ultrasound-guided needle aspiration of calcific deposits (NACD). NACD has proven to be an effective therapy in the vast majority of patients[8-19] and it is considered a safe procedure as only minor complications, such as chemical bursitis, vagal reactions and post-procedural pain have been reported[20]. Analyses of complications of the procedure in large series are however scarce.

Despite the growing interest in the effectiveness of NACD, only a few studies describe the results of NACD in terms of complete relief of pain or symptoms. Most papers on the outcome of NACD use functional scores, e.g. the Constant-Murley score as primary outcome measurement[8-11, 13, 16-19]. As relief of pain is the primary goal of NACD, more data on the relief of pain following NACD in the longer term is necessary to gain insight in the effectiveness of NACD.

Due to the persistence or recurrence of symptoms after NACD, a repeated NACD procedure is, according to literature, necessary in 18 to 45% of patients. As the only two studies on the effectiveness of these repeated procedures reported conflicting results in terms of the outcome, little is known about the effectiveness of repeated NACD procedures[11, 12].

The first goal of the present study was to assess the effectiveness of NACD in terms of complete relief of pain or symptoms and to analyze the effectiveness of repeated procedures in case of persistence or recurrence of symptoms. Secondly, the complications of the NACD procedure were evaluated.

Materials and Methods

Study design

A series of 431 consecutive patients treated between January 2010 and June 2013 was analyzed. The effectiveness of NACD was assessed at two weeks and six months in a mixed-methods cohort study. The two-week outcome was studied prospectively; the six-month outcome was evaluated retrospectively. Both the two - week and six-month outcome were part of regular treatment evaluation. According to the Medical Ethical Committee of Medisch Spectrum Twente, Enschede, the Netherlands, the current study did not meet the criteria necessary for an assessment by a medical ethical committee according to the Dutch law (ID number: METC/15283.hui; K-nr.: K15-63).

Study population

The study population consisted of patients referred to the department of radiology by either orthopedic surgeons or general practitioners for the treatment of symptomatic CTRC. The department of radiology is well experienced in performing NACD procedures, performing over 200 procedures every year. Prior to the NACD procedure, all patients were screened by the radiologist performing the NACD procedure to confirm that NACD was indicated. Criteria for a NACD procedure as applied by the radiologists were:

1. Clinical symptoms of calcific tendinitis:
    - Pain in the shoulder region:
        - Pain worsened by elevation of the arm above the shoulder level
        - Pain worse at night
        - Pain worse by lying on the shoulder
    - Stiffness of the shoulder
    - Weakness of the shoulder
2. Presence of calcific deposits was confirmed on radiographs and/or ultrasound examination
3. Absence of other causes for shoulder complaints (e.g. frozen shoulder, subacromial bursitis).

All patients who underwent NACD were registered by the radiologist performing the NACD procedure. Inclusion criteria were checked by the researcher (BO) before entering patients in the study database.

Only the treatment of the first shoulder was analyzed in patients who underwent bilateral treatment (n=32).

Technical procedure

NACD procedures were performed by well-experienced musculoskeletal radiologists in an ultrasound room, using the Logic P3 Ultrasound system (GE Healthcare). Prior to the procedure all patients underwent an ultrasound examination of the affected shoulder to evaluate the rotator cuff and subacromial space. Especially the presence of partial rotator cuff tears and subacromial bursitis was evaluated. Subacromial bursitis was diagnosed when there was fluid distension, synovial proliferation and/or thickening of the bursal walls > 2 mm. Partial rotator cuff tears (PRCT) were diagnosed in case of tears that did not cover the complete thickness of the tendon at either the bursal or articular side of the tendon. Patients were treated in supine position. After sterile preparation, the skin and subcutaneous tissue as well as the subacromial subdeltoid bursa were anesthetized by local injection of lidocaine 1%. Thereafter ultrasound-guided NACD was performed using a 20 or 21 gauge needle. After maneuvering the needle into the calcific deposit, the deposits were infiltrated with lidocaine 1%, fragmented and removed by aspiration. No second needle for the outflow of the lavage fluid was used. The lavage was continued until the aspirate was free of visible calcium. After completing the aspiration, the subacromial bursa was infiltrated with 4 ml Bupivacaine (2,5mg/ml) and 1ml Kenacort (40mg/ml). Patients were advised to use the treated arm within pain limits and to avoid heavy duties in the first two weeks, no specific rehabilitation program was prescribed. Furthermore, they were advised to use Paracetamol 1000mg to a maximum of four times a day in case of pain in the first days following the NACD procedure.

Follow-up and complications

Prior to the NACD and two weeks post-treatment, patients were asked to indicate their pain score on an 11-point numeric rating scale (NRS). The post-treatment score was sent by e-mail to the radiologist who performed the treatment. In case of repeated procedures, this was done as well. 69% of patients replied after an average of 2.2 (±0.6) weeks post-treatment. Responders were comparable to non-responders regarding age, sex, duration of symptoms and pre-treatment NRS scores ($p>0.05$).

To assess the outcome six months post-treatment, patients were approached by telephone by an independent researcher (BO) who was not involved in the previous

NACD procedure. Patients were asked whether they were free of symptoms or not and whether they had needed any alternative treatments in the six months following the last NACD procedure.

All complications during the NACD procedure and in the six months following the last NACD procedure were reported. A clinically relevant bursitis was defined as an increase of pain after NACD in combination with the following ultrasound findings: thickening of the bursa and/or evidence of fluid in the subacromial bursa. In case of the combination with fever and raised levels of inflammatory markers, the diagnosis septic bursitis was considered.

A frozen shoulder was diagnosed in case of an increase of pain after the NACD procedure in combination with a loss of both active and passive range of motion of the shoulder

Repeated procedures

In case of persisting symptoms, patients were scheduled for another NACD procedure. Criteria for a repeated NACD procedure were clinical symptoms of calcific tendinitis, calcific deposits on ultrasound examination and absence of another cause for shoulder complaints (e.g. frozen shoulder, subacromial bursitis). A minimal term of six weeks between the first and second NACD procedure or the second and third NACD procedure was applied. Prior to these repeated NACD procedures, patients were asked to indicate their pain using a NRS again.

Outcomes

Two-week outcome

This was assessed by using the 11-point NRS pre- and two weeks post-treatment. Based on the NRS the following values were determined:

- Reduction of pain: the difference between pre- and post-treatment scores showed the reduction of pain in the two weeks following NACD;
- Minimal clinically important difference (MCID): according to Salaffi et al., differences between pre- and post-treatment scores greater than 1,6 points were considered clinically relevant[21];
- Patient acceptable symptomatic state (PASS): a post-treatment NRS score equal or lower than 3 was considered PASS.

Six-month outcome

This was determined on a dichotomous symptom scale (free of symptoms or persistence of symptoms) at six months post-treatment. Persistence of symptoms six months after the last NACD procedure or requiring an alternative treatment within six months after the last NACD procedure (e.g. surgical removal of calcific deposits) was considered as failure of NACD. The two week outcome of NACD was compared between patients who reported complete relief of symptoms at six months post-treatment and those with persistent symptoms.

Number and effectiveness of repeated NACD procedures

NACD procedures performed within six months of a previous NACD procedure were considered repeated procedures. The two week and six months effectiveness were assessed for the repeated procedures and were compared to the effectiveness of the primary NACD procedure.

Statistical analysis

Demographic and clinical characteristics were described as continuous or categorical variables as appropriate. Normality was assessed by visual inspection of histograms. The difference between the NRS score prior to the NACD procedure and the NRS score at two weeks post-treatment was analyzed using the paired samples t-test. The outcome at six months post-treatment was presented as the percentage of patients who reported complete relief of symptoms. Independent T-tests and Mann-Whitney U tests were used to analyze differences in the reduction of NRS scores and post-treatment NRS scores between patients who reported complete relief of symptoms at six months post-treatment and patients with persistent symptoms. In order to investigate the association between the short term results and the results at six months post-treatment, odds ratios (OR) were calculated for complete relief of symptoms at six months post-treatment in patients who reached MCID and PASS.

Because the number of patients who underwent a third NACD procedure was small (n=27), the analysis of the short term effectiveness was limited to the primary and second NACD procedure. IBM SPSS Statistics 20 was used for statistical analysis. P values <0.05 were considered to be statistically significant.

Results

Patient characteristics

Of the 431 included patients, 277 (64%) were female and the average age was 51 (±9.9; range 25-87) years. Half of the patients (50%) were referred by an orthopedic surgeon and 47% was referred by a general practitioner. The large majority (93%) of the calcific deposits occurred in the supraspinatus tendon. The average duration of symptoms prior to the NACD procedure was 2.4 years and the mean NRS-score prior to the NACD procedure was 7.5 (±1.6).

Ultrasound examination of the affected shoulder prior to the NACD procedures showed partial rotator cuff tears in 70 (16%) patients and subacromial bursitis in 60 (14%) patients.

Two-week outcome

As demonstrated in figure 1, a significant improvement in NRS for pain was found two weeks after NACD (mean reduction of NRS 4.4 points, $p<0.001$). In addition, 84% of patients demonstrated a MCID in NRS pain scores (Δ NRS $\geq$ 1.6 points). PASS (NRS $\leq$ 3) was reached in 77% of patients.

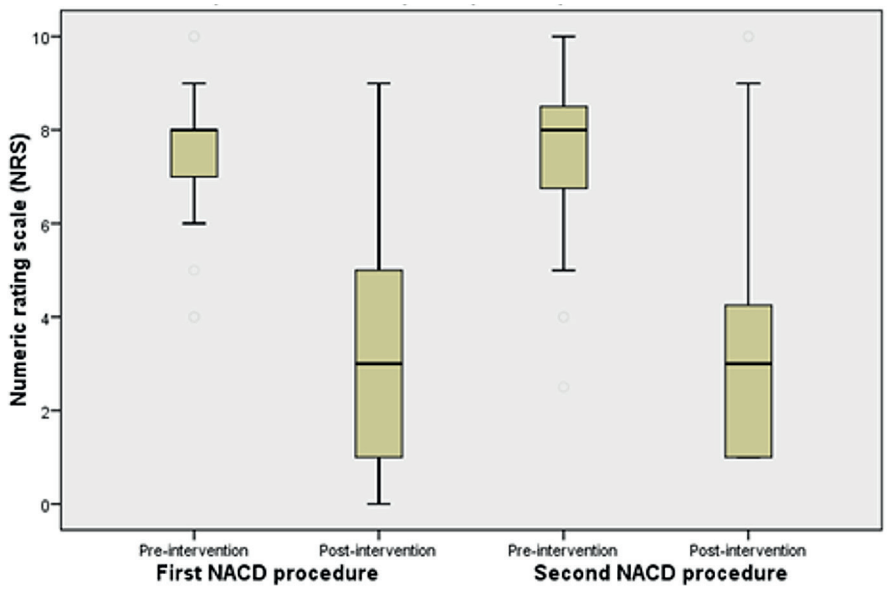

Figure 1: NRS scores prior to and two weeks after the first and the second NACD procedure

Six-month outcome

Complete relief of symptoms at six months post-treatment was reported by 74% of the patients. 13% of patients reported persistence of symptoms six months after the last NACD procedure. The other 13% of patients underwent surgery within six months after the last NACD procedure because of persisting symptoms.

The differences in the short-term outcome between patients who reported complete relief of symptoms at six months post-treatment and patients with persistent symptoms are presented in table 1. Patients who reported complete relief of symptoms at the six-month follow-up had significantly lower NRS scores at two weeks post-treatment after both primary and secondary NACD procedures. Furthermore, a significantly greater reduction of NRS scores was seen in patients who reported to have complete relief of symptoms after a second NACD procedure. In addition, these patients reached PASS and MCID (only after second procedure) more often. When reaching PASS, an OR for complete relief of symptoms at six months post-treatment of 2.2 was found. After a possible second procedure, the OR for complete relief of symptoms when reaching PASS is 4.6, when reaching MICD the OR is 5.5 (Table 2).

Number and effectiveness of repeated NACD procedures

143 (33%) patients required a second NACD procedure. Of the patients who required a second procedure, 27 (19%) patients needed a third procedure. In the short term, a significant improvement of NRS scores was noted two weeks after the second NACD procedure (mean reduction of NRS 4.1 points, $p<0.001$; figure 1). MCID was found in 81% of patients and PASS was reached in 63% of patients.

The results of the first, second and third NACD procedure were equally effective in terms of complete relief of symptoms; respectively 52, 55 and 52% of the patients were free of symptoms at six months follow-up.

Complications of the NACD procedures

Complications of the NACD procedure were seen in 31 (7.2%) patients. 21 patients (4.9%) developed a subacromial bursitis after the NACD procedure that was usually treated with a bursal injection of corticosteroids. Seven patients (1.6%) developed a frozen shoulder. A septic bursitis was found in three patients (0.7%). In two patients this condition was treated by arthroscopic debridement of the subacromial space and antibiotic treatment. One patient was treated conservatively with antibiotics.

Table 1: Comparison of short-term results between patients who reported to be free of symptoms and patients who experienced persisting symptoms at six months post-NACD

	First NACD procedure			Second NACD procedure		
	Free of symptoms	Persisting symptoms	p	Free of symptoms	Persisting symptoms	p
NRS 2 weeks post-NACD	2.8 ± 2.1	3.4 ± 2.5	0.01	2.8 ± 2.1	4.9 ± 3.3	0.013
Reduction of NRS	4.6 ± 2.5	4.0 ± 2.7	0.09	4.7 ± 2.5	2.5 ± 2.3	0.001
MCID	86%	78%	0.12	89%	60%	0.005
PASS	72%	54%	<0.01	74%	38%	0.004

NRS: numeric rating scale; MCID: minimal clinically important difference; PASS: patient acceptable symptomatic state, NACD: needle aspiration of calcific deposits.

Table 2: Odds ratios for complete relief of symptoms after reaching MCID and PASS

	MCID			PASS		
	OR	**95% CI**	**p**	**OR**	**95% CI**	**p**
Primary NACD procedure	1.7	0.9-3.3	0.124	2.2	1.3-3.8	0.003
Second NACD procedure	5.5	1.5-20.4	0.005	4.6	1.6-13.7	0.004

MCID: minimal clinically important difference. PASS: patient acceptable symptomatic state. OR: odds ratio. CI: confidence interval.

Table 3: Complications of NACD

Subacromial bursitis	21 (4,9%)
Frozen shoulder	7 (1,6%)
Septic bursitis	3 (0,7%)
Total	**31 (7,2%)**

Discussion

This study demonstrated that 74% of patients had complete relief of symptoms at six months after ultrasound-guided needle aspiration of calcific deposits (NACD). The vast majority of patients noticed the effects of NACD within two weeks. Reaching a patient acceptable symptomatic state (PASS; NRS $\leq$ 3) in the short-term increased the odds of complete relief of symptoms at six months post-treatment. Repeated procedures were necessary in 33% of patients. The percentage of patients who reported complete relief of symptoms after the NACD procedure was similar for the primary, second and third procedure. Complications were seen in 7% of the patients, three patients (0.7%) developed a septic bursitis that required surgery in two patients.

Outcome of NACD

Several authors have reported that symptoms of CTRC will initially worsen in the first couple of days following NACD[11, 22]. Del Cura et al., for example, reported a temporary worsening of symptoms that lasted approximately 48 hours after which symptoms disappeared quickly[11]. Results of NACD within the first month are, however, rarely reported in current literature. In a non-randomized controlled trial, Serafini et al. reported that 219 patients who underwent NACD had a significantly greater reduction of pain one month after NACD compared to 68 patients who refused NACD and served as the control group[18]. The good two week results of the present study add evidence to the fact that NACD provides quick relief of pain in patients with CTRC.

With regard to the outcome of NACD in the longer term, Farin et al. were the first to describe the effects of NACD in terms of complete relief of symptoms[12]. In their study, 74% of the 61 patients had complete relief of symptoms at one year follow-up which is comparable to our outcome at six months follow-up. Ever since, studies on the outcome of NACD focus mainly on the improvement of shoulder function after NACD and not on relief of symptoms.

As the short and longer-term effects of NACD might be caused by different mechanisms, it is unknown to what extend good short-term results relate to good results in the long-term. The short-term effects of NACD are considered to be mainly attributable to the subacromial injection of corticosteroids. Corticosteroids are known to be effective in the short-term in particular[23]. We believe that the results of NACD in the longer term are more likely attributable to the initiation of

the remodeling phase by the fragmentation and aspiration of the calcific deposits. Interestingly, we found that patients who reported to be symptom free at six months follow-up had lower post-treatment pain scores. Similarly, reaching PASS after the primary procedure gives an odds ratio (OR) for complete relief of symptoms at six months post-treatment of 2.2. After a possible second NACD procedure the OR is even doubled. Therefore, patients with good short-term results are more likely to have good results in the longer term. We therefore recommend monitoring patients with raised levels of pain in the short-term closely, since they are more susceptible to develop persisting symptoms in the longer term.

Number and effectiveness of repeated NACD procedures

The percentage of patients in which multiple NACD procedures were necessary (33%) found in this study corresponds well with the reported rate found in literature (18-42%)[11, 12]. Nonetheless, little is known about the effectiveness of these repeated treatments. In the current study, the percentage of patients having complete relief of symptoms at six months post-treatment was similar for patients undergoing a single, two or even three NACD procedures. This is in contrast to findings by Farin et al. who found complete relief of pain in only 36% (4/14) of the patients who underwent a second procedure compared to 63% (40/63) after the primary procedure[12]. Del Cura et al. found no significant long-term differences between shoulders that were treated once and those treated twice[11].

Complications of the NACD procedures

A recent systematic review reported a complication rate of NACD of 10%. Bursitis was the most common complication, found in 7% of all procedures. Other complications included mild vagal reactions (2%), frozen shoulder (0.2%), seizures (0.2%), tenosynovitis of the bicipital long head (0.1%) and loss of consciousness (0.1 %)[20]. In the present study, bursitis was found in 4.9% of all procedures and a frozen shoulder in 1.6%. More importantly, three patients developed a septic bursitis as a result of the NACD procedure. This has only been reported once in literature in a case report by Sconfienza et al.[24]. In two cases in the present study and in the case report by Sconfienza et al., hospital admission and arthroscopic debridement was necessary. So, although NACD is considered a safe procedure, the risk of infection should always be accounted for.

Limitations

To our knowledge, this study is the largest study on the outcome of NACD so far. However, some limitations need to be taken into account when interpreting the results. First of all, this study is a non-controlled, non-randomized cohort follow-up study. Therefore, the improvement reported in this study could also be the result of spontaneous resorption of calcific deposits. Calcific tendinitis of the rotator cuff is supposedly a self-limiting disease, but spontaneous resorption can take years. Bosworth reported radiographic resolution of calcific deposits to be 6,4% per year and only 9,5% of patients showed complete resolution of the calcific deposits after three years[25]. Wolk et al. reported that 82% of the deposits were resorbed within 8,6 years[26]. Ogon et al. studied the outcome of non-operative therapy for calcific tendinitis. After six months of follow-up 73% of patients were free of pain[6]. In the present study, the average duration of symptoms before treatment was 2.4 years and the majority of patients already underwent unsuccessful conservative therapy. It therefore seems rather unlikely that the improvement of symptoms is due to other mechanisms than the NACD procedure. We do, however, advise that NACD is only performed on patients who underwent unsuccessful conservative therapy before. Secondly, the results at two weeks post-treatment were collected prospectively by e-mail. As no reminders were sent to non-responders, the results might be influenced by selection bias; one could hypothesize patients with higher post-treatment pain scores might be more likely to reply. This could have led to an underestimation of the presented good short-term effectiveness. Furthermore, as this is a retrospective study, we were unable to retrieve some data that could be of interest for the effectiveness of NACD. We were, for example, unable to analyse whether calcium was aspirated during the procedure or not. This could be interesting as literature is inconclusive about the association between the ability to aspirate calcium during the procedure and the effectiveness of NACD[8, 11].

Up to date, there are only two randomized controlled trials (RCT) investigating the effectiveness of NACD. A recent RCT conducted by Kim et al. showed that NACD is more effective in terms of restoration of shoulder function and pain relief than extracorporeal shock wave therapy[16]. Additionally, de Witte et al. demonstrated that the one-year results of NACD are superior to those of subacromial injection therapy[10]. Apart from these studies, studies investigating the effectiveness of NACD are mainly non-controlled studies. Therefore, more well-designed controlled studies comparing NACD to other treatments for CTRC are needed.

Conclusions

Needle aspiration of calcific deposits (NACD) is an effective treatment for calcific tendinitis of the rotator cuff in the majority of patients. Furthermore, NACD has a low complication rate. However, the risk of infection should always be accounted for. Patients who showed good results after two weeks were more likely to have good results at six months. Approximately one third of patients will require multiple procedures, which were equally effective as the primary procedure in these series. Based on this data, patients should not be withheld a second or third NACD procedure in case of persistent symptoms after the primary procedure.

References

1. Ottenheijm RP, van't Klooster IG, Starmans LM, Vanderdood K, de Bie RA, Dinant GJ, et al. Ultrasound-diagnosed disorders in shoulder patients in daily general practice: a retrospective observational study. BMC Fam Pract. 2014;15:115,2296-15-115.
2. Speed CA, Hazleman BL. Calcific tendinitis of the shoulder. N Engl J Med. 1999;340(20):1582-4.
3. Cho NS, Lee BG, Rhee YG. Radiologic course of the calcific deposits in calcific tendinitis of the shoulder: does the initial radiologic aspect affect the final results? J Shoulder Elbow Surg. 2010;19(2):267-72.
4. Diehl P, Gerdesmeyer L, Gollwitzer H, Sauer W, Tischer T. Calcific tendinitis of the shoulder. Orthopade. 2011;40(8):733-46.
5. Gosens T, Hofstee DJ. Calcifying tendinitis of the shoulder: advances in imaging and management. Curr Rheumatol Rep. 2009;11(2):129-34.
6. Ogon P, Suedkamp NP, Jaeger M, Izadpanah K, Koestler W, Maier D. Prognostic factors in nonoperative therapy for chronic symptomatic calcific tendinitis of the shoulder. Arthritis Rheum. 2009;60(10):2978-84.
7. Wolk T, Wittenberg RH. Calcifying subacromial syndrome--clinical and ultrasound outcome of non-surgical therapy. Z Orthop Ihre Grenzgeb. 1997;135(5):451-7.
8. Aina R, Cardinal E, Bureau NJ, Aubin B, Brassard P. Calcific shoulder tendinitis: treatment with modified US-guided fine-needle technique. Radiology. 2001;221(2):455-61.
9. De Conti G, Marchioro U, Dorigo A, Boscolo N, Vio S, Trevisan M, et al. Percutaneous ultrasound-guided treatment of shoulder tendon calcifications: Clinical and radiological follow-up at 6 months(). J Ultrasound. 2010;13(4):188-98.
10. de Witte PB, Selten JW, Navas A, Nagels J, Visser CP, Nelissen RG, et al. Calcific tendinitis of the rotator cuff: a randomized controlled trial of ultrasound-guided needling and lavage versus subacromial corticosteroids. Am J Sports Med. 2013;41(7):1665-73.
11. del Cura JL, Torre I, Zabala R, Legorburu A. Sonographically guided percutaneous needle lavage in calcific tendinitis of the shoulder: short- and long-term results. AJR Am J Roentgenol. 2007;189(3):W128-34.
12. Farin PU, Rasanen H, Jaroma H, Harju A. Rotator cuff calcifications: treatment with ultrasound-guided percutaneous needle aspiration and lavage. Skeletal Radiol. 1996;25(6):551-4.
13. Fusaro I, Orsini S, Diani S, Saffioti G, Zaccarelli L, Galletti S. Functional results in calcific tendinitis of the shoulder treated with rehabilitation after ultrasonic-guided approach. Musculoskelet Surg. 2011;95 Suppl 1:S31-6.
14. Galletti S, Magnani M, Rotini R, Mignani G, Affinito D, Pelotti P, et al. The echo-guided treatment of calcific tendinitis of the shoulder. Chir Organi Mov. 2004;89(4):319-23.
15. Giacomoni P, Siliotto R. Echo-guided percutaneous treatment of chronic calcific tendinitis of the shoulder. Radiol Med. 1999;98(5):386-90.
16. Kim YS, Lee HJ, Kim YV, Kong CG. Which method is more effective in treatment of calcific tendinitis in the shoulder? Prospective randomized comparison between ultrasound-guided needling and extracorporeal shock wave therapy. J Shoulder Elbow Surg. 2014;23(11):1640-6.

17. Lin JT, Adler RS, Bracilovic A, Cooper G, Sofka C, Lutz GE. Clinical outcomes of ultrasound-guided aspiration and lavage in calcific tendinosis of the shoulder. HSS J. 2007;3(1):99-105.
18. Serafini G, Sconfienza LM, Lacelli F, Silvestri E, Aliprandi A, Sardanelli F. Rotator cuff calcific tendonitis: short-term and 10-year outcomes after two-needle us-guided percutaneous treatment--nonrandomized controlled trial. Radiology. 2009;252(1):157-64.
19. Yoo JC, Koh KH, Park WH, Park JC, Kim SM, Yoon YC. The outcome of ultrasound-guided needle decompression and steroid injection in calcific tendinitis. J Shoulder Elbow Surg. 2010;19(4):596-600.
20. Lanza E, Banfi G, Serafini G, Lacelli F, Orlandi D, Bandirali M, et al. Ultrasound-guided percutaneous irrigation in rotator cuff calcific tendinopathy: what is the evidence? A systematic review with proposals for future reporting. Eur Radiol. 2015;25(7):2176-83.
21. Salaffi F, Stancati A, Silvestri CA, Ciapetti A, Grassi W. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. Eur J Pain. 2004;8(4):283-91.
22. Pfister J, Gerber H. Chronic calcifying tendinitis of the shoulder-therapy by percutaneous needle aspiration and lavage: a prospective open study of 62 shoulders. Clin Rheumatol. 1997;16(3):269-74.
23. Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: a systematic review of randomised controlled trials. Lancet. 2010;376(9754):1751-67.
24. Sconfienza LM, Randelli F, Sdao S, Sardanelli F, Randelli P. Septic bursitis after ultrasound-guided percutaneous treatment of rotator cuff calcific tendinopathy. PM R. 2014;6(8):746-8.
25. Bosworth BM. Calcium deposits in the shoulder and subacromial bursitis: a survey of 12122 shoulders. JAMA. 1941;116:2477–2482.
26. Wolk T, Wittenberg RH. Calcifying subacromial syndrome clinical and ultrasound outcome of non-surgical therapy. Z Orthop Ihre Grenzgeb 1997;135:451–7

Chapter 3

Smoking and morphology of calcific deposits affect the outcome of needle aspiration of calcific deposits (NACD) for calcific tendinitis of the rotator cuff

Bart W. Oudelaar
Edwin M. Ooms
Rianne Huis In 't Veld
Relinde Schepers-Bok
Anne J.H. Vochteloo

Eur J Radiol. 2015;84:2255-60

Abstract

Introduction

Although NACD has proven to be an effective minimal invasive treatment for calcific tendinitis of the rotator cuff, little is known about the factors associated with treatment failure or the need for multiple procedures.

Methods

Patients with symptomatic calcific tendinitis who were treated by NACD were evaluated in a retrospective cohort study. Demographic details, medical history, sonographic and radiographic findings were collected from patient files. Failure of NACD was defined as the persistence of symptoms after a follow-up of at least six months. NACD procedures performed within six months after a previous NACD procedure were considered repeated procedures. Multivariate logistic regression analysis was used to determine factors associated with treatment failure and multiple procedures.

Results

431 patients (277 female; mean age 51.4 ± 9.9 years) were included. Smoking (adjusted odds ratio (AOR): 1.7, 95% CI 1.0-2.7, p=0.04) was significantly associated with failure of NACD. Patients with Gärtner and Heyer (GH) type I calcific deposits were more likely to need multiple NACD procedures (AOR: 3.4, 95% CI 1.6-7.5, $p<0.01$) compared to patients with type III calcific deposits. Partial thickness rotator cuff tears were of no influence on the outcome of NACD or the number of treatments necessary.

Conclusion

Smoking almost doubled the chance of failure of NACD and the presence of GH type I calcific deposits significantly increased the chance of multiple procedures. Partial thickness rotator cuff tears did not seem to affect the outcome of NACD. Based on the findings in this study, the importance of quitting smoking should be emphasized prior to NACD and partial thickness rotator cuff tears should not be a reason to withhold patients NACD.

Introduction

Calcific tendinitis of the rotator cuff (CTRC) is a common cause of shoulder complaints with a prevalence of 8 to 20% in asymptomatic adults and up to 54% in patients with shoulder complaints[1-5]. Several theories regarding the pathophysiology of CTRC, such as ischemia and degeneration of the rotator cuff, have been suggested[6-11]. Currently, the most accredited theory is the multiphasic theory proposed by Uhthoff et al.. Uhthoff et al. state that CTRC is caused by an active process of cell-mediated calcification of the rotator cuff tendons which is usually followed by spontaneous phagocytic resorption[12-14]. Despite the fact that CTRC is a self-limiting disease, treatment of this condition is indicated as the spontaneous resorption of calcific deposits may take years. CTRC is preferably treated conservatively, e.g. non-steroidal anti-inflammatory drugs (NSAIDs), physiotherapy and/or subacromial steroid injections, with reported success rates ranging from 70-90%[3,15-17]. When conservative treatment fails, ultrasound-guided needle aspiration of calcific deposits (NACD) is often performed. NACD has proven to be effective in 70-75% of patients[2,18,19]. Previous research suggests that the success rate of NACD depends on the radiographic morphology of the calcific deposits[20]. However, little is known about other variables that can predict the outcome of NACD.

Besides pain and functional outcome, the effectiveness of NACD could also be assessed in terms of the number of NACD procedures needed to obtain permanent results. Although up to 45% of patients will require multiple NACD procedures[21], no studies investigating factors associated with multiple procedures have been conducted, to the authors knowledge.

Therefore, the purpose of this study was to define factors associated with successful treatment and factors associated with the need for multiple NACD procedures.

Materials and methods

Study design

A retrospective cohort study was conducted to evaluate the outcome of NACD in patients treated between January 2010 and June 2013. Data on the outcome of NACD were obtained from routine treatment evaluation, therefore, approval by a medical ethics review board was not deemed necessary.

Study population

The study population consisted of patients referred to the department of radiology by either orthopedic surgeons or general practitioners for the treatment of symptomatic CTRC. The radiology department is well experienced in performing NACD procedures, performing over 200 procedures every year. Prior to the NACD procedure, all patients were screened by the radiologist performing the NACD procedure to confirm that NACD was indicated. Criteria for a NACD procedure as applied by the radiologists were:

1. Clinical symptoms of calcific tendinitis:
    - Pain in the shoulder region:
        - Pain worsened by elevation of the arm above the shoulder level
        - Pain worse at night
        - Pain worse by lying on the shoulder
    - Stiffness of the shoulder
    - Weakness of the shoulder
2. Presence of calcific deposits was confirmed on radiographs and/or ultrasound examination
3. Absence of other causes for shoulder complaints (e.g. frozen shoulder, subacromial bursitis).

All patients that underwent NACD were registered by the radiologist performing the NACD procedure. Inclusion criteria were checked by the researcher (BO) before entering patients in the study database.

Only the treatment of the first shoulder was analyzed in patients who underwent bilateral treatment (n=32).

Technical procedure

NACD procedures were performed by a well-experienced musculoskeletal radiologist in an ultrasound room, using the Logic E9 Ultrasound system (GE Healthcare). Patients

were treated in supine position. After sterile preparation, the skin and subcutaneous tissue were anesthetized by local injection of lidocaine 1%. Thereafter ultrasound-guided NACD was performed using a 20 or 21 gauge needle. After maneuvering the needle into the calcific deposit, the deposits was infiltrated with lidocaine 1%, fragmented and removed by aspiration. The lavage was continued until no visible calcium could be aspirated. After completing the aspiration, the subacromial bursa was infiltrated with 4 ml bupivacaine (2,5mg/ml) and 1ml kenacort (40mg/ml). Patients were advised to use the treated arm within pain limits and to avoid heavy duties in the first six weeks; no specific rehabilitation program was prescribed. Furthermore, they were advised to use paracetamol 1000mg to a maximum of four times a day in case of pain in the first days following the NACD procedure.

Repeated procedures

In case of persisting symptoms, patients were scheduled for another NACD procedure. Criteria for a repeated NACD procedure were clinical symptoms of calcific tendinitis, calcific deposits on ultrasound examination and absence of another cause for shoulder complaints (e.g. frozen shoulder, subacromial bursitis). A minimal term of six weeks between the first and second NACD procedure or the second and third NACD procedure was applied.

Data collection and outcome measures

An overview of the prognostic factors evaluated in this study is presented in figure 1.

Demographic details
Gender
Age

Medical history
Duration of symptoms
Bilateral occurrence
Previous SAI therapy
Pre-treatment pain score

Sonographic findings
Subacromial bursitis
Partial rotator cuff tears

Radiographic findings
Gärtner and Heyer classification

Tendon healing influencing factors
Smoking
Diabetes Mellitus

Figure 1: *overview of factors investigated in this study. SAI: subacromial injection.*

As a standard, medical history, duration of symptoms, unilateral or bilateral occurrence, previous subacromial injection (SAI) therapy and specifically, tendon healing influencing factors, such as smoking and diabetes mellitus were registered. Smoking was defined as smoking on a daily basis for the minimum duration of one year. Prior to the NACD procedure, patients were asked to indicate their pain score on an 11-point numeric rating scale (NRS).

The primary endpoint in this study was successful treatment. Successful treatment was defined as complete relief of symptoms six months after the last NACD procedure measured by a dichotomous outcome (free/not free of symptoms). Persistence of symptoms six months after the last NACD procedure or requiring an alternative treatment (e.g. surgical removal of calcific deposits) within six months after the last NACD procedure was considered as failure of NACD. NACD procedures performed within six months of a previous NACD procedure were considered repeated treatments.

To assess the outcome at six months post-treatment, patients were approached by telephone by an independent researcher (BO) who was not involved in the NACD procedure(s). Patients were asked whether they were free of symptoms or not and whether they had needed any alternative treatments in the six months following the last NACD procedure.

Radiographic assessment

According to the classification described by Gärtner and Heyer, calcific deposits were categorized into three different types of calcific deposits[11]. Type I deposits are dense with well-defined borders, type II deposits dense with indistinct borders or transparent with well-defined borders and type III deposits transparent with indistinct borders (figure 2). The radiographic assessment consisted of a standardized anteroposterior (AP) X-ray. These X-rays were analyzed by an independent researcher (BO). Because of logistic considerations, not all patients underwent radiographic assessment prior to NACD. In total 289 patients (67%) were radiographically assessed prior to the NACD procedure. Patients who were assessed radiographically were comparable to those who were not assessed with regards to the evaluated prognostic factors ($p>0.10$).

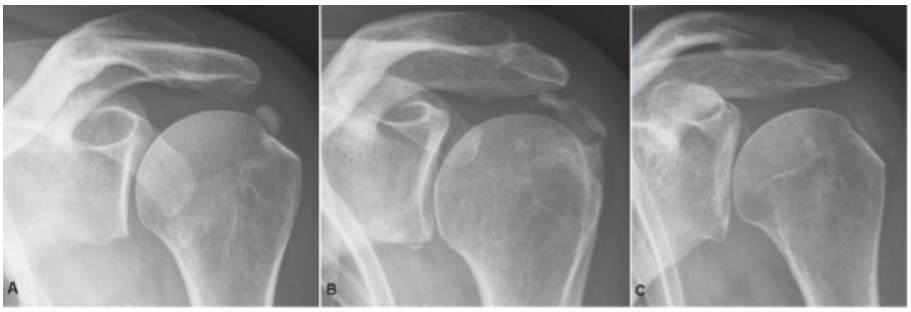

Figure 2: *Gärtner and Heyer classification of calcific deposits. (A) type I calcific deposit: dense with a well-defined border; (B) type II calcific deposit: dense with a indistinct border or transparent with a well-defined border; (C) type III calcific deposit: transparent with a indistinct border.*

Sonographic assessment

Besides the presence of calcific deposits, findings on ultrasound examination of particular interest for the purpose of this study were subacromial bursitis and partial rotator cuff tears**.** Subacromial bursitis was diagnosed when the bursa was thickened and/or there was evidence of fluid in the subacromial bursa. Partial rotator cuff tears (PRCT) were diagnosed in case of tears that did not cover the complete thickness of the tendon and communicated with either the subacromial bursa or glenohumeral joint. The presence of rotator cuff tears was verified during the NACD procedure. In case of a partial rotator cuff tear, the fluid used for the lavage will leak into the subdeltoid subacromial bursa (in case of a bursal sided partial tear) or in the direction of the glenohumeral joint (in case of an articular sided partial tear) during the NACD procedure; in case of a full thickness tear, the fluid used for the lavage will leak into both the subdeltoid subacromial bursa and in the direction of the glenohumeral joint. The sonographic assessments of the rotator cuff were performed following a standardized method by an experienced musculoskeletal radiologist.

Statistical analysis

Visual inspection of histograms was used to determine whether continuous variables followed a normal distribution. Demographic and clinical characteristics were described as continuous or categorical variables as appropriate.

Patients were grouped based on whether they were or were not free of symptoms at six months post-treatment and based on whether they received a single NACD procedure or multiple (>1) procedures. To determine whether factors differed between the groups (free of symptoms vs. not free of symptoms and single procedure vs. multiple procedures) independent t-tests (parametric) and $\chi 2$ test (non-parametric) were used. Factors that differed significantly between the groups ($p < 0{,}10$) were included for multivariate logistic regression analysis. Irrespective of the outcome of the univariate analysis, the factors gender and age were added to the multivariate logistic regression analysis.

Stepwise backwards binary logistic regression was performed to determine factors associated with treatment failure or multiple treatments. A significance level of $p < 0.05$ was used to define factors that significantly increased the probability of failure of NACD or multiple treatments. Additionally, in-depth analyses were performed in order to define factors associated with the type of calcific deposit. The factors associated with the type of calcific deposit were determined using the same procedure as described above.

In order to avoid the influence of missing data, data of patients without any missing values were initially analyzed to determine model fit. After logistic regression was completed, the model was applied on the entire population to obtain definitive adjusted odds ratios (AOR). All statistical analyses were performed using the statistical package SPSS version 20.0 (IBM, Armonk, NY, USA).

Results

Table 1 lists the baseline characteristics of the 431 patients. At six months post-treatment, 317 (74%) patients reported to be free of symptoms. Two or more NACD procedures were performed in 143 (33%) patients. Of the 114 (26%) patients with failure of the NACD procedure, 57 (13%) patients underwent surgery.

Table 1: Baseline characteristics (n=431)	
Demographic details	
Male (%)	154 (36)
Female (%)	277 (64)
Age (±SD)	51.4 (±9.9)
Medical history	
Duration of symptoms (±SD)	2.4 (±2.4)
Bilateral occurrence (%)	32 (7)
Previous SAI therapy (%)*	90 (48)
Pre-treatment NRS score (±SD)	7.5 (±1.6)
Sonographic findings	
Subacromial bursitis (%)	14
Partial rotator cuff tears (%)	16
Full thickness rotator cuff tears (%)	1
Radiographic findings**	
G&H type I (%)	40
G&H type II (%)	40
G&H type III (%)	20
Tendon healing influencing factors	
Smoking (%)	26
Diabetes Mellitus (%)	7

* Based on data from 188 patients. ** Based on data from 289 patients. Values are presented as mean ± standard deviation or number (%) unless otherwise indicated. NRS: numeric rating scale.

Factors associated with failure of treatment

The results of the univariate analysis are presented in table 2.

Patients in the failure group were significantly younger (p=0.02) and more often smokers (p=0.02). Presence of subacromial bursitis or partial rotator cuff tears on sonographic examination, or the type of calcific deposit on radiographic assessment were of no influence on failure of NACD (p>0.05).

Multivariate logistic regression analysis showed that only smoking (AOR 1.7, 95% CI 1.0-2.7, p=0.04) was significantly associated with failure of treatment at six months post NACD (table 3).

Factors associated with multiple treatments

As illustrated in table 2, patients in the multiple treatment group reported higher NRS scores pre-treatment (p=0.02). Type I calcific deposits were seen significantly more often among patients in the multiple treatment group, type III calcific deposits were seen significantly less often (p=0.01). Presence of partial rotator cuff tears or subacromial bursitis were of no influence on the number of NACD procedures (p>0.05).

In the multivariate logistic regression analysis only the type of calcific deposit was significantly associated with multiple procedures: type I calcific deposits give an AOR of 3.4 (95% CI 1.6-7.5, p<0.01) for the need for a second NACD procedure compared to type III calcific deposits. No significant association was found between the pre-treatment NRS score and the need for multiple procedures (p=0.07; 95% CI 1.0-1.6) (table 3).

Table 2: Univariate analysis for failure of NACD and multiple procedures

	Outcome of NACD			Number of NACD procedures		
	Successful	**Failure**	**p**	**Single procedure**	**Multiple procedures**	**p**
Male (%)	75	25	0.69	70	30	0.28
Female (%)	73	27		65	35	
Age (±SD)	52.1 (±10.1)	49.4 (±9.1)	0.02	51.9 (±10.4)	50.2 (±8.7)	0.09
Smoking (%)	23	35	0.02	28	23	0.31
Diabetes Mellitus (%)	8	5	0.35	7	7	0.88
Duration of symptoms (±SD)	2.4 (±2.4)	2.5 (±2.6)	0.79	2.2 (±2.2)	2.7 (±2.9)	0.27
Bilateral occurrence (%)	7	10	0.29	7	8	0.88
Previous SAI therapy (%)	46	51	0.44	49	45	0.58
Pre-treatment NRS score (±SD)	7.5 (±1.6)	7.5 (±1.3)	0.76	7.4 (±1.7)	7.7 (±1.2)	0.02
Subacromial bursitis (%)	15	11	0.22	14	13	0.79
Partial rotator cuff tears (%)	16	18	0.66	17	15	0.73
G&H type I (%)	39	42	0.79	34	50	0.01
G&H type II (%)	41	36		41	39	
G&H type III (%)	20	22		25	11	

Values are presented as mean ± standard deviation (SD) or number (%) unless otherwise indicated.
NRS: numeric rating scale, G&H: Gärtner & Heyer classification, SAI: subacromial injection.

Table 3: Summary of binary logistic regression analysis predicting failure of NACD and the need for multiple NACD procedutres

Factor	p	AOR	95% CI
Factors predicting failure of NACD			
Smoking	0.04	1.7	1.0-2.7
Factors predicting the need for multiple NACD procedures			
Age	0.26	1.0	1.0-1.1
Pre-treatment NRS score	0.07	1.3	1.0-1.6
Type I calcific deposits*	<0.01	3.4	1.6-7.5

AOR: adjusted odds ratio. 95% CI: 95% confidence interval. NRS: numeric rating score.
* Based on Gärtner and Heyer classification.

Table 4: The association between smoking and the type of calcific deposit

G&H classification			
	Type I	**Type II**	**Type III**
Non-smokers	43%	37%	20%
Smokers	29%	51%	20%

G&H classification: Gärtner and Heyer classification.

Discussion

The current study demonstrated that smoking significantly increased the chance of failure of NACD and that Gärtner and Heyer type I calcific deposits increased the chance of multiple procedures. Furthermore, partial rotator cuff tears did not affect the outcome of NACD.

Factors associated with failure of treatment

First of all, results of this study demonstrate that smoking almost doubles the chance of failure of NACD. No such results have been published in literature to our knowledge. One could hypothesize that smoking compromises the vascular supply to rotator cuff tendons and smoking, therefore, might impede recovery of tendon tissue. This hypothesis is supported by a cadaveric study by Kane et al. who reported that the presence of advanced microscopic rotator cuff pathology was more than twice as likely in patients with a history of smoking[22]. However, associations between rotator cuff tendinopathy and smoking have never been reported. In fact, according to a population-based study by Rechardt et al.[23], smoking is not associated with chronic rotator cuff tendinitis. Additionally, little is known about the influence of smoking on the outcome of treatment of rotator cuff tendinopathies. In contrast, smoking is associated with less improvement of pain and worse functional results postoperatively in patients who underwent rotator cuff repair[24,25,26]. Based on the findings in this study, the importance of quitting smoking should also be emphasized in patients with CTRC prior to NACD.

A second important and clinically relevant finding of this study is that partial rotator cuff tears were of no effect on the outcome of NACD. Although rotator cuff tears have been reported in up to 25% of patients with CTRC[27], no studies investigating the influence of partial rotator cuff tears on the outcome of NACD have been conducted to our knowledge. The larger studies investigating the outcome of NACD all excluded patients with partial rotator cuff tears, therefore it is unknown whether the presence of a partial rotator cuff tear affects the outcome of NACD or whether treatment of CTRC should be altered in case of a concomitant partial rotator cuff tear[12,28-30]. Based on the current study, NACD for CTRC can be performed successfully in presence of a concomitant partial rotator cuff tear and partial rotator cuff tears should therefore not be regarded as a contraindication for NACD.

Factors associated with multiple treatments

The morphology (based on the Gärtner and Heyer classification) of the calcific deposits was significantly associated with the number of NACD procedures needed: the odds for multiple treatments in patients with type I deposits were over 3 times higher compared to patient with type III deposits. In the current study, plain radiographs were used to classify the calcific deposits. According to Farin et al., classification of the calcific deposits is preferably based on plain radiographs as classification of calcific deposits with ultrasound does not correlate well with the phase of calcification[31]. With regard to the ultrasound findings of CTRC, three types of calcifications can be found: (1) a hyperechoic focus with a well-defined shadow; (2) a hyperechoic focus with a faint shadow; and (3) a hyperechoic focus with no shadow (figure 3). Although type 1 calcifications usually present with an acoustic shadow on ultrasound, no significant correlation was found between type 3 calcifications and calcifications without an acoustic shadow. Therefore, the use of plain radiographs is advised for classification of calcific deposits[31].

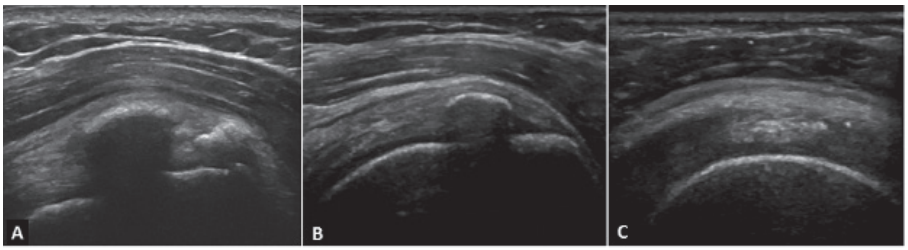

Figure 3: sonographic findings of calcific deposits as described by Farin et al.. (A) A hyperechoic focus with a well-defined shadow; (B) a hyperechoic focus with a faint shadow; and (C) a hyperechoic focus with no shadow.

Associations between the consistency or the morphology of the calcific deposit and the number of NACD procedures necessary have never been investigated before. As type III calcific deposits are already in the resorptive phase, the calcific deposit is more fluid-like and therefore easier to aspirate. This is in contrast to type I calcific deposits, which are more solid, which makes it harder to aspirate the calcium. Literature is inconclusive about the association between the ability to aspirate calcium during the procedure and the effectiveness of NACD[32,33]. We hypothesize that NACD in type I calcific deposits initiates the resorption of calcific deposits, whereas in type III calcific deposits the resorptive phase is shortened by removing the calcium. As,

after initiating the resorption in type I calcific deposits, the body itself is not always capable of eliminating all of the calcium, patients will stay in a prolonged resorptive phase and will therefore need a second NACD procedure more often. This hypothesis is supported by the finding of Gärtner et al.[11], who reported a decreased rate of resolution of calcific deposits in type I calcific deposits after NACD. As managing patient expectations is becoming increasingly important, this information might be useful in informing patients about what to expect prior to the NACD procedure.

In order to define factors associated with the type of calcific deposit, additional in-depth analyses were performed. Remarkably, only smoking was significantly associated with the type of calcific deposit (p=0.024). As presented in table 4, type I calcifications were less common among smokers, whereas type II calcifications were more common among smokers. Assuming that type I calcifications give an increased chance for multiple procedures, one could hypothesize that multiple procedures are less often needed among smokers. However, logistic regression analysis of factors predicting the need for multiple procedures showed that smoking was of no influence on the amount of necessary NACD procedures. As the effects of smoking on calcific tendinitis have never been described before, it is uncertain whether this finding is an incidental finding or that smoking influences the course of the disease and thereby the type of calcific deposit found in the tendon. To gain more insight into the effects of smoking on calcific tendinitis, more longitudinal studies are needed.

Limitations

To our knowledge, the current study is one of the largest cohort studies on the outcome of NACD. However, given the retrospective character of this study, there are some methodological issues. First of all, because the information on patients being symptom-free or not at six months post-treatment was collected retrospectively, there is a substantial variability in the time between the six months post-treatment term and the moment of the actual obtaining of these data (recall bias). However, the percentage of patients that reported to be free of symptom at six months post-treatment did not differ substantially from percentages mentioned in literature (70-75%)[2,9,10]. Secondly, the radiographic assessment prior to the NACD procedure could not be performed in one third of the patients. However, patients who did and did not undergo the radiographic assessment were comparable for all of the evaluated prognostic factors in this study. Furthermore, in-depth analysis revealed

no differences between the statistic model without and the model with missing values. We therefore assume that the influence of these missing values on the outcome is limited. Finally, as the current study was designed to identify factors associated with persisting symptoms, all symptoms of CTRC six months after the last NACD procedure were regarded persisting symptoms. Persisting symptoms that were considered tolerable by patients were also regarded persisting symptoms. In order to gain more insight in what factors contribute to complete relief of symptoms or tolerable persisting symptoms following NACD, future research using quality of life questionnaires or functional scales is needed.

Conclusions

Smoking almost doubled the chance of failure of NACD and Gärtner and Heyer type I calcific deposits increased the chance of multiple procedures. Partial rotator cuff tears did not affect the outcome of NACD and should therefore not be considered a contraindication for NACD.

References

1. Welfling J, Kahn MF, Desroy M, Paologgi JB, Seze SD. Calcification of the shoulder. The disease of multiple tendinous calcifications. Rev Rheumatology 1965 32:325–334
2. Lin JT, Adler RS, Bracilovic A, Cooper G, Sofka C, Lutz GE. Clinical outcomes of ultrasound-guided aspiration and lavage in calcific tendinosis of the shoulder. HSS J. 2007 Feb;3(1):99-105. doi: 10.1007/s11420-006-9037-9.
3. Diehl P, Gerdesmeyer L, Gollwitzer H, Sauer W, Tischer T. Calcific tendinitis of the shoulder. Orthopade 2011 Aug;40(8):733-46. doi: 10.1007/s00132-011-1817-3.
4. Speed CA, Hazleman BL. Calcific tendinitis of the shoulder. N Engl J Med 1999 May 20;340(20):1582-4.
5. Uhthoff HK, Sarkar K. Calcifying tendinitis. Baillieres Clin Rheumatol. 1989;3:567-581.
6. Harvie P, Pollard TC, Carr AJ. Calcific tendinitis: natural history and association with endocrine disorders. J Shoulder Elbow Surg. 2007 Mar-Apr;16(2):169-73.
7. Gohr CM, Fahey M, Rosenthal AK. Calcific tendonitis : a model. Connect Tissue Res. 2007;48(6):286-91.
8. Codman EA. The shoulder, rupture of the supraspinatus tendon and other lesions in or about the subacromial bursa. Boston, MA: T. Todd Co: 1934.
9. Schulz CU, Maier M, Glaser C, Anetzberger H, Müller-Gerbl M. Pathologic glenohumeral stress distribution in calcific tendinosis of the supraspinatus. Z Orthop Ihre Grenzgeb. 2006 May-Jun;144(3):311-5.
10. Riley GP, Harrall RL, Constant CR, Chard MD, Cawston TE, Hazleman BL. Tendon degeneration and chronic shoulder pain: changes in the collagen composition of the human rotator cuff tendons in rotator cuff tendinitis. Ann Rheum Dis. 1994 Jun;53(6):359-66.
11. Refior HJ, Krödel A, Melzer C. Examinations of the pathology of the rotator cuff. Arch Orthop Trauma Surg. 1987;106(5):301-8.
12. Uhthoff HK. Calcifying tendinitis, an active cell-mediated calcification. Virchows Arch A Pathol Anat Histol. 1975;366(1):51-8.
13. Uhthoff HK, Sarkar K, Maynard JA. Calcifying tendinitis: a new concept of its pathogenesis. Clin Orthop Relat Res. 1976 Jul-Aug;(118):164-8.
14. Uhthoff HK. Calcifying tendinitis. Ann Chir Gynaecol. 1996;85(2):111-5. Review.
15. Gosens T, Hofstee DJ. Calcifying tendinitis of the shoulder: Advances in imaging and management. Curr Rheumatol Rep 2009 Apr;11(2):129-34.
16. Wölk T, Wittenberg RH. Calcifying subacromial syndrome--clinical and ultrasound outcome of non-surgical therapy. Z Orthop Ihre Grenzgeb. 1997 Sep-Oct;135(5):451-7.
17. Ogon P, Suedkamp NP, Jaeger M, Izadpanah K, Koestler W, Maier D. Prognostic factors in nonoperative therapy for chronic symptomatic calcific tendinitis of the shoulder. Arthritis Rheum 2009 Oct;60(10):2978-84. doi: 10.1002/art.24845.
18. Yoo JC, Koh KH, Park WH, Park JC, Kim SM, Yoon YC. The outcome of ultrasound-guided needle decompression and steroid injection in calcific tendinitis. J Shoulder Elbow Surg. 2010 Jun;19(4):596-600. doi: 10.1016/j.jse.2009.09.002.

19. Farin PU, Rasanen H, Jaroma H, Harju A. Rotator cuff calcifications: Treatment with ultrasound-guided percutaneous needle aspiration and lavage. Skeletal Radiol 1996 Aug;25(6):551-4.
20. Gartner J, Heyer A. Calcific tendinitis of the shoulder. Orthopade 1995 Jun;24(3):284-302.
21. De Conti G, Marchioro U, Dorigo A, Boscolo N, Vio S, Trevisan M, Meneghini A, Baldo V, Angelini F. Percutaneous ultrasound-guided treatment of shoulder tendon calcifications: Clinical and radiological follow-up at 6 months. J Ultrasound 2010 Dec;13(4):188-98. doi: 10.1016/j.jus.2010.10.012.
22. Kane SM, Dave A, Haque A, Langston K. The incidence of rotator cuff disease in smoking and non-smoking patients: a cadaveric study. Orthopedics. 2006 Apr;29(4):363-6.
23. Rechardt M, Shiri R, Karppinen J, Jula A, Heliövaara M, Viikari-Juntura E. Lifestyle and metabolic factors in relation to shoulder pain and rotator cuff tendinitis: a population-based study. BMC Musculoskelet Disord. 2010 Jul 20;11:165. doi: 10.1186/1471-2474-11-165.
24. Santiago-Torres J, Flanigan DC, Butler RB, Bishop JY. The Effect of Smoking on Rotator Cuff and Glenoid Labrum Surgery: A Systematic Review. Am J Sports Med. 2015 Mar;43(3):745-51. doi: 10.1177/0363546514533776.
25. Mallon WJ, Misamore G, Snead DS, Denton P. The impact of preoperative smoking habits on the results of rotator cuff repair. J Shoulder Elbow Surg. 2004 Mar-Apr;13(2):129-32.
26. Carbone S, Gumina S, Arceri V, Campagna V, Fagnani C, Postacchini F. The impact of preoperative smoking habit on rotator cuff tear: cigarette smoking influences rotator cuff tear sizes. J Shoulder Elbow Surg. 2012 Jan;21(1):56-60. doi: 10.1016/j.jse.2011.01.039.
27. Jim YF, Hsu HC, Chang CY, Wu JJ, Chang T. Coexistence of calcific tendinitis and rotator cuff tear: an arthrographic study. Skeletal Radiol. 1993;22(3):183-5.
28. Serafini G, Sconfienza LM, Lacelli F, Silvestri E, Aliprandi A, Sardanelli F. Rotator cuff calcific tendonitis: Short-term and 10-year outcomes after two-needle us-guided percutaneous treatment--nonrandomized controlled trial. Radiology 2009 Jul;252(1):157-64. doi: 10.1148/radiol.2521081816.
29. Giacomoni P, Siliotto R. Echo-guided percutaneous treatment of chronic calcific tendinitis of the shoulder. Radiol Med. 1999 Nov;98(5):386-90.
30. Vignesh KN, McDowall A, Simunovic N, Bhandari M, Choudur HN. Efficacy of ultrasound-guided percutaneous needle treatment of calcific tendinitis. AJR Am J Roentgenol. 2015 Jan;204(1):148-52. doi: 10.2214/AJR.13.11935.
31. Farin PU, Jaroma H. Sonographic findings of rotator cuff calcifications. J Ultrasound Med. 1995 Jan;14(1):7-14.
32. del Cura JL, Torre I, Zabala R, Legorburu A. Sonographically guided percutaneous needle lavage in calcific tendinitis of the shoulder: Short- and long-term results. AJR Am J Roentgenol 2007 Sep;189(3):128-34.
33. Aina R, Cardinal E, Bureau NJ, Aubin B, Brassard P. Calcific shoulder tendinitis: Treatment with modified US-guided fine-needle technique. Radiology 2001 Nov;221(2):455-61.

Chapter 4

Prognostic factors for the outcome of needle aspiration of calcific deposits for rotator cuff calcific tendinitis

Bart W. Oudelaar
Rianne Huis In 't Veld
Relinde Schepers-Bok
Edwin M. Ooms
Rob G.H.H. Nelissen
Anne J.H. Vochteloo

Eur Radiol. 2020;30:4082-4090

Abstract

Objective

To identify prognostic factors for the effectiveness of needle aspiration of calcific deposits (NACD) for rotator cuff calcific tendinitis (RCCT).

Methods

One hundred forty-nine patients with symptomatic RCCT were included in a prospective cohort study. Pain (VAS), shoulder function (SST and DASH) and quality of life (EQ-5D) were assessed at baseline and at 3, 6 and 12 months post-NACD. Univariate analyses (independent t-tests or Mann-Whitney U tests depending on the distribution of data) were performed to build a multivariable linear regression model. Stepwise regression analysis through backward elimination was performed to evaluate the effect of predefined prognostic factors on the outcome.

Results

Patients who underwent multiple NACD procedures had less reduction of pain ($p<0.01$). Furthermore, a larger reduction in VAS pain scores at 3 months post-NACD was associated with a larger reduction in VAS pain scores at 12 months ($p<0.01$). More improvement of SST and DASH scores at 3 months were associated with better SST, DASH and EQ-5D scores at 12 months ($p<0.01$). Smaller-size calcific deposits were associated with less improvement of DASH ($p=0.03$) and EQ-5D scores ($p=0.01$). A longer duration of symptoms prior to NACD was associated with less improvement of EQ-5D scores ($p=0.01$).

Conclusions

A good initial response after NACD is associated with better outcomes at 12 months. Patients with a longer duration of symptoms prior to NACD and patients who require multiple procedures showed inferior outcomes in terms of pain reduction and improvement of quality of life. Smaller-size calcific deposits are associated with a less favorable outcome of shoulder function and quality of life scores and might therefore be less susceptible for NACD.

Introduction

Rotator cuff calcific tendinitis (RCCT) is a frequently diagnosed shoulder disease, which is found in up to 54% of patients with shoulder complaints[1]. It is suggested that RCCT is a self-limiting disease that can be treated with conservative measures (rest, non-steroidal anti-inflammatory drugs (NSAIDs) or physiotherapy)[2,3,4]. However, a substantial number of patients has persisting symptoms requiring other therapies such as subacromial injections with corticosteroids, needle aspiration of calcific deposits (NACD) or extracorporeal shockwave therapy (ESWT)[5]. A recently published meta-analysis comparing these therapies concluded that NACD is the most effective treatment considering relevant clinical outcomes within a follow-up term of two years[6]. However, up to 42% of patients experience persisting or recurrent shoulder complaints after NACD[7,8]. Female gender, smoking and type I calcifications according to the classification by Gärtner and Heyer are considered predictors for persisting shoulder complaints[7,9,10]. However, the majority of studies investigating prognostic factors for the effectiveness of NACD are retrospective and to our knowledge, no prospective studies investigating prognostic factors have been conducted. As more evidence is needed on this highly prevalent shoulder disease, we conducted a prospective cohort study to further identify prognostic factors for the effectiveness of NACD.

Materials and Methods

Study design and study population

A prospective cohort study was conducted at the departments of orthopaedic surgery and radiology. All consecutive patients referred to the department of radiology between October 2014 and August 2016 for the treatment of symptomatic RCCT were included. Inclusion criteria were clinical signs of calcific tendinitis defined as pain in the deltoid region worsening by elevation of the arm above the shoulder level and/or at night and the presence of calcific deposits on radiographs and/or ultrasound examination. Exclusion criteria were age <18 years, being unable to read and write the Dutch language, previous NACD treatment or surgery of the affected shoulder and the presence of other causes for shoulder complaints (e.g. full thickness tear of the rotator cuff, frozen shoulder). Only the treatment of the first shoulder was analyzed in patients who underwent bilateral treatment.

Since it was a prospective cohort study evaluating current treatment and follow-up standards of our department, the study was declared free from subject to the medical research involving human subjects act and the IRB approved the local study execution.

Data collection and outcome measures

After the participating patients signed informed consent forms, baseline data, including demographics and data related to the medical history and previous treatments, were collected.

Prior to the NACD procedure, baseline scores were completed by all patients: visual analogue scale for pain (VAS 0-100mm where 0mm represents 'no pain' and 100mm 'the worst pain ever possible'), the Simple Shoulder Test (SST; 0 (worst score) to 12 (best score)), the Disabilities of the Arm, Shoulder and Hand questionnaire (DASH; 0 (no disability) to 100 (most severe disability)) and the EQ-5D (0 (worst score) to 1 (best score).

Every two weeks during the first ten weeks following the NACD procedure, patients reported a VAS pain score, whether they had physiotherapy and whether they had used analgesic medication (type and dose).

At three months, six months and one year after the NACD procedure, patients reported the VAS pain score, SST, DASH and EQ-5D questionnaires. Furthermore, the number of NACD procedures patients underwent was noted. The indication to perform a repeated NACD

procedure was persisting clinical symptoms of calcific tendinitis with calcific deposits on ultrasound examination in the absence of another cause for shoulder complaints (e.g. frozen shoulder, subacromial bursitis). A minimum period of six weeks between the first and second NACD procedure or the second and third NACD procedure was applied.

The primary endpoints were: reduction of pain at 12 months post-NACD (ΔVAS baseline-12 months); improvement of shoulder function at 12 months post-NACD (ΔSST baseline-12 months and ΔDASH baseline-12 months); improvement of quality of life (QoL) at 12 months post-NACD (ΔEQ-5D baseline-12months). Minimal clinically important differences (MCID; ≥14mm for VAS[11], ≥2.0 for SST[12], ≥10.83 for DASH[13] and ≥ 0.07 for EQ-5D[14]) were used to determine whether the reduction of pain and improvement of shoulder function and QoL were clinically relevant.

Radiographic assessment and technical procedure

All patients had both radiographic and ultrasound assessment of the affected shoulder prior to the NACD procedure.

Standard anteroposterior and axial radiographs were used to examine the size and number of calcific deposits and the affected tendon(s). Calcific deposits were categorized into three different types using the classification described by Gärtner and Heyer[9]: type I calcifications are dense with well-defined borders; type II calcifications are either dense with indistinct borders or transparent with well-defined borders and type III calcifications are transparent with indistinct borders. The location of the calcific deposits was determined based on the method used by Ogon et al.[3] in which negative values represent a medial calcification border.

Ultrasound was performed using a standardized protocol by experienced musculoskeletal radiologists. The size, the number of calcific deposits and the affected tendon(s) were recorded. Furthermore, the presence of subacromial bursitis, partial rotator cuff tears and subacromial impingement was assessed prior to the NACD procedure.

During the NACD procedure the consistency of the calcific deposits was assessed as either soft (toothpaste like) or hard. Furthermore, the possibility to aspirate the calcific deposit was reported.

Ultrasound-guided NACD was performed using a single needle technique with 20 or 21 gauge needle. After maneuvering the needle into the calcific deposit, the deposits was

infiltrated with lidocaine 1%, fragmented in case of a hard calcific deposit and removed by aspiration. After completing the aspiration, the subacromial bursa was infiltrated with 4 ml bupivacaine (2,5mg/ml; Aurobindo Pharma B.V) and 1ml kenacort (40mg/ml; Bristol-Myers Squibb B.V.). No specific rehabilitation program was prescribed.

Statistical analysis

Univariate analyses (independent t-tests in case of normally distributed data and the Mann-Whitney U tests in case the data was not normally distributed) were performed to build a multivariable linear regression model. Factors that approached a significant correlation ($p < 0.10$) were included for multivariable linear regression analysis.

Stepwise regression analysis through backward elimination was performed to determine factors associated with better reduction of pain, better improvement of shoulder function and better improvement of QoL. All the previously selected factors were entered into the equation after which the factor that contributed the least (i.e. highest p-value) was deleted. This process was continued until all factors in the equation had a significance level of $p < 0.05$.

All statistical analyses were performed using the statistical package SPSS version 20.0 (IBM).

Results

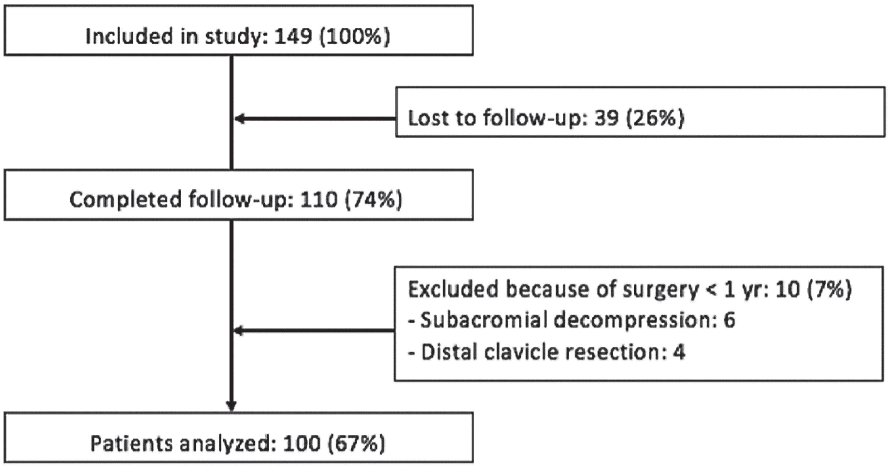

Figure 1: flowchart of patient inclusion and drop-out.

149 consecutive patients were included of which 39 patients were lost to follow-up as these patients did not complete the 12-month follow-up questionnaires (figure 1). The baseline characteristics of the patients included in this study are presented in table 1. The average duration of symptoms prior to NACD was 29 months and over one fifth of patients reported absenteeism from work due to shoulder complaints. The majority of patients underwent other therapies prior to the NACD procedure: over 75% of patients had physiotherapy and over 50% of patients already had subacromial injection(s) with corticosteroids.

Except for age (55yr in the analyzed group vs. 51yr in the drop-out group; p=0,016), none of the other demographic or baseline values differed significantly between these groups.

During the course of the study, 10 patients failed NACD treatment and had arthroscopic surgery due to persisting symptoms (Figure 1). In the patients requiring surgery, bilateral occurrence of RCCT was more common (5/10 vs. 20/100, Fisher's exact test $p<0.046$) and these 10 patients had less pain relief at three months post NACD compared to the non-failed group ((ΔVASbaseline-VAS3months 9mm vs. 33mm, independent t-test $p<0.043$). None of the other prognostic factors studied in this study differed significantly between patients that required surgery and those who did not.

During the NACD procedure successful aspiration of calcium was achieved in 51% (50/98 patients) of patients.

Table 1: Baseline characteristics	
Demographic details	
Male (%)	49 (45%)
Female (%)	61 (55%)
Age (SD;range)	54,9 (8,2; 36-77)
Medical history	
Duration of symptoms in months (SD; range)	29 (33; 1-120)
Bilateral occurence (%)	25 (22,7)
Dominant arm affected (%)	65 (59,1)
Heavy physical work (%)	50 (46,3)
Absenteeism from work due to shoulder complains (%)	23 (22,5)
Average amount of days of absenteeism from work (SD; range)	78 (99; 2-360)
Smoking (%)	21 (21)
Diabetes (%)	10 (10)
Previous treatment	
Analgesics (%)	69 (62,7)
Fysiotherapy (%)	84 (76,4)
Shockwave (%)	14 (12,7)
Subacromial injection (%)	59 (53,6)
Ultrasound findings	
Affected tendon(s)	
Supraspinatus (%)	103 (93,6)
Infraspinatus (%)	2 (1,8)
Subscapularis (%)	17 (15,5)
Subacromial bursitis (%)	19 (18,4)
Partial thickness rotator cuff tear (%)	27 (25,7)
Subacromial impingement (%)	8 (13,3)
Radiographic findings	
Size in mm (SD; range)	16,5 (9,4; 2,0-44,9)
Numer of calcific deposits	
One (%)	61 (59,8)
Multiple (%)	41 (40,2)
Gartner & Heyer classification	
Type I (%)	60 (58,2)
Type II (%)	29 (28,2)
Type III (%)	14 (13,6)

Table 1 (Continued)

Location according to Ogon et al. In mm (SD; range)	-6,4 (13,1; -36,1-26,4)
Features of AC osteoarthritis (%)	48 (44,4)
Post NACD	
Analgesics during first 6 weeks post NACD (%)	57 (56,4)
Fysiotherapie during first 6 weeks post NACD (%)	33 (33,0)
Average amount of physiotherapy visits (SD; range)	3,5 (2,5; 1-11)

SD: standard deviation

Improvement of pain, function and QoL at three, six and 12 months

At 12 months follow-up 83% (91/110) of patients had lower pain scores compared to their preintervention baseline score and 70% (77/110) of patient reached MCID. The average decrease of VAS scores was 31mm (SD 24.3).

With regard to function, respectively 74% (81/110) and 78% (86/110) of patients showed improved SST and DASH scores (average improvement SST 3.6 (SD 3.5); average improvement DASH 17.5 (SD 15.9)) and respectively 65% (72/110) and 64% (70/110) of patients reached MCID. QoL improved in 56% (62/110) of the patients and remained the same in 24% (26/110); 46% (51/110) of patients showed a clinical important improvement. The average improvement in EQ 5D was 0.12 (SD 0.26).

The largest decrease of pain, improvement of function and QoL was seen at three months following the NACD procedure after which the level of pain, shoulder function and QoL scores remained within the MCID interval (figure 2).

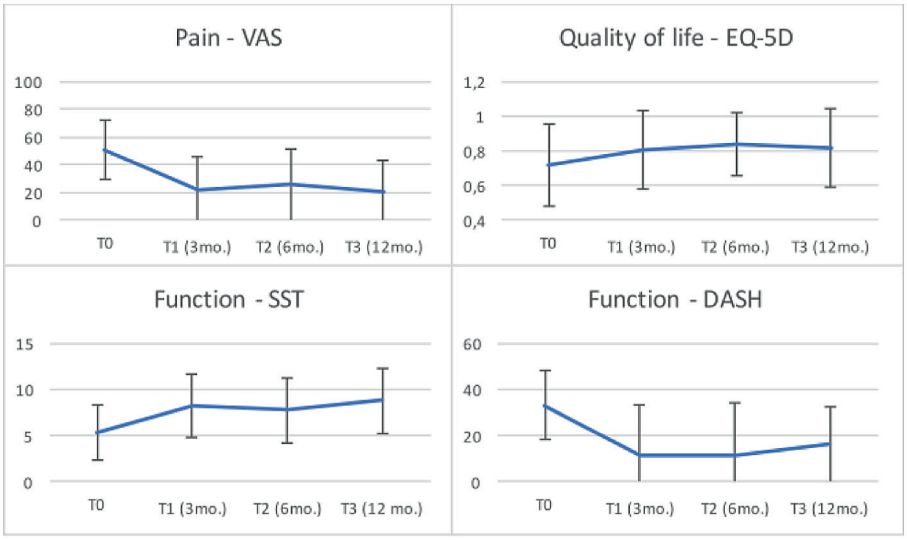

Figure 2: course of pain (VAS), shoulder function (SST and DASH) and QoL (EQ-5D) during the course of this study.

Factors associated with decrease of pain, improvement of shoulder function and improvement of QoL

A summary of the results of the univariate analyses for factors related to decrease of pain, improvement of shoulder function and QoL is presented in table 2. A complete overview of the results of the univariate analyses can be found in supplementary file I.

With regard to reduction of pain, multiple NACD procedures were associated with more pain 12 months after the intervention. A greater reduction of pain at three months after NACD was associated with more pain relief at 12 months (table 3). For the improvement of shoulder function and QoL, improved SST and DASH scores at three months were strongly associated with more improvement of the shoulder function and QoL at 12 months. A longer duration of symptoms prior to the NACD procedure was associated with less improvement of QoL. The size of the calcification was positively associated with DASH and QoL scores: larger-size calcific deposits showed better outcome at 12 months (table 3).

Table 2: Summary of univariate analyses for reduction of pain (VAS), improvement of shoulder function (SST and DASH) and improvement of QoL (EQ-5D).

	Factor		Value	p-value
Pain - VAS	Multiple NACD procedures	Mean difference (95% CI)	15,5mm (5,1 to 25,9mm)	0.004
	ΔVAS at three months	Pearson correlation coefficient (95% CI)	0,500 (0,327 to 0,674)	<0.001
	ΔDASH at three months	Pearson correlation coefficient (95% CI)	0,267 (0,074 to 0,461)	0.007
Function - SST	Size of calcific deposit	Pearson correlation coefficient (95% I)	0,232 (0,028 to 0,425)	0.029
	Multiple NACD procedures	Mean difference (95% CI)	1,8 (0,3 to 3,3)	0.023
	ΔSST at three months	Pearson correlation coefficient (95% CI)	0,362 (0,176 to 0,549)	<0.001
	ΔDASH at three months	Pearson correlation coefficient (95% CI)	0,282 (0,09 to 0,474)	0.004
Function - DASH	Absenteeism from work due to shoulder complaints	Mean difference (95% CI)	9,3 (-1,1 to 19,7)	0.078
	Analgesics use prior to the NACD procedure	Mean difference (95% CI)	5,6 (-0,4 to 11,6)	0.067
	Physiotherapy prior to the NACD procedure	Mean difference (95% CI)	8,6 (1,3 to 15,8)	0.021
	Subacromial impingement	Mean difference (95% CI)	11,1 (-0.9 to 23,1)	0.068
	Size of calcific deposit	Pearson correlation coefficient (95% CI)	0,225 (0,022 to 0,413)	0.031
	Multiple NACD procedures	Mean difference (95% CI)	8,2 (1,4 to 15,1)	0.019
	ΔSST at three months	Pearson correlation coefficient (95% CI)	0,267 (0,074 to 0,460)	0.007
	ΔDASH at three months	Pearson correlation coefficient (95% CI)	0,441 (0,261 to 0,621)	<0.001
Quality of life - EQ-5D	Duration of symptoms	Pearson correlation coefficient (95% CI)	0,246 (0,051 to 0,443)	0.026
	Size of calcific deposit	Pearson correlation coefficient (95% CI)	0,254 (0,052 to 0,452)	0.018
	Multiple NACD procedures	Mean difference (95% CI)	0,10 (-0,01 to 0,21)	0.088
	ΔSST at three months	Pearson correlation coefficient (95% CI)	0,262 (0,069 to 0,456)	0.008
	ΔDASH at three months	Pearson correlation coefficient (95% CI)	0,185 (-0,012 to 0,382)	0.063

CI: confidence interval. Mean differences were calculated using independent t-tests or Mann-Whitney U tests depending on the distribution of data.
Only factors with a p-value of 0.10 or less are presented in this table. For a complete overview of all factors, see supplementary file I.

Table 3: Results of multivariable regression analysis for reduction of pain (VAS), improvement of shoulder function (SST and DASH) and improvement of QoL (EQ-5D).

	Factor	Comparison	Regression coefficient (95% CI)	p-value
Pain - VAS	Number of NACD procedures	Multiple procedures vs. single procedure	-12.34 (-21.47 to -3.22)	0.009
	ΔVAS at three months	Per 1 mm	0.409 (0.262 to 0.555)	< 0.001
Function - SST	ΔSST at three months	Per point	0.258 (0.134 to 0.382)	< 0.001
	ΔDASH at three months	Per point	0.048 (0.019 to 0.078)	0.002
Function - DASH	ΔSST at three months	Per point	0.692 (0.124 to 1.26)	0.018
	ΔDASH at three months	Per point	0.323 (0.196 to 0.449)	< 0.001
	Size of calcific deposit	Per 1 mm increase in size	0,313 (0.028 to 0.598)	0.032
Quality of life - EQ-5D	Duration of symptoms	Per months increase of symptoms	-0.002 (-0.003 to 0.000)	0.012
	Size of calcific deposit	Per 1 mm increase in size	0.006 (0.001 to 0.011)	0.011
	ΔSST at three months	Per point	0.012 (0.003 to 0.022)	0.013
	ΔDASH at three months	Per point	0.003 (0.001 to 0.005)	0.013

Discussion

Our prospective study on clinical and radiographic predictors for the outcome after NACD for rotator cuff calcific tendinitis showed that the majority of patients had less pain and improvement of both shoulder function as well as quality of life (QoL) one year after NACD. A good initial response after NACD was associated with a better outcome at 12 months, whereas patients who required multiple procedures and patients with a longer duration of symptoms prior to the NACD procedure showed less favorable results. Furthermore, smaller size calcific deposits were associated with worse shoulder function outcome and less improvement of QoL.

In our study, 70% of patients had a clinical relevant decrease of VAS pain scores. Furthermore, 64% to 65% of patients showed clinically important improvement of shoulder function, respectively measured by the SST and DASH. In 46% of the patients QoL scores were clinically relevant improved at 1 year after NACD. The largest decrease in pain and improvement of shoulder function and QoL was seen at three months post-intervention after which the improvement seemed to stabilize (figure 2). A similar pattern of decrease in pain scores and improvement of shoulder function was found by Serafini et al.[15]; the largest decrease of pain and improvement of shoulder function was also seen after three months after which the level of pain and shoulder function stayed relatively stable to up to ten years of follow-up. The importance of this initial response to NACD seems to be one of the most important prognostic factors for a good outcome at one year. Thus, patients with less decrease of pain after NACD seem to have a higher likelihood of persisting pain at one year follow-up. Accordingly, patients with less improvement of the SST and DASH scores at three months report worse functional scores at one year follow-up. Thus, short-term results of NACD seem to be a good predictor for the long-term outcome which is useful in the evaluation of the treatment and in the management of patient expectations. This is a new finding compared to previous studies.

Prognostic factors for negative outcomes of NACD found in this study were multiple NACD procedures, smaller size calcific deposits and a longer duration of symptoms prior to NACD. The latter is a well-known negative prognostic factor which is supported by multiple studies[3,7].

Regarding the effects of multiple procedures on the outcome of NACD doubt could exist about if this variable represents a cause of bad prognosis or simply represents

the consequence of attempting the same procedure in non-responding patients. Studies on the effect of multiple procedure on the outcome of NACD are scarce and inconclusive. Farin et al., for example, found that the outcomes of second and third procedures were inferior to the outcome of the primary NACD procedure[16]. On the other hand, studies by del Cura et al. and Oudelaar et al. found no difference in outcome between shoulders that were treated once and those treated twice or even three times[8,17]. As the results of this study add evidence to the theory that the number of NACD procedures do negatively affect the outcome of NACD, physicians treating patients with RCCT should be aware of the inferior results of multiple procedures and should manage patient expectations likewise prior to a second NACD procedure.

With regard to the size of calcific deposits, larger size calcific deposits have been associated with worse outcomes in the conservative treatment of RCCT and after ESWT[3,18]. In NACD however, no such associations have been described. This study shows that smaller size calcific deposits are associated with less improvement of shoulder function. Smaller size calcific deposits are therefore perhaps less suitable for NACD. A possible explanation for these inferior outcomes is that shoulder complaints in patients with smaller size calcific deposits are most probable due to more complex inflammatory pathology and not due to a more localized post-inflammatory deposit of one or several “large” calcific deposits. Another explanation for the inferior outcome of NACD in smaller size calcific deposits could be that patients with smaller size calcific deposits have less complaints and are therefore less likely to demonstrate improvement. Additional in-depth analyses did however demonstrate that there was no correlation between baseline scores and the size of the calcific deposit (VAS: r=-0.35, p=0.738; SST: r=-0.149, p=0.153; DASH: r=0.099, p=0.345). It seems therefore unlikely that patients with smaller size calcific deposits have less complaints compared to patients with larger size calcific deposits which makes it more likely that the shoulder complaints in patients with smaller size calcific deposits have another cause, such as a more complex inflammatory pathology.

Calcific tendinitis is not always symptomatic as it is found in up to 35% of adults without shoulder complaints[19]. However, larger calcific deposits will sooner or later always result in shoulder complaints according to Bosworth et al.[19]. This statement is supported by a study by Louwerens et al. in which patients with calcific deposits of >1.5 cm in length had the highest chance of suffering from symptomatic calcific

tendinitis[20]. Based on the findings of this study and the mentioned literature, clinicians should be careful in attributing shoulder complaints to smaller size calcific deposits and be perhaps more cautious in referring for NACD as the outcomes in patients with smaller size calcific deposits are less favorable.

Earlier studies on prognostic factors for the effectiveness of NACD, which were all retrospective, found that smoking, female gender, dominant arm involvement, bilateral disease, longer duration of symptoms and multiple calcifications all were associated with less favorable outcomes[7,9,10]. Surprisingly, besides a longer duration of symptoms, none of these factors were associated with improvement of pain, shoulder function or QoL in this study. These differences can possibly be explained by a difference in outcome measures as a wide range of different outcome measures has been used such as the WORC, DASH and a binary scale which evaluated whether patients were free of complaints of not. More likely, the differences can be explained by a difference in the duration of follow-up. In a study by de Witte et al. for example, patients were followed-up after 14 years[7]. A substantial part of patients reported persisting shoulder complaints, but it is unclear whether the persisting shoulder complaints are due to persisting or recurrent RCCT or due to ageing (ie. degeneration of the rotator cuff)[21].

Twenty-eight possible prognostic factors for the outcome after NACD were evaluated of which only the size of the calcific deposit and the duration of symptoms prior to the intervention were associated with the outcome. Additionally, it is important to acknowledge that NACD is often performed after other therapies have failed. Even more important, little is known on the effect of these previous (failed) therapies on the perceived outcome of NACD. Results of this study demonstrate that previous unsuccessful treatments, in particular ESWT and subacromial injections with corticosteroids, did not affect the outcome of NACD. NACD is therefore also indicated after failure of other therapies for RCCT. Furthermore, other radiological findings such as AC osteoarthritis and partial thickness rotator cuff tears are often present in RCCT[22]. In the current study, these radiological findings did not affect the outcome of NACD and are therefore not a contraindication for NACD. Results of the current study also demonstrate that aspiration of the calcific deposit during the NACD procedure had no evident effect on the clinical outcome of NACD. In this study successful aspiration of calcium could be achieved in 51% of the patients using a 20- or 21-gauge needle. Only two other studies reported on the possibility of aspirating

calcium during the NACD procedure. Del Cura et al.[17] were able to aspirate calcium in 75% of patients using a 20-gauge needle whereas Aina et al.[23] reported successful aspiration in only 33% of patients using a 22 gauge needle. In literature a wide range of needle sizes has been reported varying from 18- to 22-gauge[23,25]. Larger size needles can facilitate the aspiration of calcium but might on the other hand damage the residual tendon fibers[23]. Current literature is inconclusive about the effect of aspiration of calcium during the NACD procedure on the outcome of NACD as the above-mentioned studies demonstrate conflicting results[17,23]. Results of this study demonstrate that successful aspiration of calcium during the NACD procedure is not a prerequisite for a good outcome.

This is the first prospective study evaluating prognostic factors for the effectiveness of NACD. Nevertheless, this study has several limitations. First, a relatively large number of patients (39 patients; 26%) was lost to follow-up at 12 months. However, a certain drop-out rate could be expected as others reported drop-out rates of 30% for web-based surveys[24]. Secondly, the study does not have a control group. Although it would have been ideal to have a control group to rule out that the outcome is because of the self-limiting history of RCCT, we believe that, for the purpose of identifying prognostic factors, a large prospective cohort study is of sufficient methodological quality. Finally, the follow-up term of this study was 1 year, this is comparable to other studies[16,17,25], but some long-term studies on RCCT show that a substantial part of patients still have persisting shoulder complaints in the long term[7,26]. More research is needed to gain insight in predictive factors for persisting shoulder complaints in the long term.

In conclusion, NACD provides early pain relief and improvement of shoulder function and quality of life. A good initial response to NACD is associated with a better outcome whereas a longer duration of symptoms prior to NACD, multiple NACD procedures and smaller size calcific deposits are associated with inferior outcomes.

References

1. Speed CA, Hazleman BL (1999) Calcific tendinitis of the shoulder. N Engl J Med 340(20):1582-4.
2. Gosens T, Hofstee DJ (2009) Calcifying tendinitis of the shoulder: Advances in imaging and management. Curr Rheumatol Rep 11(2):129-34.
3. Ogon P, Suedkamp NP, Jaeger M, Izadpanah K, Koestler W, Maier D (2009) Prognostic factors in nonoperative therapy for chronic symptomatic calcific tendinitis of the shoulder. Arthritis Rheum 60(10):2978-84.
4. Wölk T, Wittenberg RH (1997) Calcifying subacromial syndrome-clinical and ultrasound outcome of non-surgical therapy. Z Orthop Ihre Grenzgeb. 135(5):451-7.
5. Merolla G, Singh S, Paladini P, Porcellini G (2016) Calcific tendinitis of the rotator cuff: state of the art in diagnosis and treatment. J Orthop Traumatol. 17(1):7-14.
6. Arirachakaran A, Boonard M, Yamaphai S, Prommahachai A, Kesprayura S, Kongtharvonskul J (2017) Extracorporeal shock wave therapy, ultrasound-guided percutaneous lavage, corticosteroid injection and combined treatment for the treatment of rotator cuff calcific tendinopathy: a network meta-analysis of RCTs. Eur J Orthop Surg Traumatol. 27(3):381-390.
7. de Witte PB, van Adrichem RA, Selten JW, Nagels J, Reijnierse M, Nelissen RG (2016) Radiological and clinical predictors of long-term outcome in rotator cuff calcific tendinitis. Eur Radiol. 26(10):3401-11.
8. Oudelaar BW, Schepers-Bok R, Ooms EM, Huis In 't Veld R, Vochteloo AJ (2016) Needle aspiration of calcific deposits (NACD) for calcific tendinitis is safe and effective: Six months follow-up of clinical results and complications in a series of 431 patients. Eur J Radiol. 85(4):689-94.
9. Gartner J, Heyer A (1995) Calcific tendinitis of the shoulder. Orthopade 24(3):284-302.
10. Oudelaar BW, Ooms EM, Huis In 't Veld R, Schepers-Bok R, Vochteloo AJ (2015) Smoking and morphology of calcific deposits affect the outcome of needle aspiration of calcific deposits (NACD) for calcific tendinitis of the rotator cuff. Eur J Radiol. 84(11):2255-60.
11. Tashjian RZ, Deloach J, Porucznik CA, Powell AP (2009) Minimal clinically important differences (MCID) and patient acceptable symptomatic state (PASS) for visual analog scales (VAS) measuring pain in patients treated for rotator cuff disease. JSES 18(6):927-32.
12. Tashjian RZ, Deloach J, Green A, Porucznik CA, Powell AP (2010) Minimal clinically important differences in ASES and simple shoulder test scores after nonoperative treatment of rotator cuff disease. JBJS Am. 92(2):296-303.
13. Franchignoni F, Vercelli S, Giordano A, Sartorio F, Bravini E, Ferriero G. (2014) Minimal clinically important difference of the disabilities of the arm, shoulder and hand outcome measure (DASH) and its shortened version (QuickDASH). J Orthop Sports Phys Ther. 44(1):30-9.
14. Jansson KÅ, Granath F (2011) Health-related quality of life (EQ-5D) before and after orthopedic surgery. Acta Orthop. 82(1):82-9.
15. Serafini G, Sconfienza LM, Lacelli F, Silvestri E, Aliprandi A, Sardanelli F (2009) Rotator cuff calcific tendonitis: short-term and 10-year outcomes after two-needle us-guided percutaneous treatment-nonrandomized controlled trial. Radiology. 252(1):157-64.

16. Farin PU, Rasanen H, Jaroma H, Harju A (1996) Rotator cuff calcifications: treatment with ultrasound-guided percutaneous needle aspiration and lavage. Skeletal Radiol. 25(6):551-4.
17. del Cura JL, Torre I, Zabala R, Legorburu A (2007) Sonographically guided percutaneous needle lavage in calcific tendinitis of the shoulder: short- and long-term results. AJR Am J Roentgenol. 189(3):W128-34.
18. Chou WY, Wang CJ, Wu KT, Yang YJ, Ko JY, Siu KK (2017) Prognostic factors for the outcome of extracorporeal shockwave therapy for calcific tendinitis of the shoulder. Bone Joint J. 99-B(12):1643-1650.
19. Bosworth BM (1941) Calcium deposits in the shoulder and subacromial bursitis: a survey of 12122 shoulders. JAMA. 116:2477–2482.
20. Louwerens JK, Sierevelt IN, van Hove RP, van den Bekerom MP, van Noort A (2015) Prevalence of calcific deposits within the rotator cuff tendons in adults with and without subacromial pain syndrome: clinical and radiologic analysis of 1219 patients. JSES 24(10):1588-93.
21. Raz Y, Henseler JF, Kolk A, Riaz M, van der Zwaal P, Nagels J, Nelissen RG, Raz V (2015) Patterns of Age-Associated Degeneration Differ in Shoulder Muscles. Front Aging Neurosci. 22;7:236.
22. Jim YF, Hsu HC, Chang CY, Wu JJ, Chang T (1993) Coexistence of calcific tendinitis and rotator cuff tear: an arthrographic study. Skeletal Radiol. 22(3):183-5.
23. Aina R, Cardinal E, Bureau NJ, Aubin B, Brassard P (2001) Calcific shoulder tendinitis: Treatment with modified US-guided fine-needle technique. Radiology 221(2):455-61.
24. Galesic M (2006) Dropouts on the Web: Effects of Interest and Burden Experienced During an Online Survey. Journal of Official Statistics 22(2): 313–328.
25. de Witte PB, Selten JW, Navas A, Nagels J, Visser CP, Nelissen RG, Reijnierse M (2013) Calcific tendinitis of the rotator cuff: a randomized controlled trial of ultrasound-guided needling and lavage versus subacromial corticosteroids. AJSM 41(7):1665-73.
26. de Witte PB, Kolk A, Overes F, Nelissen RG, Reijnierse M (2017) Rotator Cuff Calcific Tendinitis: Ultrasound-Guided Needling and Lavage Versus Subacromial Corticosteroids: Five-Year Outcomes of a Randomized Controlled Trial. AJSM 45(14):3305-3314.

Supplementary file I: Univariate analyses for reduction of pain (VAS), improvement of shoulder function (SST and DASH) and improvement of QoL (EQ-5D).

	Pain		Function				Quality of life	
	diffVAS	p	diffSST	p	diffDASH	p	diffEQ-5D	p
Demographic details								
Gender (male vs. female)	2,9 (-6,9 to 12,7)	0,558	0,6 (-0,7 to 2,0)	0,360	-2,6 (-9,0 to 3,8)	0,426	0,05 (-0,06 to 0,15)	0,367
Age	-	0,793	-	0,443	-	0,361	-	0,145
Medical history								
Duration of symptoms in months	-	0,441	-	0,143	-	0,495	-	0,026*
Bilateral occurence	-9,5 (-21,8 to 2,8)	0,128	1,1 (-0,7 to 2,8)	0,240	-2,0 (-10,1 to 6,1)	0,626	-0,03 (-0,16 to 0,10)	0,599
Dominant arm affected	-2,6 (-12,6 to 7,4)	0,602	-0,5 (-2,0 to 0,9)	0,452	3,7 (-2,8 to 10,2)	0,263	-0,05 (-0,15 to 0,06)	0,373
Heavy physical work	3,1 (-6,9 to 13,1)	0,545	-0,2 (-1,6 to 1,3)	0,826	2,9 (-3,6 to 9,4)	0,380	0,03 (-0,08 to 0,13)	0,615
Absenteeism from work due to shoulder complaints	3,5 (-9,1 to 16,2)	0,582	-1,0 (-2,7 to 0,8)	0,271	9,3 (-1,1 to 19,7)	0,078*	0,01 (-0,12 to 0,14)	0,909
Smoking	1,8 (-10,8 to 14,4)	0,775	-0,6 (-2,4 to 1,3)	0,540	-0,9 (-9,5 to 7,8)	0,846	0,08 (-0,04 to 0,21)	0,189
Diabetes	-5,9 (-21,7 to 9,9)	0,457	1,5 (-0,8 to 3,8)	0,192	-8,9 (-19,6 to 1,9)	0,104	0,07 (-0,11 to 0,24)	0,414
Previous treatment								
Analgesics	4,3 (-5,7 to 14,2)	0,396	-0,9 (-2,2 to 0,4)	0,173	5,6 (-0,4 to 11,6)	0,067*	0,06 (-0,05 to 0,16)	0,282
Physiotherapy	8,1 (-3,1 to 19,3)	0,156	-0,8 (-2,4 to 0,8)	0,325	8,6 (1,3 to 15,8)	0,021*	-0,01 (-0,13 to 0,11)	0,837
Shockwave therapy	4,8 (-9,1 to 18,7)	0,495	0,3 (-1,7 to 2,3)	0,743	1,7 (-7,4 to 10,9)	0,711	-0,09 (-0,24 to 0,06)	0,215
Subacromial injection	3,6 (-6,1 to 13,3)	0,465	1,1 (-0,3 to 2,4)	0,132	-5,3 (-11,5 to 1,0)	0,100	-0,05 (-0,16 to 0,05)	0,310
Sonographic findings								
Subacromial bursitis	-3,7 (-16,5 to 9,0)	0,562	-0,5 (-2,3 to 1,4)	0,626	-2,3 (-8,6 to 4,0)	0,466	-0,08 (-0,22 to 0,07)	0,291
Partial thickness rotator cuff tear	7,0 (-3,9 to 17,9)	0,205	0,2 (-1,4 to 1,8)	0,795	1,3 (-6,1 to 8,6)	0,735	-0,01 (-0,13 to 0,11)	0,848
Subacromial impingement	14,2 (-4,2 to 32,7)	0,128	-1,8 (-4,3 to 0,7)	0,144	11,1 (-0.9 to 23,1)	0,068*	-0,08 (-0,28 to 0,12)	0,446

Supplementary file I (Continued)

Radiographic findings								
Size in mm	-	0,273	-	0,029*	-	0,031*	-	0,018*
Numer of calcific deposits (one vs. multiple)	-3,5 (-13,7 to 6,6)	0,492	0,5 (-1,0 to 2,0)	0,492	0,0 (-6,7 to 6,7)	0,991	0,01 (-0,11 to 0,12)	0,904
Gartner & Heyer classification								
Type I	29	0,375	-3,5	0,649	18	0,472	0,08	
Type II	37		-4,1		19		0,16	0,391
Type III	30		-3,3		13		0,08	
Location according to Ogon et al. In mm	-	0,982	-	0,651	-	0,591	-	0,517
Features of AC osteoarthrosis	-6,3 (-16,1 to 3,6)	0,207	0,3 (-1,2 to 1,7)	0,733	-2,8 (-9,3 to 3,7)	0,390	-0,04 (-0,14 to 0,07)	0,466
Findings during NACD								
Aspiration of calficic deposit during procedure	-0,2 (-10,1 to 9,8)	0,975	0,5 (-0,9 to 1,9)	0,475	-1,7 (-8,2 to 4,8)	0,614	0,07 (-0,04 to 0,17)	0,196
Post NACD								
Analgesics during first 6 weeks post NACD	5,9 (-4,4 to 16,3)	0,259	-0,9 (-2,3 to 0,7)	0,250	4,4 (-2,3 to 11,1)	0,195	-0,08 (-0,20 to 0,03)	0,141
Physiotherapy during first 6 weeks post NACD	7,2 (-3,8 to 18,2)	0,199	-1,0 (-2,6 to 0,6)	0,208	4,8 (-2,3 to 12,0)	0,183	0,07 (-0,06 to 0,18)	0,320
Number of NACD procedures								
One vs. multiple procedures	15,5 (5,1 to 25,9))	<0,01*	1,8 (0,3 to 3,3)	0,023*	8,2 (1,4 to 15,1)	0,019*	0,10 (-0,01 to 0,21)	0,088*
Results 3 months postNACD								
DiffVAS	-	<0,01*	-	0,265	-	0,316	-	0,150
DiffSST	-	0,118	-	<0,01*	-	<0,01*	-	0,005*
DiffDASH	-	<0,01*	-	<0,01*	-	<0,01*	-	0,063*

Average differences are presented with the 95% confidence interval within the parentheses. -: no average difference could be presented as correlation coefficients were calculated. *: p<0.10 and hence inclusion in multivariate analysis.

Chapter 5

Concentrations of blood components in commercial platelet-rich plasma separation systems: a review of the literature

Bart W. Oudelaar
Joost C. Peerbooms
Rianne Huis In 't Veld
Anne J.H. Vochteloo

Am J Sports Med. 2019;47:479-487.

Abstract

Background

Platelet-rich plasma (PRP) has proven to be a very safe therapeutic option in the treatment of tendon, muscle, bone and cartilage injury. Currently, several commercial PRP separation systems are available for the preparation of PRP. The concentrations of blood components in PRP among these separation systems vary substantially.

Purpose

To systematically review and evaluate the differences between the concentration of blood components in PRP produced by various PRP separation systems.

Methods

MEDLINE/Pubmed, the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE were searched for studies that compared the concentration of blood components and growth factors in PRP between various separation systems and studies that reported on the concentration of blood components and growth factors of single separation systems. The primary outcomes were platelet count, leukocyte count, and concentration of growth factors (Platelet Derived Growth Factor-AB (PDGF-AB), Transforming Growth Factor-B1 (TGF-B1), Vascular Endothelial Growth Factor (VEGF). Furthermore, the preparation protocols and prices of the systems were compared.

Results

1079 studies were found of which 19 studies were selected for inclusion in this review. The concentration of platelets and leukocytes in PRP differed largely between, and to a lesser extend within, the studied PRP separation systems. Additionally, large difference both between and within the studied PRP separation systems were found for all the growth factors. Furthermore, preparation protocols and prices varied widely between systems.

Conclusion

There is a large heterogeneity between PRP separation systems regarding concentrations of platelets, leukocytes and growth factors in PRP. The choice for the most appropriate type of PRP should be based on the specific clinical field of application. As the ideal concentration of blood components and growth factors for the specific fields of application are yet to be determined for most of the fields of application, future research should focus on which type of PRP is most suitable for the specific fields of application.

Introduction

Platelet-rich plasma (PRP) is small volume of autologous blood plasma that has been enriched with blood-derived platelets[21]. PRP is considered to have beneficial effects on many healing processes as a result of the growth factors contained in the platelets alphagranules[43]. The use of PRP for clinical applications in periodontal and oral surgery, maxillofacial surgery, plastic surgery and the treatment of chronic skin and soft-tissue ulcers has been extensively investigated[22,33,47,53]. PRP has proven to be a very safe therapeutic option; complication are rarely reported as PRP is derived from autologous blood[42]. In orthopaedic surgery and sports medicine, the use of PRP is of increasing interest over the last decade. PRP has shown to have a beneficial effect on the healing of tendon, muscle, bone and cartilage injury[15,58]. Clinical studies on the efficacy of platelet-rich plasma in the treatment of symptomatic knee osteoarthritis[31,39,52] and chronic tendinopathy such as patellar tendinopathy[14,17] and lateral epicondylitis[19,23,40,41] have shown beneficial effects of PRP injections.

Currently, several commercial PRP separation systems are available for the preparation of PRP[15]. The concentrations of blood components in PRP (platelets, leukocytes and growth factors e.g. PDGF, TGF-B1 and VEGF) among these separation systems vary substantially[15]. Studies comparing the differences in blood components in PRP from these separation systems report varying outcomes in terms of concentration of blood components and growth factors[7,36,50]. To gain more insight into the differences between the concentration of blood components and growth factors in PRP produced by the different separation systems, we conducted a systematic review of literature on studies investigating the blood components and growth factors in PRP.

Materials and methods

Inclusion criteria

Studies

The literature search performed for this review was limited to studies that compared the concentration of blood components and growth factors in PRP between different PRP separation systems and studies that reported on the concentration of blood components and growth factors of single PRP separation systems. We only included studies investigating human blood taken from healthy adult (>18 years) volunteers. The literature search was limited to papers in the English, German, French and Dutch language.

PRP separation systems

Only studies reporting on PRP separation systems that are currently commercially available were included.

Outcome measures

This review primarily focused on the platelet count, the leukocyte count, the platelet enrichment factor([platelet concentration in PRP]/[platelet concentration in whole blood]) and growth factors (Platelet Derived Growth Factor-AB (PDGF-AB), Platelet Derived Growth Factor-BB (PDGF-BB), Transforming Growth Factor-B1 (TGF-B1), Vascular Endothelial Growth Factor (VEGF), Epidermal Growth Factor (EGF), Fibroblast Growth Factor-2 (FGF-2), Hepatocyte Growth Factor (HGF) and Insulin-like Growth Factor (IGF)). Furthermore, the preparation protocols (amount of whole blood needed, number of centrifugations, time of centrifugation) and prices of the different PRP separation systems were compared.

Search strategy

We searched MEDLINE/Pubmed, the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE up until March 2017 to identify relevant studies concerning the concentration of blood components in PRP. There were no constraints based on publication status. In MEDLINE, the following search strategy was used and was modified for uses in other databases:

1. Humans
2. Platelet-Rich Plasma
3. 1 AND 2
4. Blood Platelets or platelet count
5. Leukocytes or leukocyte count
6. Platelet-Derived Growth Factor
7. 3 AND 4 AND 5
8. 3 AND 6
9. 7 OR 8

The search was performed by one of the authors (B.O.). References of retrieved publications were also used to add studies potentially meeting the inclusion criteria that were missed by the electronic search. Abstracts from scientific meetings and review articles were excluded.

Review process

To identify relevant articles for this review, the title and abstract of the articles found by the above-mentioned search strategy were reviewed. After the selection, the full manuscripts were reviewed for definitive selection. All identified studies were independently reviewed by two reviewers (B.O. and J.P.) for inclusion using the above-mentioned criteria. In case of disagreement, a third reviewer (A.V.) was consulted to resolve the disagreement.

Data collection

The following data were extracted from the included trials: study design (comparative study or study describing one separation device), study characteristics (e.g. number of blood samples), concentration analysis methods, type of outcome, results of the study and the main conclusion(s) of the study. This information was extracted by one author (B.O.). If necessary, authors were contacted for additional information about their specific paper.

The companies producing the PRP separation systems were contacted to gain information about the specific preparation protocols. In case a company did not respond to the request, literature was searched for the preparation protocol.

Statistical analysis

First, the 95% confidence intervals (CI) were calculated for each of the blood components studied in the included studies using the mean concentration, the standard deviation and number of samples. The following formula was used: $x \pm \times \frac{\sigma}{\sqrt{n}}$ where x is the mean concentration, γ the critical value of the t distribution based on the sample size of the study, σ the standard deviation and n the number of samples studied. Forest plots were created using the mean and the 95% CI. Differences in concentrations within and between the different PRP separation systems were explored informally by eye-ball test. Additional statistical analyses of differences within and between the different separation systems were not conducted. As a substantial part of the data in the included studies was presented in graphs, which led to missing quantitative data, descriptive results of the studies that compared two or more PRP preparation systems were summarized in a table. Analyses were conducted in SPSS (version 15.0; SPSS, Chicago, Illinois) and Microsoft Excel, Microsoft Office 365 (Microsoft Corporation, Redmond, WA, USA).

Results

Search results

The search was performed on September 17, 2016, with a final search update to check for recently published relevant articles on April 11, 2017. The search of MEDLINE/Pubmed, the Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE databases provided 1079 citations of which 179 were duplicates. After reviewing the titles and abstracts of the 900 remaining studies, 791 studies were excluded for not meeting the inclusion criteria. The manuscripts of the remaining 109 studies were reviewed after which 90 studies were excluded: 19 studies were selected for inclusion in this review (figure 1).

No additional studies were found by checking the references of the selected articles.

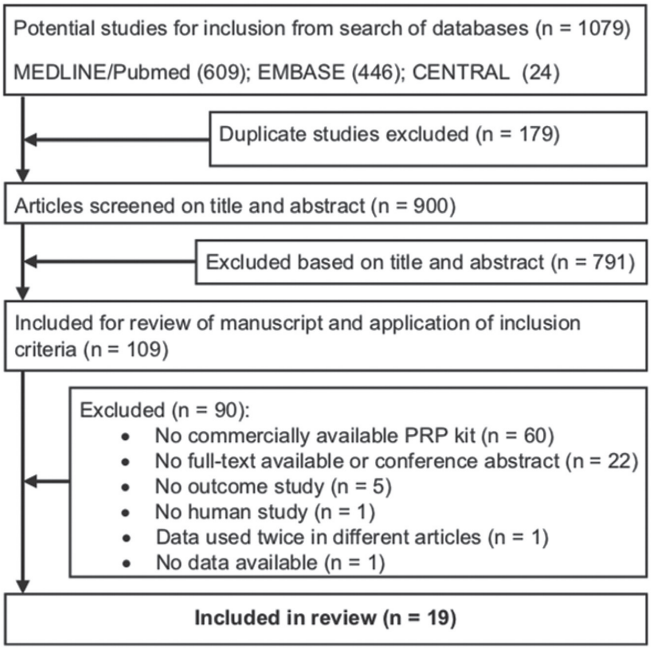

Figure 1: flow diagram of the search process.

Characteristics of the included studies

The characteristics of the included studies are summarized in table 1. 14 studies compared the concentration of blood components in PRP between different PRP

separation systems. In eight studies commercially available separation systems were compared. Five studies reported the concentration of blood components of single separation systems. The number of samples analyzed varied between 3 and 102. Ten different commercially available separation systems were studied. The GPSIII system was studied the most: ten times in total followed by the ACP system which was studied in five studies. The PRGF, Magellan and SmartPrep systems were all studied three times; the Cascade and RegenPRP were studied in two studies and the Prosys, KYOCERA and GLO systems were only studied in one study.

Outcome measures

The platelet concentration was the most studied outcome measure, studied in thirteen of seventeen studies. Other outcome measures were the leukocyte concentration (12/17), red blood cell concentration (5/17) and the platelet enrichment factor (7/17). With regard to growth factors, TGF-B1 was studied the most (9/17), followed by PDGF-AB and VEGF (both 8/17). Other reported growth factors were IGF (4/17), PDGF-BB (3/17), EGF (3/17), HGF (2/17) and FGF-2 (1/17). As TGF-B1, PDGF-A and VEGF were by far the most studied growth factors, further statistical analyses were only performed for these three growth factors.

PRP separation systems

The preparation protocols for the different PRP separation systems are summarized in table 2. The majority of the systems use a dual spin method (6/10). Both the centrifugal force (range 350-2008g) as the total centrifugation time (range 5-21 minutes) differed largely between systems. Also, a wide variation in price per kit (range 95-500$) was found between the systems.

Table 1: Study characteristics of the studies included in this review

Study	Number of samples	Number of PRP kits studied	PRP kits studied	Outcome measures
Anitua 2013[2]	3	1	Endoret	PEF, WBCC, PDGF-AB, VEGF, HGF, IGF-I
Castillo 2011[7]	5	3	Biomet GPS III, Cascade, Magellan	PC, WBCC, RBC, PEF, PDGF-AB, PDGF-BB, TGF-B1, VEGF, PCE, FC
Dragoo 2012[13]	40	1	Biomet GPS III	PDGF-BB, TGF-B1, VEGF, IGF
Evanson 2014[16]	102	1	Arthrex ACP	PC, WBCC, RBC, PDGF-AB, PDGF-BB, TGF-B1, VEGF, EGF, FGF, HGF, IGF-1
Everts 2008[18]	20	1	Magellan	PC, WBCC, PEF
Hamilton 2013[24]	10	1	Biomet GPS III	PC, WBCC, PDGF-AB, HGF, IGF-1 and VEGF
Howard 2014[25]	4	2	Cascade, Harvest SmartPRep	PC, PEF, PDGF-AB, TGF-B1
Kaux 2011(1)[27]	6	1	Biomet GPS III	PC, WBCC, RBCC
Kaux 2011 (2)[26]	5	1	Biomet GPS III	WBCC, RBCC, PEF
Kushida 2014[29]	5	3	GLO, Kyocera, Magellan	PC, PDGF-AB, TGF-B1, VEGF
Leitner 2006[30]	3	1	Harvest SmartPReP	PC, WBCC, RBCC
Magalon 2014[32]	10	3	Arthrex ACP, Biomet GPS III, RegenPRP	PC, WBCC, PEF, PDGF-AB, TGF-B1, VEGF, EGF, PCE
Mazzocca 2012[36]	8	2	Arthrex ACP, Biomet GPS III	PC, WBCC, RBCC, PDGF-AB, TGF-B1, VEGF, EGF, FGF-2, HGF, IGF
Mazzucco 2009[37]	Not provided	1	RegenPRP	PC, PEF, PDGF-BB, TGF-B1, VEGF, EGF and IGF-I
Oh 2015[46]	14	3	Arthrex ACP, Biomet GPS III, Prosys PRP	PC, WBCC
Schar 2015[51]	11	1	Biomet GPS III	TGF-B1, VEGF
Sundman 2011[54]	11	2	Arthrex ACP, Biomet GPS III	PC, WBCC, PEF
Weibrich 2005[56]	51	1	Endoret	PC, WBCC, PDGF-AB, TGF-B1, PCE
Weibrich 2012[57]	54	2	Endoret, Harvest SmartPReP	PC, WBCC, PDGF-AB, TGF-B1, IGF

PC: platelet concentration; WBCC: white bloodcell concentration; RBCC: red bloodcell concentration; PEF: platelet enrichmentfactor; PDGF-AB: platelet-derived growth factor-AB; PDGF-BB: platelet-derived growth factor-BB; TGF-B1: transforming growth factor-B1; VEGF: vascular endothelial growth factor; EGF: epidermal growth factor; FGF-2: fibroblast growth factor-2; HGF: hepatocyte growth factor; IGF: insuline-like growth factor; PCE: platelet capture efficiency; FC: fibrinogen concentration.

Table 2: Preparation protocols and costs for the different PRP separation systems

System	Type of system	Whole blood volume (mL)	Centrifugal force (g) first spin	Centrifugal force (g) second spin	Centrifugation time (min) first spin	Centrifugation time (min) second spin	Final volume of PRP (mL)	Cost/kit ($)
ACP	Plasma-based	11	350	-	5	-	2.0-5.0	150
GPS III	Buffy coat	54	1100	-	15	-	6.0	350
Cascade	Plasma-based	9	1100	1450	6	15	2	*
PRGF	*	9	580	-	8	-	2.0	*
GLO	Buffy coat	9	1200	600	5	2	0.6	50-75
SmartPrep	Buffy coat	60	1250	1050	14	7.0-10.0	*	
Kyocera	*	20	600	2000	7	5	2	60
Magellan	Buffy coat	60	610	1240	4	6	3	500
Prosys	*	30	1660	2008	3	3	3	*
RegenPRP	*	8	1500	-	5	-	4	*

*= unknown/not provided by producer

Laboratory results

Concentration platelets, leukocytes and platelet enrichment factor

The concentrations of platelets and leukocytes found in the included studies are presented in figure 2. The concentration of platelets in PRP differed largely between, and to a lesser extend within, the studied PRP separation systems. The highest concentration of platelets was produced by the Cascade system; the lowest concentration of platelets was produced by the ACP system. Regarding the concentration of leukocytes in PRP, large differences were found between, but not within, the separation systems. The highest concentration of leukocytes was found in the PRP produced by the GPS III system, the PRP produced by the ACP system contained the lowest number of leukocytes. Although only reported in four studies, large difference between PRP separation systems were found for the platelet enrichment factor. The highest platelet enrichment factors were found for the GPS III and SmartPrep system (respectively 3.93[32] and 3.79[30]); the lowest for the ACP, RegenPRP and Cascade systems (respectively 1.31[32], 1.59[32] and 1.62[7]).

Concentration growth factors

The concentrations of the growth factors PDGF-AB, TGF-B1 and VEGF found in the included studies are presented in figure 3. Large differences both between and within the studied PRP separation systems were found for all the growth factors. Additionally, no differences in concentration of PDGF-AB and TGF-B1 were found between the higher (GPSIII, SmartPrep and Magellan) and lower platelet yielding devices (ACP, Cascade, PRGF and RegenPRP) as for the higher (GPSIII, SmartPrep, Magellan and RegenPRP) and lower leukocyte yielding devices (ACP and Cascade). However, the concentration of VEGF tended to be higher in PRP produced by systems that yield higher concentrations of platelets and leukocytes (GPS, Magellan).

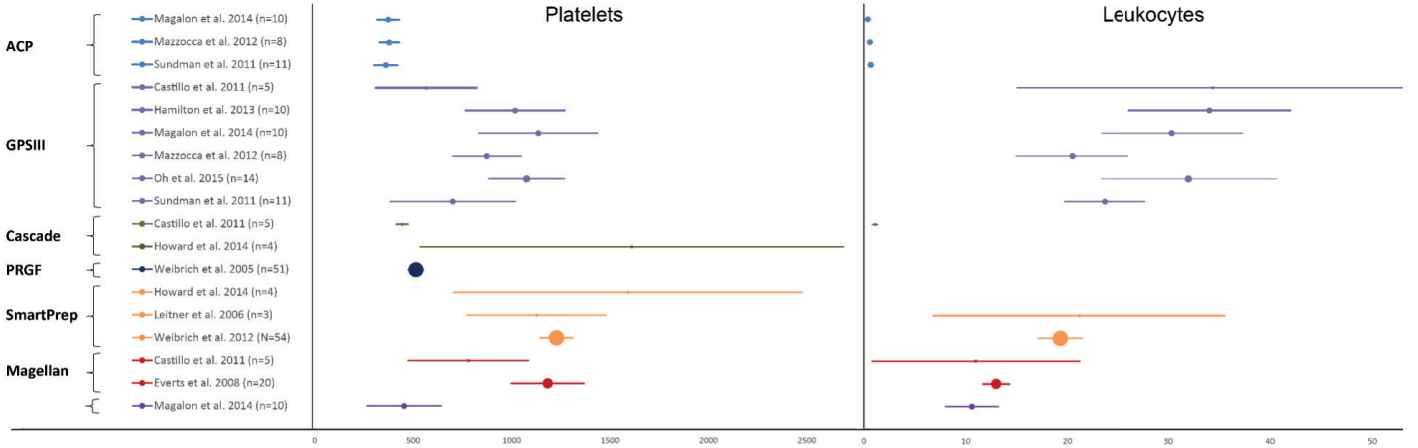

Figure 2: the concentrations of platelets (x10^3µL) and leukocytes (x10^3µL) found in the included studies

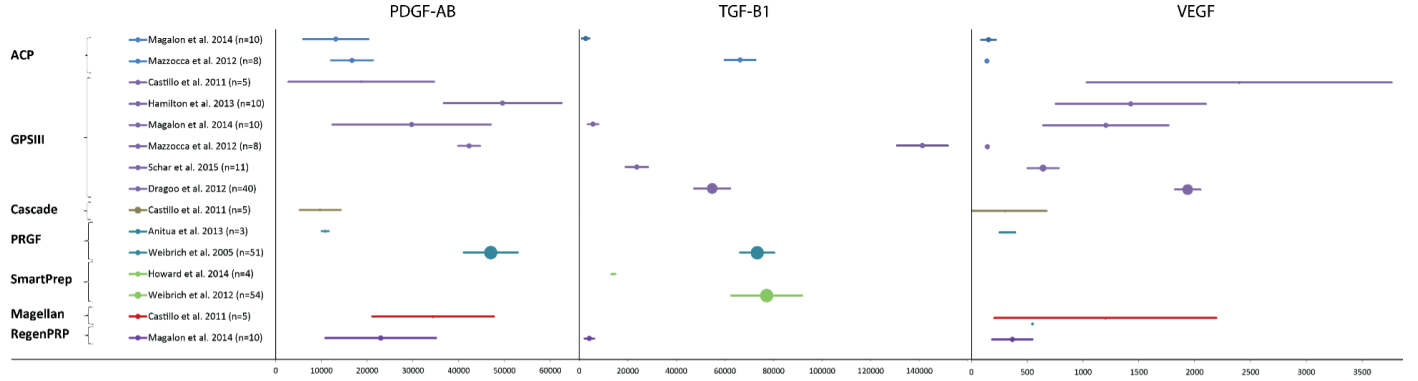

Figure 3: the concentration of PDGF-AB (pg/mL), TGF-B1 (pg/mL) and VEGF (pg/mL) found in the included studies.

Results comparative studies

As not all selected studies provided exact data, descriptive results of the studies comparing two or more PRP separation systems were used[7,25,29,32,36,46,54,57]. The Arthrex ACP and Biomet GPS III separation kits were the only kits that have been compared in more than one study: the concentration of platelets, leukocytes and growth factors was significantly higher in favor of the Biomet GPS III[32,36,46,54]. Overall, the Arthrex ACP showed lower platelet and leukocyte concentrations in studies comparing the ACP with the systems other than the GPS III; the concentration of growth factors, however, was largely comparable[32,46]. The Biomet GPS III on the other hand, showed significantly higher concentrations of leukocytes compared to other devices[7,32,46]. Furthermore, the GPS III produced a higher concentration of platelets than the RegenPRP-kit and the Prosys PRP Kit[32,46], but no significant differences in platelet concentrations were found between the Biomet GPS III kit and the Cascade and the Magellan kit[7]. The concentration of growth factors did not significantly differ in most of the studies.

Discussion

The objective of this review was to assess the differences between the concentrations of blood components and growth factors in PRP between the various PRP separation systems. The findings in this review demonstrate that there is a large heterogeneity among various systems regarding the concentrations of platelets and leukocytes. Regarding the concentrations of growth factors, there is a large heterogeneity both between and within the different systems. Furthermore, the concentration of VEGF tended to be higher in PRP produced by systems that produce higher concentrations of platelets and leukocytes.

Concentration platelets

There was a large difference in concentration of platelets between the systems studied in this review. Roughly, the systems studied in this review can be divided in high- and low-yielding devices. This division in high- and low-yielding devices has been described before by Dhurat et al.[11]. Dhurat et al. described that PRP devices can usually be divided into lower (2.5-3 times baseline concentration) and higher (5-9 times baseline concentration) systems. The low-yielding devices in this review produce PRP with a platelet concentration around 500x10^3 µL, whereas the high-yielding devices generally produce platelet concentrations over 750x10^3 µL. Among the high-yielding devices were the GPSIII, SmartPrep and the Magellan systems; the lower concentration systems concerned the ACP, Cascade, PRGF and RegenPRP systems. These findings correlate well with the findings in this review.

The concentration of platelets in PRP is of importance as the mechanism of action of PRP is mainly based on the growth factors and cytokines found in the α-granules in the platelets. However, there is no consensus about the optimal concentration of platelets in PRP: some authors report platelet concentrations of >200x10^3 uL[37] to be a therapeutic concentration, whereas others report concentrations of 1000x10^3 uL[35]. In the present study, the platelet concentrations of all of the PRP separation systems exceeded a platelet concentration of >200*103 uL which implies that all the devices met the definition for therapeutic effective PRP as defined by Mazzucco[37].

Concentration leukocytes

Comparable to the concentration of platelets in PRP, the concentration of leukocytes differed largely between the systems studied in this review. Additionally, no

large differences within the systems were found. PRP separation systems can be divided into systems producing high and systems producing a low concentration of leukocytes. The concentration of leukocytes in PRP is a direct result of the preparation method that is used. Buffy coat-based systems, for example, produce PRP with high concentrations of leucocytes as the buffy coat is rich in leukocytes. Plasma-based systems, in contrast, are designed to separate only the platelet and plasma portions of whole blood and therefore contain low concentrations of leukocytes[11,15,50]. The majority of separation systems in current literature yield leukocyte-rich PRP. As also shown in this review, the ACP, Cascade and PRGF systems are known to produce leukocyte-poor PRP. Currently, the inclusion of leukocytes in PRP is subject to debate as both beneficial and adverse effects of leukocyte inclusion have been suggested[50]. Potential beneficial effects of leukocyte inclusion include their role in tissue remodeling and their increased antibacterial and immunological resistance[12,44]. Furthermore, the presence of leukocytes in PRP is associated with an increased concentration of growth factors, especially VEGF[9,10,28,64]. On the other hand, the inclusion of leukocytes might have catabolic and inflammatory effects on the targeted tissue as a result of the release of pro-inflammatory cytokines by leukocytes which is associated with decreased proliferation and with increased apoptosis[1,4,5,8,38,49,59,60,61,62]. As the aim of this review was to evaluate the differences between the concentration of blood components in PRP produced by the various PRP separation systems, no definitive answer can be provided on whether leukocyte-rich or leukocyte-poor is best based on the results of this review. There is, however, increasing evidence that the type of PRP (leukocyte-rich or leukocyte-poor) should be matched to the specific clinical field of application. In the treatment of knee osteoarthritis, for example, the use of leukocyte-poor PRP seems to be more beneficial than leukocyte-rich PRP[48]. In the treatment of chronic tendinopathy in contrast, the use of leukocyte-rich PRP is superior to leukocyte-poor PRP[20]. To gain more insight in the specific indications for the different types of PRP, future research should focus on which type of PRP is most suitable for the specific fields of application.

Concentration growth factors

A wide variation was found regarding the concentrations of growth factors both between different systems as within systems. These differences can partly be explained by the use of the specific ELISA kits. The assays of growth factors contained

in the platelets may be influenced by the incomplete removal of platelets and red blood cells and therefore give variable results[36]. Data within studies are comparable but comparison between studies is less reliable which limits the relevance of these findings. In this review, it seemed, however, that the concentration of VEGF tended to be higher in PRP produced by PRP kits that produce higher concentrations of platelets and leukocytes. Higher amounts of growth factors have indeed been correlated with higher amounts of platelets and leukocytes[55,63]. Although evidence about the role of the specific growth factors is scarce, in vitro studies suggest that that PDGF and TGF-b are the two most important growth factors in PRP[3,6,34,45]. In contrast to the platelet and leukocyte concentration, there is no evidence about an ideal concentration of growth factors in PRP for tissue regeneration. Therefore, future studies are necessary to reveal the exact mechanisms of growth factors in PRP and their role in tissue regeneration.

Preparation protocols

Besides a large heterogeneity in concentrations of platelets, leukocytes and growth factors between systems, the preparation protocols for the different systems also differed largely. Wide ranges were found for both the centrifugal force (350-2008g) as the total centrifugation time (5-21 minutes). There are many ways of preparing PRP, the most common methods are the plasma-based and the buffy coat- based method[29]. Although not known for all systems in this review, most systems used the buffy coat-based method. As mentioned earlier, buffy coat-based systems produce PRP with high concentrations of leucocytes as the buffy coat is rich in leukocytes[11,15,50]. Although the ideal concentration of blood components and growth factors for the specific field of application has yet to be determined by future research, the field of application should play an important role in the choice for the most appropriate PRP separation system. Other factors like the volume of whole blood needed, the final volume of PRP and the usability and reliability of the separation system could also be taken into consideration. Finally, the price of the systems can be taken into consideration as a wide variation in price per kit (range 95-500$) was found.

Strength and limitations

This is the first systematic review that offers a comprehensive overview of the concentration of blood components in PRP produced by all the commercially available

PRP separation systems and that analyzes the differences between the systems in terms of concentration of blood components and growth factors. Initially this study was designed as a meta-analysis. Unfortunately, despite all authors were contacted, we had to deal with a lot of missing data and no raw data was available for the majority of the studies. This limited the statistic options available for analyzing the differences between systems and therefore a meta-analysis could not be conducted. To overcome the missing data, descriptive results of the studies that compared two or more PRP preparation devices were summarized. Furthermore, the number of samples studied in the included studies was rather small; only five of the 19 studies used 20 or more samples and ten of the 19 studies used even 10 or less samples, which also limits the comparison between systems.

However, as the review of literature provided in the discussion showed, future research on the components of PRP should not focus on the concentration of the components, but rather on the optimal concentration of platelets, leukocytes and growth factors for the different fields of application. The use of leukocyte-rich PRP in chronic tendinopathy has been extensively investigated and been proven to be superior to leukocyte-poor PRP[20]. For other applications, osteoarthritis for example, the evidence is limited and well-designed clinical studies are necessary to gain more insight into which formulation of PRP is most suitable.

In conclusion, this review demonstrates that there is a large heterogeneity between different systems with regard to the concentrations of platelets, leukocytes and growth factors in PRP. Also, the preparation protocols for the different systems differ largely. The choice for the most appropriate type of PRP should be based on the specific clinical field of application. As the ideal concentration of blood components and growth factors for the specific fields of application are yet to be determined for most of the fields of application, future research should focus on which type of PRP is most suitable for the specific fields of application.

References

1. Anitua E, Zalduendo M, Troya M, Padilla S, Orive G. Leukocyte inclusion within a platelet rich plasma-derived fibrin scaffold stimulates a more pro-inflammatory environment and alters fibrin properties. PLoS One. 2015;10(3):e0121713.
2. Anitua E, Zalduendo MM, Alkhraisat MH, Orive G. Release kinetics of platelet-derived and plasma-derived growth factors from autologous plasma rich in growth factors. Ann Anat. 2013;195(5):461-6.
3. Anitua E. Plasma rich in growth factors: preliminary results of use in the preparation of future sites for implants. Int J Oral Maxillofac Implants 1999;14:529-35.
4. Assirelli E, Filardo G, Mariani E, Kon E, Roffi A, Vaccaro F, Marcacci M, Facchini A, Pulsatelli L. Effect of two different preparations of platelet-rich plasma on synoviocytes. Knee Surg Sports Traumatol Arthrosc. 2015;23(9):2690-703.
5. Braun HJ, Kim HJ, Chu CR, Dragoo JL. The effect of platelet-rich plasma formulations and blood products on human synoviocytes: implications for intra-articular injury and therapy. Am J Sports Med. 2014;42(5):1204-10.
6. Carlson NE, Roach RB. Platelet-rich plasma-clinical applications in dentistry. J Am Dent Assoc 2002;133:1383-6.
7. Castillo TN, Pouliot MA, Kim HJ, et al..Comparison of growth factor and platelet concentration from commercial platelet-rich plasma separation systems.Am J Sports Med. 2011;39:266–271.
8. Cavallo C, Filardo G, Mariani E, Kon E, Marcacci M, Pereira Ruiz MT, Facchini A, Grigolo B. Comparison of platelet-rich plasma formulations for cartilage healing: an in vitro study. J Bone Joint Surg Am. 2014;96(5):423-9.
9. Davis VL, Abukabda AB, Radio NM, Witt-Enderby PA, Clafshenkel WP, Cairone JV, Rutkowski JL. Platelet-rich preparations to improve healing. Part II: platelet activation and enrichment, leukocyte inclusion, and other selection criteria. J Oral Implantol. 2014;40(4):511-21.
10. Denapoli PM, Stilhano RS, Ingham SJ, Han SW, Abdalla RJ. Platelet-Rich Plasma in a Murine Model: Leukocytes, Growth Factors, Flt-1, and Muscle Healing. Am J Sports Med. 2016;44(8):1962-71.
11. Dhurat R, Sukesh M. Principles and Methods of Preparation of Platelet-Rich Plasma: A Review and Author's Perspective. J Cutan Aesthet Surg. 2014;7(4):189-97.
12. Dohan Ehrenfest DM, Rasmusson L, Albrektsson T. Classification of platelet concentrates: from pure platelet-rich plasma (P-PRP) to leucocyte- and platelet-rich fibrin (L-PRF). Trends Biotechnol. 2009;27:158–167.
13. Dragoo J.L., Korotkova T., Wasterlain A.S., Pouliot M.A., Kim H.J., Golish S.R. Age-Related Changes of Chondrogenic Growth Factors in Platelet-Rich Plasma. Oper Tech Orthop 2012;22(2):49-55.
14. Dupley L, Charalambous CP. Platelet-Rich Plasma Injections as a Treatment for Refractory Patellar Tendinosis: A Meta-Analysis of Randomised Trials. Knee Surg Relat Res. 2017;29(3):165-171.
15. Engebretsen L, Steffen K, Alsousou J, Anitua E, Bachl N, Devilee R, Everts P, Hamilton B, Huard J, Jenoure P, Kelberine F, Kon E, Maffulli N, Matheson G, Mei-Dan O, Menetrey J, Philippon M, Randelli P, Schamasch P, Schwellnus M, Vernec A, Verrall G. IOC consensus paper on the use of platelet-rich plasma in sports medicine. Br J Sports Med. 2010;44(15):1072-81.

16. Evanson JR, Guyton MK, Oliver DL, Hire JM, Topolski RL, Zumbrun SD, et al. Gender and age differences in growth factor concentrations from platelet-rich plasma in adults. Mil Med 2014;179(7):799-805.
17. Everhart JS, Cole D, Sojka JH, Higgins JD, Magnussen RA, Schmitt LC, Flanigan DC. Treatment Options for Patellar Tendinopathy: A Systematic Review. Arthroscopy. 2017;33(4):861-872.
18. Everts PA, Devilee RJ, Brown Mahoney C, van Erp A, Oosterbos CJ, Stellenboom M, Knape JT, van Zundert A. Exogenous application of platelet-leukocyte gel during open subacromial decompression contributes to improved patient outcome. A prospective randomized double-blind study. Eur Surg Res. 2008;40(2):203-10.
19. Filardo G, Di Matteo B, Kon E, Merli G, Marcacci M. Platelet-rich plasma in tendon-related disorders: results and indications. Knee Surg Sports Traumatol Arthrosc. 2016.
20. Fitzpatrick J, Bulsara M, Zheng MH. The Effectiveness of Platelet-Rich Plasma in the Treatment of Tendinopathy: A Meta-analysis of Randomized Controlled Clinical Trials. Am J Sports Med. 2017;45(1):226-233.
21. Foster TE, Puskas BL, Mandelbaum BR, Gerhardt MB, Rodeo SA. Platelet-rich plasma: from basic science to clinical applications. Am J Sports Med. 2009;37: 2259-72.
22. Gentile P, Cervelli V. Use of platelet-rich plasma in maxillofacial surgery. J Craniofac Surg. 2012;23(5):1580-2.
23. Gosens T, Peerbooms JC, van Laar W, den Oudsten BL. Ongoing positive effect of platelet-rich plasma versus corticosteroid injection in lateral epicondylitis: a double-blind randomized controlled trial with 2-year follow-up. Am J Sports Med. 2011;39(6):1200-8.
24. Hamilton B, Tol JL, Knez W, Chalabi H. Exercise and the platelet activator calcium chloride both influence the growth factor content of platelet-rich plasma (PRP): overlooked biochemical factors that could influence PRP treatment. Br J Sports Med 2015;49(14):957-960.
25. Howard D, Shepherd JH, Kew SJ, Hernandez P, Ghose S, Wardale JA, et al. Release of growth factors from a reinforced collagen GAG matrix supplemented with platelet rich plasma: Influence on cultured human meniscal cells. J Orthop Res 2014;32(2):273-278.
26. Kaux JF, Le Goff C, Renouf J, Peters P, Lutteri L, Gothot A, Crielaard JM. Comparison of the platelet concentrations obtained in platelet-rich plasma (PRP) between the GPS™ II and GPS™ III systems. Pathol Biol (Paris). 2011;59(5):275-7.
27. Kaux JF, Le Goff C, Seidel L, Peters P, Gothot A, Albert A, et al. Comparative study of five techniques of preparation of platelet-rich plasma. Pathol Biol (Paris) 2011;59(3):157-160.
28. Kobayashi Y, Saita Y, Nishio H, Ikeda H, Takazawa Y, Nagao M, Takaku T, Komatsu N, Kaneko K. Leukocyte concentration and composition in platelet-rich plasma (PRP) influences the growth factor and protease concentrations. J Orthop Sci. 2016;21(5):683-9.
29. Kushida S, Kakudo N, Morimoto N, Hara T, Ogawa T, Mitsui T, et al. Platelet and growth factor concentrations in activated platelet-rich plasma: a comparison of seven commercial separation systems. J Artif Organs 2014;17(2):186-192.
30. Leitner GC, Gruber R, Neumuller J, Wagner A, Kloimstein P, Hocker P, et al. Platelet content and growth factor release in platelet-rich plasma: a comparison of four different systems. Vox Sang 2006;91(2):135-139.
31. Lisi C, Perotti C, Scudeller L, Sammarchi L, Dametti F, Musella V, Di Natali G. Treatment of knee osteoarthritis: platelet-derived growth factors vs. hyaluronic acid. A randomized controlled trial. Clin Rehabil. 2017.
32. Magalon J, Bausset O, Serratrice N, Giraudo L, Aboudou H, Veran J, et al. Characterization and comparison of 5 platelet-rich plasma preparations in a single-donor model. Arthroscopy 2014;30(5):629-638.

33. Martinez-Zapata MJ, Martí-Carvajal AJ, Solà I, Expósito JA, Bolíbar I, Rodríguez L, Garcia J, Zaror C. Autologous platelet-rich plasma for treating chronic wounds. Cochrane Database Syst Rev. 2016;(5):CD006899.

34. Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. Platelet-rich plasma: growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1998;85:638-46.

35. Marx RE. Platelet-rich plasma (PRP): what is PRP and what is not PRP? Implant Dent. 2001;10:225-8.

36. Mazzocca AD, McCarthy MB, Chowaniec DM, et al..Platelet-rich plasma differs according to preparation method and human variability.J Bone Joint Surg Am. 2012;94:308–316.

37. Mazzucco L, Balbo V, Cattana E, Guaschino R, Borzini P. Not every PRP-gel is born equal. Evaluation of growth factor availability for tissues through four PRP-gel preparations: Fibrinet, RegenPRP-Kit, Plateltex and one manual procedure. Vox Sang 2009;97(2):110-118.

38. McCarrel TM, Minas T, Fortier LA. Optimization of leukocyte concentration in platelet-rich plasma for the treatment of tendinopathy. J Bone Joint Surg Am. 2012;94(19):e143(1-8).

39. Meheux CJ, McCulloch PC, Lintner DM, Varner KE, Harris JD. Efficacy of Intra-articular Platelet-Rich Plasma Injections in Knee Osteoarthritis: A Systematic Review. Arthroscopy. 2016;32(3):495-505.

40. Mi B, Liu G, Zhou W, Lv H, Liu Y, Wu Q, Liu J. Platelet rich plasma versus steroid on lateral epicondylitis: meta-analysis of randomized clinical trials. Phys Sportsmed. 2017;45(2):97-104.

41. Mishra AK, Skrepnik NV, Edwards SG, Jones GL, Sampson S, Vermillion DA, Ramsey ML, Karli DC, Rettig AC. Efficacy of platelet-rich plasma for chronic tennis elbow: a double-blind, prospective, multicenter, randomized controlled trial of 230 patients. Am J Sports Med. 2014;42(2):463-71.

42. Mlynarek RA, Kuhn AW, Bedi A. Platelet-Rich Plasma (PRP) in Orthopedic Sports Medicine. Am J Orthop (Belle Mead NJ). 2016;45(5):290-326.

43. Molloy T, Wang Y, Murrell G. The roles of growth factors in tendon and ligament healing. Sports Med. 2003;33:381-394.

44. Moojen DJ, Everts PA, Schure RM, et al. Antimicrobial activity of platelet-leukocyte gel against Staphylococcus aureus. J Orthop Res. 2008;26:404–410.

45. Ogino Y, Ayukawa Y, Kukita T, Koyano K. The contribution of platelet-derived growth factor, transforming growth factor-beta1, and insulin-like growth factor-I in platelet-rich plasma to the proliferation of osteoblast-like cells. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006;101(6):724-9.

46. Oh JH, Kim W, Park KU, Roh YH. Comparison of the Cellular Composition and Cytokine-Release Kinetics of Various Platelet-Rich Plasma Preparations. Am J Sports Med. 2015;43(12):3062-70.

47. Plachokova AS, Nikolidakis D, Mulder J, Jansen JA, Creugers NH. Effect of platelet-rich plasma on bone regeneration in dentistry: a systematic review. Clin Oral Implants Res. 2008;19(6):539-45.

48. Riboh JC, Saltzman BM, Yanke AB, Fortier L, Cole BJ. Effect of Leukocyte Concentration on the Efficacy of Platelet-Rich Plasma in the Treatment of Knee Osteoarthritis. Am J Sports Med. 2016;44(3):792-800.

49. Rubio-Azpeitia E, Bilbao AM, Sánchez P, Delgado D, Andia I. The Properties of 3 Different Plasma Formulations and Their Effects on Tendinopathic Cells. Am J Sports Med. 2016;44(8):1952-61.

50. Russell RP, Apostolakos J, Hirose T, Cote MP, Mazzocca AD. Variability of platelet-rich plasma preparations. Sports Med Arthrosc. 2013;21(4):186-90.

51. Schar MO, Diaz-Romero J, Kohl S, Zumstein MA, Nesic D. Platelet-rich concentrates differentially release growth factors and induce cell migration in vitro. Clin Orthop Relat Res 2015;473(5):1635-1643.

52. Shen L, Yuan T, Chen S, Xie X, Zhang C. The temporal effect of platelet-rich plasma on pain and physical function in the treatment of knee osteoarthritis: systematic review and meta-analysis of randomized controlled trials. J Orthop Surg Res. 2017;12(1):16.

53. Sommeling CE, Heyneman A, Hoeksema H, Verbelen J, Stillaert FB, Monstrey S. The use of platelet-rich plasma in plastic surgery: a systematic review. J Plast Reconstr Aesthet Surg. 2013;66(3):301-11.

54. Sundman EA, Cole BJ, Fortier LA. Growth factor and catabolic cytokine concentrations are influenced by the cellular composition of platelet-rich plasma. Am J Sports Med 2011;39(10):2135-2140.

55. Weibrich G, Kleis WK, Hafner G, et al. Comparison of platelet, leukocyte, and growth factor levels in point-of-care platelet-enriched plasma, prepared using a modified Curasan kit, with preparations received from a local blood bank. Clin Oral Implants Res. 2003;14:357–362.

56. Weibrich G, Kleis WK, Hitzler WE, Hafner G. Comparison of the platelet concentrate collection system with the plasma-rich-in-growth-factors kit to produce platelet-rich plasma: a technical report. Int J Oral Maxillofac Implants. 2005;20(1):118-23.

57. Weibrich G, Kleis WK, Streckbein P, Moergel M, Hitzler WE, Hafner G. Comparison of point-of-care methods for preparation of platelet concentrate (platelet-rich plasma). Int J Oral Maxillofac Implants. 2012;27(4):762-9.

58. Willits K, Kaniki N, Bryant D. The use of platelet-rich plasma in orthopaedic injuries. Sports Med Arthrosc. 2013;21(4):225-30.

59. Yin W, Qi X, Zhang Y, Sheng J, Xu Z, Tao S, Xie X, Li X, Zhang C. Advantages of pure platelet-rich plasma compared with leukocyte- and platelet-rich plasma in promoting repair of bone defects. J Transl Med. 2016;14:73.

60. Yin WJ, Xu HT, Sheng JG, An ZQ, Guo SC, Xie XT, Zhang CQ. Advantages of Pure Platelet-Rich Plasma Compared with Leukocyte- and Platelet-Rich Plasma in Treating Rabbit Knee Osteoarthritis. Med Sci Monit. 2016;22:1280-90.

61. Zhang L, Chen S, Chang P, Bao N, Yang C, Ti Y, Zhou L, Zhao J. Harmful Effects of Leukocyte-Rich Platelet-Rich Plasma on Rabbit Tendon Stem Cells In Vitro. Am J Sports Med. 2016;44(8):1941-51.

62. Zhou Y, Zhang J, Wu H, Hogan MV, Wang JH. The differential effects of leukocyte-containing and pure platelet-rich plasma (PRP) on tendon stem/progenitor cells - implications of PRP application for the clinical treatment of tendon injuries. Stem Cell Res Ther. 2015;6:173.

63. Zimmermann R, Arnold D, Strasser E, et al. Sample preparation technique and white cell content influence the detectable levels of growth factors in platelet concentrates. Vox Sang. 2003;85:283–289.

64. Zimmermann R, Jakubietz R, Jakubietz M, Strasser E, Schlegel A, Wiltfang J, Eckstein R. Different preparation methods to obtain platelet components as a source of growth factors for local application. Transfusion. 2001;41(10):1217-24.

Chapter 6

Efficacy of adjuvant application of platelet-rich plasma after needle aspiration of calcific deposits for the treatment of rotator cuff calcific tendinitis: a double-blinded, randomized controlled trial with 2-year follow-up

Bart W. Oudelaar
Rianne Huis In 't Veld
Edwin M. Ooms
Relinde Schepers-Bok
Rob G.H.H. Nelissen
Anne J.H. Vochteloo

Am J Sports Med. 2021;49:873-882

Abstract

Background

Needle aspiration of calcific deposits (NACD) is a frequently used treatment for rotator cuff calcific tendinitis (RCCT). However, a substantial part of patients experiences recurrent or persisting shoulder complaints after NACD.

Purpose

To compare the effects of adjuvant application of PRP after NACD (NACP+PRP) with conventional NACD with corticosteroids (NACD+corticosteroids) on pain, shoulder function and quality of life (QoL).

Methods

In a single-center, double-blinded, randomized controlled trial, 80 adults with symptomatic RCCT, were randomly allocated to receive NACD+corticosteroids or NACD+PRP. Pain, shoulder function and QoL were assessed at baseline; 6 weeks; and 3, 6, 12 and 24 months after-treatment using a numeric rating scale for pain (NRS), the Constant-Murley score (CMS), the Disabilities of the Arm, Shoulder and Hand questionnaire (DASH), the Oxford Shoulder Score (OSS) and the EuroQol five dimension scale (EQ-5D). Additionally, resorption of calcific deposits and integrity of rotator cuff tendons were assessed by using standard radiographs and ultrasound examination. Results were analyzed using noninferiority analysis for NRS scores and a mixed model for repeated measures.

Results

Eighty patients were included (48 female, mean age 49±6 years; 41 patients in the NACD+PRP group). Both groups showed improvement of clinical scores at two-year follow-up ($p<0.001$ for all clinical scores). NACD+PRP was found noninferior to NACD+corticosteroids with regard to mean decrease of NRS scores (4.34 vs. 3.56; $p=0.003$). Mixed model analysis showed a significant difference in favor of NACD+PRP (CMS $p<0.001$; DASH $p=0.002$; OSS $p=0.010$; EQ-5D $p<0.001$). However, clinically relevant differences in favor of NACD+PRP were only seen at six-month follow-up for NRS and CMS scores, whereas at six-week follow-up a clinically relevant difference in favor of NACD+corticosteroids was found for all clinical scores, except for the NRS. Full resorption of calcific deposits was present in 84% of the NACD+PRP group compared to 66% in NACD+corticosteroids group

(p=0.081). In the NACD+PRP group 10 (24%) patients required a second NACD procedure compared to 19 (49%) patients in the NACD+corticosteroids group (p=0.036). 6 complications, of which 5 frozen shoulders, occurred in the NACD+PRP group compared to one complication in the NACD+corticosteroids group (p=0.11).

Conclusion

NACD+PRP resulted in worse clinical scores at six weeks follow-up but better clinical scores at six months follow-up compared to NACD+corticosteroids. At one- and two-year follow-up, results were comparable between groups. Furthermore, PRP seemed to reduce the need for additional treatments but was associated with more complications. In conclusion, NACD+corticosteroids has a favorable early effect on pain and function combined with low comorbidity. Thus, it remains the treatment of choice for patients with RCCT.

Introduction

Rotator cuff calcific tendinitis (RCCT) is a frequently diagnosed cause of shoulder complaints which is initially managed with conservative treatment strategies such as rest, non-steroidal anti-inflammatory drugs (NSAIDs) or physiotherapy[10, 16, 34, 46, 47, 50]. In patients with persistent symptoms, more invasive therapies such as subacromial injections with corticosteroids (SAI), needle aspiration of calcific deposits (NACD) or extracorporeal shockwave therapy (ESWT) are indicated[1, 25, 28, 30]. Comparative studies between these treatments are scarce. When compared with ESWT, Kim et al. found that NACD is more effective in pain relief and functional restoration in the short term[23]. De Witte et al. compared NACD with SAI and reviewed patients at one and five years[7, 8]. Results of their studies showed significantly superior results for NACD at one-year follow-up, but the results diminished at five-year follow-up. Based on their findings the authors conclude that NACD is associated with faster improvement and a lower number of patients requiring additional treatment. Nevertheless, a substantial part of patients who underwent NACD suffer from recurrent or persisting shoulder complaints after NACD[9, 38]. Several prognostic factors for persisting shoulder complaints have been identified such as female gender, smoking , Gartner and Heyer type I calcifications, smaller size calcifications and a longer duration of symptoms prior to NACD[9, 15, 35, 36]. Currently, in addition to needle aspiration or needling of the calcific deposit(s), corticosteroids are injected in the subacromial bursa to avoid an inflammatory reaction secondary to the manipulation of the calcific deposit. Corticosteroid injections are, however, known to only have short-term (4-6 weeks) effect and might, on the other hand, have detrimental effects of rotator cuff tendons[5, 27, 29, 33] which could possibly explain the recurrence of shoulder complaints after NACD.

Currently, platelet-rich plasma (PRP) is a popular treatment option in the treatment of tendinopathies in general. Several studies have shown favorable outcomes of PRP in the treatment of tendinopathies such as lateral epicondylitis and patellar tendon tendinitis[2, 4, 11, 13]. The role of PRP in the treatment of rotator cuff pathology is more controversial. Laboratory studies show promising results for the use of PRP on rotator cuff tears[17, 24, 32], but clinical studies have shown conflicting results. In arthroscopic rotator cuff repair for example, several systematic reviews conclude that PRP does not affect clinical outcome scores, does not improve re-tear rates and is not cost-effective[43, 48, 51]. In the conservative treatment of rotator cuff

disease, such as partial rotator cuff tears and tendinopathy, conflicting results have been published about the efficacy of PRP[3, 20-22, 39, 40, 44, 45, 49]. In comparison with corticosteroid injections, however, PRP seems to give superior results in the short-term in patients with partial rotator cuff tears[45, 49]. The use of PRP in the treatment of RCCT has never been investigated.

The aim of this study was to evaluate the effects of the adjuvant application of PRP compared to corticosteroids after NACD on pain and shoulder function in patients with RCCT. Secondly, the effects of the adjuvant application of PRP on the resorption of calcific deposits, the integrity of the rotator cuff tendon and the occurrence of complications was evaluated.

Materials and methods

A single-center, double-blinded randomized controlled trial with parallel groups was conducted at the departments of orthopaedic surgery and radiology of the Centre for Orthopaedic Surgery (OCON) and ZiekenhuisGroep Twente (ZGT), Hengelo, The Netherlands. Between August 2014 and June 2017 consecutive patients were included. All stages of the study were approved by an accredited medical research ethics committee (MREC) (NCT02173743) and the institutional medical ethics review board (ZGT, Hengelo) and all participating patients gave informed consent.

Study population

The study population consisted of patients aged between 18 and 55 years referred to the department of orthopaedic surgery for the treatment of shoulder complaints. Inclusion criteria were clinical signs of calcific tendinitis defined as pain in the deltoid region worsening by elevation of the arm above the shoulder level and/or at night for a minimal duration of six months, failed conservative treatment defined as at least two unsuccessful types of treatment such as non-steroidal anti-inflammatory drugs (NSAIDs), physiotherapy, subacromial injections with corticosteroids (SAI) or extracorporeal shockwave therapy (ESWT), and calcific deposits of at least 10 mm in size on standard anteroposterior (AP) radiographs. Exclusion criteria were type III calcific deposits according the classification by Gartner and Heyer, which are calcific deposits that are transparent with indistinct borders[15], history of fracture, surgery, or a previous NACD procedure of the affected shoulder, the presence of other causes for shoulder complaints (e.g. full thickness tear of the rotator cuff, frozen shoulder, glenohumeral osteoarthritis or instability). Eligible patients were referred to the coordinating investigator (BO) for inclusion.

Blinding and intervention

Patients fulfilling the inclusion criteria were randomly allocated to receive corticosteroids (NACD+corticosteroids) or PRP (NACD+PRP) following to the NACD procedure. Randomization was performed by computer-generated block randomization, with a variable block size of two, four or six. Prior to the NACD procedure patients signed informed consent forms and baseline demographics and questionnaires were completed. Standard AP and transscapular radiographs and standard ultrasound examination of the affected shoulder was obtained in all patients prior to the intervention.

Next, 54 ml of blood was drawn from all patients. In patients randomized to receive PRP after the NACD procedure, PRP was produced using the Gravitational Platelet Separation III system (GPSIII, Biomet Biologics, Warsaw, Indiana). After the blood was drawn, 6ml of sodium citrate was added and 0.5 ml of blood was collected for analysis of concentration of platelets and leukocytes. The blood was then loaded in the GPSIII tube, placed into the centrifuge and centrifuged for 15 minutes at 3200 RPM according to the GPSIII instructions. Next, the PRP was withdrawn from the tube and 8.4% sodium bicarbonate was added to buffer the PRP to physiologic pH. No activating agent was used. Approximately 6 ml PRP was obtained for each patient. 0.5 ml of PRP was collected for analysis of concentration of platelets and leukocytes. The blood of patients who were randomized to receive corticosteroids after the NACD procedure was destroyed.

All NACD procedures were performed by a single, well-experienced musculoskeletal radiologist. After sterile preparation, the skin and subcutaneous tissue were anesthetized by local injection of lidocaine 1%. Then, the ultrasound guided NACD was performed using a 20 or 21 Gauge needle. After maneuvering the needle into the calcific deposit, the deposit was infiltrated with lidocaine 1%. The calcific deposit was then repeatedly perforated and if possible, removed by aspiration. In patients randomized to the NACD+corticosteroids group, the subacromial bursa was infiltrated with 4 ml bupivacaine (2,5mg/ml) and 1 ml triamcinolonacetonide (40mg/ml) after completing the NACD procedure. In patients allocated to the NACD+PRP group, PRP was injected in and around the affected rotator cuff tendon. The syringes used for the injection of either the triamcinolonacetonide/bupivacaine or the PRP were masked with opaque tape to ensure blinding of the patients. The radiologist performing the NACD procedures was not involved in the further course of the study.

The post-intervention pain protocol consisted of paracetamol 1000mg 4 times a day which was replaced by Zaldiar (paracetamol 325 mg, tramadol (hydrochloride) 37,5 mg) in patients where paracetamol did not provide enough pain relieve. OxyContin 10 mg was prescribed for patients with persistent pain despite the use of Zaldiar. No NSAIDs were prescribed in the two weeks prior to and following the NACD procedure as NSAIDs might affect the effects of PRP.

Patients with persisting symptoms and no radiological signs of resorption of the calcific deposit three months after the NACD procedure, were scheduled for another NACD procedure. Identical to the index procedure in the NACD+corticosteroids group

received corticosteroids after the NACD procedure; patients in the NACD+PRP group received PRP after the NACD procedure. In case of persisting symptoms after a repeated NACD procedure, patients were scheduled for another NACD procedure or surgery depending on the preference of the referring orthopaedic surgeon.

Follow-up

All patients were scheduled for follow-up visits at 6 weeks and 3, 6, 12 and 24 months. At each visit the Constant-Murley Score (CS), the Disabilities of the Arm, Shoulder and Hand score (DASH), the Oxford Shoulder score (OSS), the EuroQol five dimension scale (EQ-5D) and the Numeric Rating Scale (NRS) for pain were completed. Standard radiographs were obtained at 6 and 12 months to analyze the size and resorption of the calcific deposit(s). Ultrasound examination was performed at 6, 12 and 24 months to assess the integrity of the rotator cuff in terms of full thickness, partial thickness of interstitial rotator cuff tears. Partial rotator cuff tears were defined as focal defects in the tendon that involve either the bursal or articular surface whereas interstitial rotator cuff tears were defined as concealed partial-thickness rotator cuff tears neither extending to the articular nor the bursal surface. All measurements were carried out by an independent blinded assessor.

Sample Size Calculation

The sample size calculation to determine one-sided non-inferiority was carried out using the NRS (0-10 points) as the primary outcome measure. A difference of 1.6 points was defined as a clinically relevant improvement[42]. Previous studies have shown that the standard deviation of the NRS is 2.56 points[36, 38]. In order to reach a desired power of 80% with a significant level of 0.05, a sample size of 33 patients in each study group was required. To allow for a 20% rate of loss to follow-up, 40 patients per group were included, 80 patients in total.

Statistical analysis

Descriptive data were presented as frequencies and percentages. Continuous data were presented using means and standard deviations. To investigate differences between groups, unpaired student T-tests were used for continuous normal distributed data and chi-square tests were applied for categorical or non-parametric variables.

Average platelet- and leukocyte counts were calculated in whole blood and in PRP. Platelet- and leukocyte enrichment factors were calculated by dividing the platelet- or leukocyte count in PRP by the platelet- or leukocyte count in whole blood.

To assess whether NACD+PRP was non-inferior to NACD+corticosteroids in terms of decrease of NRS scores at two-year follow-up, an intention-to-treat analysis was performed. NACD+PRP was considered non-inferior to NACD+corticosteroids if the lower boundary of the one-sided 95% confidence interval of the NRS score of the NACD+PRP group at two-year follow-up lay within the non-inferiority margin ($\triangle$=1.6 points)[42] of the mean NRS score of the NACD+corticosteroids group at two-year follow-up. A mixed model analyses with sidak correction was performed to analyze the effect of the treatment group on the secondary outcome measures. To assess whether the statistical differences found were clinically relevant, the differences between groups were compared to the questionnaire-specific minimal clinically important differences ($\geq$ 8.3 for CMS, $\geq$ 10.2 for DASH; $\geq$ 5.3 for OSS, $\geq$ 0.07 for EQ-5D)[19, 31].

Resorption rates (proportions of patients with total resorption of calcific deposits), integrity of the rotator cuff (proportions of patients with either partial thickness rotator cuff tears or interstitial rotator cuff tears), proportion of patients in both groups undergoing a second NACD procedure or surgery during the follow-up term because of persisting symptoms and complication rates in both groups were compared using chi-squared tests or Fisher exact tests.

All analyses were conducted with SPSS version 25 (IBM, Armonk, NY, USA). The level for statistical difference was set at 0.05.

Results

Baseline characteristics

During the inclusion period, 118 consecutive patients were contacted for participation in the study. Of these, seven patients did not meet the inclusion criteria and 31 patients declined participation, leaving 80 patients for randomized treatment (figure 1). In the NACD+corticosteroids group three patients were lost to follow-up before the one-year follow-up and another three patients were lost before the two-year follow-up, leaving respectively 36 and 33 patients for analysis at one- and two-year follow-up. In the intervention group (NACD+PRP) three patients were lost to follow-up before the one-year follow-up and another patient was lost before the two-year follow-up, leaving respectively 38 and 37 patients for analysis at one- and two-year follow-up. There were no patient crossovers between groups during the study.

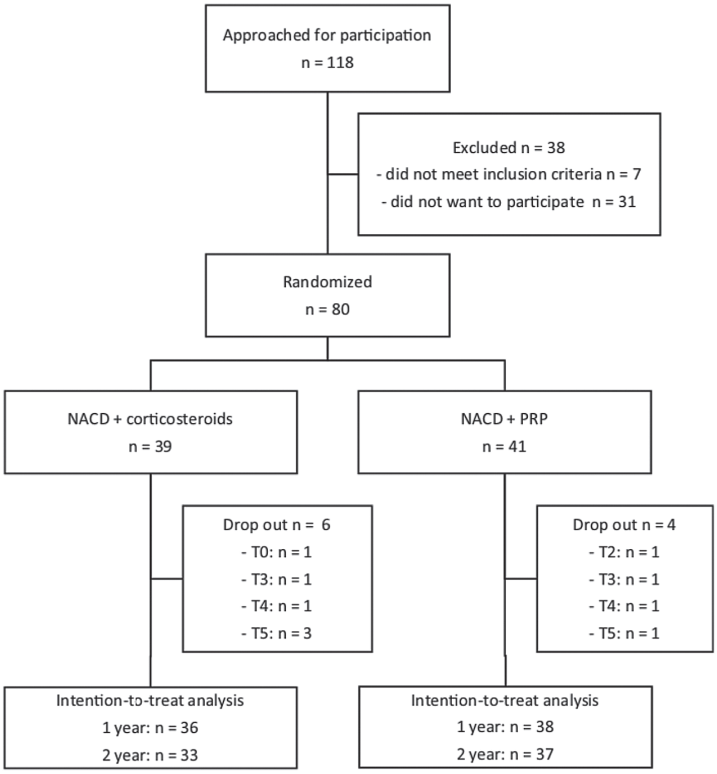

Figure 1: study flowchart. T0 = baseline; T2 = 3-month follow-up; T3 = 6-month follow-up; T4 = 1-year follow-up; T5 = 2-year follow-up. NACD: needle aspiration of calcific deposits; PRP: platelet-rich plasma.

Baseline characteristics of the final study group are presented in table 1. Baseline characteristics, baseline radiographic and ultrasound findings and baseline clinical scores did not differ between both groups except for a lower baseline EQ-5D score in the NACD+corticosteroids group and more partial thickness rotator cuff tears in the NACD+PRP group. During the NACD procedure, the calcific deposit could be (partially) aspirated in 73% of patients; in the other 27% of patients the calcific deposit could only be fragmentized. The possibility of aspiration of calcific deposit did not differ between groups (71% in the NACD+PPR group vs. 75% in the NACD+corticosteroids groups; p=0.702)

Table 1: Demographics and Baseline Characteristics

Baseline Characteristics	All patients (n=80)	Group 1: NACD + corticosteroids (n=39)	Group 2: NACD + PRP (n=41)	p-value
Age, years	48.7 ± 6.0	48.5 ± 6.3	48.8 ± 5.8	0.815
Gender, male/female, n (%)	32/48 (40/60%)	16/23 (41/59%)	16/25 (39/61%)	0.855
Affected side, right/left, n (%)	47/33 (59/41%)	25/14 (64/36%)	22/19 (54/46%)	0.343
Dominant side affected, yes/no, n (%)	47/31 (60/40%)	23/14 (62/38%)	24/17 (59/41%)	0.744
Smoking, yes/no, n (%)	20/60 (25/75%)	9/30 (23/77%)	11/30 (27/73%)	0.698
Size calcific deposit, mm	18.7 ± SD 7.9	18.8 ± 6.7	18.7 ± 8.9	0.953
Gartner and Heyer classification				
Type I, n (%)	19 (24%	9 (23%)	10 (24%)	0.890
Type II, n (%)	61 (76%)	30 (77%)	31 (76%)	
Partial thickness rotator cuff tear, yes/no, n (%)	7/73 (9/91%)	0/39 (0/100%)	7/34 (17/83%)	0.012
Interstitial rotator cuff tear, yes/no, n (%)	15/65 (19/81%)	8/31 (21/79%)	7/34 (17/83%)	0.694
Baseline clinical score				
Constant-Murley score	63.0 ± 16.6	62.3 ± 18.9	63.7 ± 14.2	0.725
DASH	40.2 ± 15.8	43.9 ± 17.3	36.6 ± 13.6	0.062
Oxford Shoulder Score	32.9 ± 6.8	33.3 ± 7.9	32.4 ± 5.5	0.560
EQ-5D	0.64 ± 0.27	0.57 ± 0.30	0.71 ± 0.22	0.022
NRS	5.4 ± 1.9	5.5 ± 2.0	5.4 ± 1.8	0.918

Values are shown as mean ± standard deviation unless otherwise indicated. DASH, Disabilities of the Arm, Shoulder and Hand questionnaire; NRS, numeric rating scale for pain (10 = severe pain).

PRP composition

A mean of 2.9 ml (±1.5ml) of PRP was injected in and around the affected rotator cuff tendon.

The average platelet count in whole blood prior to the preparation of PRP was 242x10^9/L (±56x10^9/L); the average leukocyte count prior to centrifugation was 21x10^9/L (±71x10^9/L). After PRP preparation the average platelet count was 1133x10^9/L (±408x10^9/L); the average leukocyte count was 47x10^9/L (±66x10^9/L). The average platelet- and leukocyte enrichment factor were respectively 4.8 and 4.7.

Non-inferiority analysis: decrease numeric rating scale

The lower limit of the two-sided 95% confidence interval for the mean decrease of the NRS score of the NACP + PRP group (-4.64) fell within the prespecified non-inferiority margin (-1.96), confirming non-inferiority of NACD+PRP compared to NACD+corticosteroids (figure 2). A statistically significant difference was found between groups for the mean decrease of the NRS score at two-year follow-up: -4.34 in the NACD+PRP group compared to -3.56 in the NACD+corticosteroids group (p=.003). This difference does, however, not exceed the minimal clinically important difference of 1.6 points.

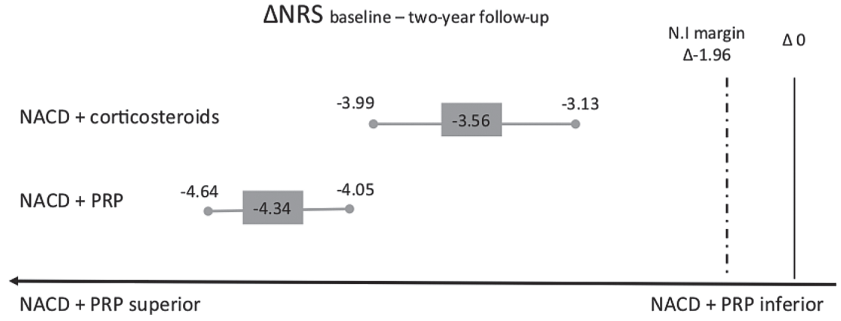

Figure 2: Results of the non-inferiority analysis of the decrease of the NRS score at two-year follow-up (ΔNRS baseline – NRS two years follow-up). Data are expressed as mean with 95% confidence interval. Dotted line indicates the non-inferiority lower boundary (mean ΔNRS NACDcorticosteroids - clinically relevant improvement of 1.6 points).

Follow-up clinical scores

In the NACD+corticosteroids group there was an improvement of all clinical scores at six weeks follow-up, followed by a deterioration of all clinical scores at three months follow-up. After this, improvement of the CMS and DASH was seen from six months follow-up onward and improvement of OSS and EQ-5D was seen from 12 months follow-up onward. In the NACD+PRP group, a gradual improvement from baseline to the 24 months follow-up was seen for all clinical scores, except for the CMS which showed a mild deterioration at six weeks follow-up after which scores

gradually improved up to the 24-month follow-up (figure 3). At 24 months follow-up both groups showed significant improvement of all clinical scores when compared to baseline scores ($p<0.001$ for all clinical scores). Mixed model analysis showed a significant difference over time between groups in favor of the NACD+PRP group for all clinical scores (CMS $p<0.001$; DASH $p=0.002$; OSS $p=0.010$; EQ-5D $p<0.001$).

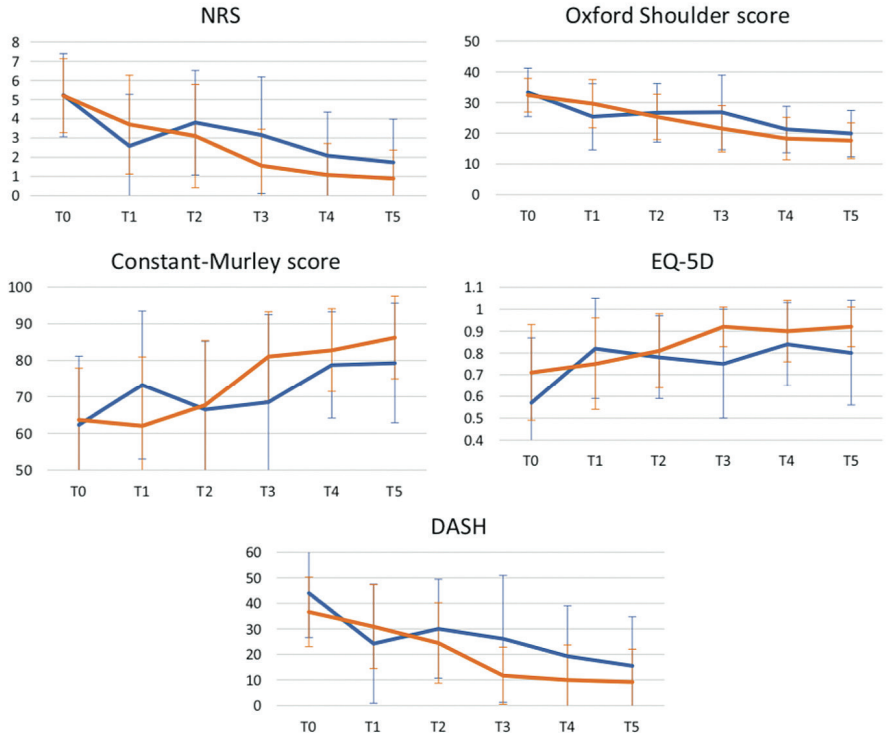

Figure 3: Clinical course of mean NRS (numeric rating scale for pain), Constant-Murley score, DASH (Disabilities of the Arm, Shoulder and Hand), Oxford Shoulder Score and EQ-5D scores with standard error after treatment for calcific tendinitis with either NACD+PRP (orange line) or NACD+corticosteroids (blue line). T0 = baseline; T1 = 6 weeks follow-up; T2 = 3 months follow-up; T3 = 6 months follow-up; T4 = 1 year follow-up and T5 = 2 year follow-up.

At the six-week follow-up, a clinically relevant difference in favor of the NACD +corticosteroids group was found for all clinical scores, except for the NRS. At six months follow-up, a clinically relevant difference of NRS and CMS scores in favor of the NACD+PRP group was seen, whereas a clinically relevant difference of EQ-5D scores was present in favor of the NACD+corticosteroids group at three months and one-year follow-up. During the further follow-up, none of the differences between groups exceeded previously defined minimal clinically important difference thresholds (table 2).

Table 2: Mean difference (95% CI) between NACD + PRP and NACD + corticosteroids compared to baseline scores

Clinical score	Δ 6 weeks	Δ 3 months	Δ 6 months	Δ 12 months	Δ 24 months
NRS	-1,2 (-0,1 to -2,4)*	0,9 (-0,3 to 2,0)	2,1 (1,0 to 3,3)*‡	1,5 (0,3 to 2,7)*	0,9 (-0,3 to 2,1)
Constant-Murley score	-12,7 (-3,9 to -21,4)*‡	0,4 (-9,4 to 10,1)	10,7 (1,5 to 19,8)*‡	3,8 (-3,7 to 11,2)	5,4 (-3,7 to 14,5)
DASH	-13,1 (-4,5 to -21,7)*‡	-2,1 (-11,2 to 7,1)	6,8 (-1,4 to 15,0)	3,9 (-5,7 to 13,6)	0,9 (-8,1 to 9,9)
Oxford Shoulder score	-5,4 (-1,1 to -9,7)*‡	0,5 (-3,6 to 4,6)	4,6 (0,4 to 8,8)*	2,7 (-1,2 to 6,7)	1,7 (-2,1 to 5,6)
EQ-5D	-0,20 (-0,32 to -0,08)*‡	-0,11 (-0,24 to 0,02)‡	0,02 (-0,11 to 0,15)	-0,07 (-0,19 to 0,06) ‡	-0,02 (-0,14 to 0,10)

DASH: Disabilities of the Arm, Shoulder and Hand questionnaire; NRS; numeric rating scale for pain (10 = severe pain). 95% CI: 95% confidence interval.
* significant at the level of 0,05
‡ exceeding previously defined minimal clinically important difference (≥ 1.6 for NRS, ≥ 8.3 for CMS, ≥ 10.2 for DASH; ≥ 5.3 for OSS, ≥ 0.07 for EQ-5D)[17, 29, 39].

Follow-up radiographic and ultrasound findings

At one-year follow-up, full resorption of calcific deposits was seen in 52 (76%) patients. There was full resorption in 21 (66%) patients in the NACD+corticosteroids group compared to 31 (84%) patients in the NACD+PRP group (p=0.081). No differences in any of the outcome measures were found between patients with full resorption of calcific deposits and patients with partial or no resorption of calcific deposits ($p>0.05$ for all of the outcome measures). Furthermore, no significant differences in the rate of full resorption between type I and type II calcific deposits were found (69% vs 77%; p=0.518). During ultrasound examination at one-year follow-up, 6 (9%) patients had partial thickness rotator cuff tears and 9 (13%) of the patients had interstitial rotator cuff tears. At two-year follow up, partial and interstitial rotator cuff tears were present in respectively 4 (6%) and 2 (3%) patients. The presence of partial thickness and interstitial rotator cuff tears was comparable between groups (one-year follow-up p=0.78; two-year follow-up p=0.44). At baseline, seven patients (NACD+PRP n=7; NACD+corticosteroids n=0) had partial rotator cuff tears, but none of these patients showed partial rotator tears or interstitial rotator cuff tears at two-year follow-up. Of the 11 patients (NACD+PRP n=5; NACD+corticosteroids n=6) with interstitial rotator cuff tears at baseline, two patients (NACD+PRP n=1; NACD+corticosteroids n=1) showed interstitial rotator cuff tears at two-year follow-up. Presence of partial thickness or interstitial rotator cuff tears did not affect the outcome ($p>0.05$ for all of the outcome measures).

Complications and additional treatment

During the two-year course, six complications (five frozen shoulders and one chemical bursitis) occurred in the NACD+PRP group compared to one complication (chemical bursitis) in the NACD+corticosteroids group (p=0.11). Of the five patients with frozen shoulders, two patients were treated with pain medication, two patients with physiotherapy and one patient with an intra-articular corticosteroid injection. At two-year follow-up, no significant differences were found between patient who had complications and those who had no complications (NRS p=0.067; CMS p=0.431; DASH p=0.991; OSS 0.966, EQ-5D 0.432). In particular, the occurrence of a frozen shoulder as complication did not influence the two-year outcome (NRS p=0.346; CMS p=0.635; DASH p=0.629; OSS 0.672, EQ-5D 0.656). Of the patients with complications, eventually two patients required surgery (which was unrelated to the complication), the other complications resolved during the course of the study.

The use of extra pain medication in the first six weeks after the procedure was comparable between groups, except during the first week, in which a higher use of Zaldiar (6 vs. 1 patient(s); p=0.095) and significantly higher use of OxyContin (5 vs. 0 patients; p=0.049) was found in the NACD+PRP group. In the NACD+corticosteroids group 19 (49%) patients required a second NACD procedure compared to 10 (24%) patients in the NACD+PRP group (p=0.036). Nine patients required surgery because of failed treatment: five patients underwent an arthroscopic subacromial decompression and four patients underwent an arthroscopic distal clavicle excision. In the NACD+corticosteroids group seven (18%) patients required surgery compared to two (5%) patients in the NACD+PRP group (p=0.084).

Discussion

Results of the present study showed no clinically relevant differences between the adjuvant application of PRP after NACD and NACD with corticosteroids at two-year follow-up. A statistically significant improvement for all clinical scores was found in favor of the NACD+PRP group, but clinically relevant differences in favor of PRP were only present at six months follow-up. In a post-hoc analysis, full resorption of calcific deposits was present in 84% of the NACD+PRP group compared to 66% in NACD+corticosteroids group and secondary NACD procedures were less often required in the NACD+PRP group; however, the complication rate was higher in the NACD+PRP group.

This is the first study investigating the use of PRP in the treatment of RCCT. There are, however, several comparative studies investigating the use of PRP in the conservative treatment of other chronic rotator cuff diseases. In the treatment of partial rotator cuff tears, superior results of PRP compared to subacromial corticosteroid injections (SAI) were seen at the 12-week follow-up, but these effects diminished at the six-month follow-up. Furthermore, none of these studies found differences in MRI between the two groups[45, 49]. In the treatment of rotator cuff impingement syndrome, superior results of PRP to SAI have been reported at eight weeks follow-up[39], but other studies have reported no significant differences between PRP and SAI after 6 months of follow-up[3]. The use of PRP has also been compared to needling, saline solution infiltrations (placebo) and physical therapy (PT). When compared to needling, significantly better reduction of pain and disability was found in the treatment of rotator cuff tendinopathy or partial rotator tears[40], whereas PRP was not more effective than placebo or PT in the treatment of chronic rotator cuff tendinopathy or partial or interstitial rotator cuff tears[20-22, 44]. Results of this study show a continuous improvement from the start of the treatment up to two-years follow-up in the NACD+PRP group. This is in contrast with the course of the clinical scores in the NACD+corticosteroids group which demonstrated improvement of clinical scores at 6 weeks follow-up, followed by recurrent symptoms at 3 months follow-up. This pattern of short-term improvement is typical for corticosteroid injections[5, 27, 33] and similar clinical courses after NACD have been described in previous studies[7,8]. Furthermore, patients in the NACD+PRP group showed significantly larger improvement compared to the NACD+corticosteroids group in the mixed model analysis. However, clinically relevant differences between groups were

only present at six weeks (in favor of NACD+corticosteroids) and at six months follow-up (in favor of NACD+PRP). An exception to this is the difference in EQ-5D scores. Although mixed model analysis showed a significant difference over time between groups in favor of the NACD+PRP group, clinically relevant differences in favor of the NACD+corticosteroids group were seen at three and 12 months. A possible explanation for these contradicting results might be the difference in baseline EQ-5D scores between groups which were significantly higher in the NACD+PRP group (0.64 vs. 0.57; p=0.022) which implies that regression toward the mean could occur. This could result in an underestimation of the effect of NACD+PRP. Another explanation could be that the EQ-5D only partially reflects patient experience. Quite recently, the internal and external responsiveness of the EQ-5D was assessed in elective shoulder surgery[12]. The authors found that the EQ-5D is adequately internally responsive to change following elective shoulder surgery but is unable to differentiate patients demonstrating minimal clinically important change. Moreover, the EQ-5D also reflects the overall well-being of the patient, thus will also be affected by this.

The adjuvant use of PRP after NACD did result in less additional treatment: 24% of patients required a second NACD procedure because of persisting symptoms in the NACD+PRP group compared to 49% in the NACD+corticosteroids group and 5% of patients in the NACD+PRP required surgery compared to 18% in the NACD+corticosteroids group. This difference could possibly be explained by the pro-inflammatory properties of PRP which might enhance the removal of residual calcium after aspiration or fragmentation of the calcific deposit during the NACD procedure. Corticosteroids have anti-inflammatory properties that might on the other hand delay the removal of residual calcium after the NACD procedure. This is supported by the finding that the rate of total resorption of calcific deposits is higher in NACD+PRP group (84% vs. 66% in the NACD+corticosteroids group). Nevertheless, the rate of secondary NACD procedures is rather high in the NACD+coricosteroids group. In literature rates of up to 45% have been published[35]. A possible explanation might be that patients with Gartner and Heyer type 3 calcifications were excluded from participation in this study. It is known that patients with Gärtner and Heyer type I calcific deposits are more likely to need multiple NACD procedures compared to patients with type III calcific deposits[35]. Furthermore, patients were monitored more closely during the study, which could be a possible other explanation for the relatively high rate of secondary procedures.

Current studies on PRP give limited information about the blood components of the PRP used. For example, only two out of the nine earlier mentioned studies on the use of PRP in rotator cuff disease reported the concentration of platelets and leukocytes in the PRP. Not all PRP products are equivalent as several commercial separation systems are available for the preparation of PRP that yield a variety of final PRP products in terms of concentration of platelets and leukocytes[37]. The ideal composition of PRP differs per specific field of application[37]. As the components of PRP in the administrated volume are often not reported in comparative studies, the optimal concentration of blood components in PRP to achieve optimal healing is unknown. The latter is one of the reasons for the large heterogeneity of studies, which obscures interpretation of results on the effect of PRP. In the treatment of chronic tendinopathy leukocyte-rich PRP seems to be superior over the use of leukocyte-poor PRP[14]. In the current study leukocyte-rich PRP was used. The platelet- and leukocyte-enrichment factors found in this study were respectively 4.8 and 4.7. In the above-mentioned studies on the efficacy of PRP in rotator cuff disease only two studies used leukocyte-rich PRP which could possibly explain the positive effects that were found in this study compared to the lack of effect of PRP in the previous studies.

A possible disadvantage of the pro-inflammatory properties of PRP could be the higher complication rate that was observed in this study in a post-hoc analysis. In particular the development of a frozen shoulder is a concern as 12% (5/41) of patients developed a frozen shoulder in the NACD+PRP group. Schwitzguebel et al. reported similar findings in a study comparing the effects of PRP and infiltration of a placebo in the treatment interstitial supraspinatus tears; in their study 20% (8/41) patients developed a frozen shoulder[44].

Although the current study was adequately powered and was performed as a blinded randomized controlled trial, some limitations need to be addressed. First, conventional NACD with corticosteroids was compared to NACD with PRP but there was no placebo control group to evaluate the additive use of corticosteroids or PRP or even the effect NACD as such. However, a recent study by Darrieutort-laffite et al. compared NACD with corticosteroids to NACD without corticosteroids[6]. Results of their study demonstrated that NACD with corticosteroid was superior to NACD without corticosteroid in decreasing pain and disability in the short term without any effect on the rate of resorption of calcific deposits. These findings indicate that the beneficial effects of NACD+PRP found in this study are not the result of a detrimental effect of

corticosteroids on the outcome of NACD. Further research comparing NACD+PRP to a placebo could possibly give more insights in the efficacy of PRP in the treatment of RCCT and the effects of NACD as such. Second, as this is the first study comparing PRP to corticosteroids for the treatment of RCCT, this study was designed as a non-inferiority study. This does not imply that this study is unable to detect superiority. Interpreting a non-inferiority trial as a superiority trial is credible and without a need for a statistical penalty for multiple testing whereas the opposite approach (interpreting a superiority trial as a non-inferiority trial) is not valid[18]. Furthermore, the statements on the effect of the adjuvant application of PRP after NACD and the need for additional treatment are based on post hoc analyses, and the differences found might be due to a type II error. Further research is needed to confirm these findings. Additionally, although analysis of the composition of PRP was performed, the concentrations of specific growth factors such as IL-1β and TGF-β1 were not analyzed. Kim et al. recently published a study in which cut-off values for these growth factors were presented to predict meaningful improvement in patients with degenerative rotator cuff tendinopathy[22]. Although higher numbers of platelets and leukocytes are associated with an increase in growth factors[37], analysis of concentrations of specific growth factors in addition to the concentration of platelets and leukocyte in PRP might give more insight in the optimal concentration of PRP for tendon healing. Finally, the follow-up of tendon integrity was performed using ultrasound examination, whereas MRI is often performed in previous studies. Ultrasound and MRI do, however, have comparable sensitivity (91% vs. 98%) and specificity (85% vs. 79%) for the detection of any rotator cuff tear[26]. Furthermore, ultrasound has a good intra-observer variability for the detection of partial rotator cuff tears (κ-value 0.79)[41].

In summary, the adjuvant application of PRP after NACD results in clinically relevant better clinical scores at the six-month follow-up when compared to NACD with corticosteroids, but it did not improve the outcome of NACD in the longer term in terms of clinically relevant pain relieve and improvement of shoulder function. Additionally, the adjuvant application of PRP after NACD resulted in worse clinical scores at the six-week follow-up. Furthermore, the adjuvant use of PRP is associated with an increased risk of complications, in particular frozen shoulder. The adjuvant use of PRP does seem to reduce the need for additional NACD procedures. To conclude, because of its early effect on pain and function, combined with its low comorbidity and low costs, NACD with corticosteroids remains the treatment of choice for patients with RCCT.

References

1. Arirachakaran A, Boonard M, Yamaphai S, Prommahachai A, Kesprayura S, Kongtharvonskul J (2017) Extracorporeal shock wave therapy, ultrasound-guided percutaneous lavage, corticosteroid injection and combined treatment for the treatment of rotator cuff calcific tendinopathy: a network meta-analysis of RCTs. Eur J Orthop Surg Traumatol. 27(3):381-390.
2. Balasubramaniam U, Dissanayake R, Annabell L. Efficacy of platelet-rich plasma injections in pain associated with chronic tendinopathy: A systematic review. Phys Sportsmed. 2015 Jul;43(3):253-61. doi: 10.1080/00913847.2015.1005544.
3. Barreto RB, Azevedo AR, Gois MC, Freire MRM, Silva DS, Cardoso JC. Platelet-Rich Plasma and Corticosteroid in the Treatment of Rotator Cuff Impingement Syndrome: Randomized Clinical Trial. Rev Bras Ortop (Sao Paulo). 2019 Dec;54(6):636-643. doi: 10.1016/j.rboe.2018.03.002.
4. Chen X, Jones IA, Park C, Vangsness CT Jr. The Efficacy of Platelet-Rich Plasma on Tendon and Ligament Healing: A Systematic Review and Meta-analysis With Bias Assessment. Am J Sports Med. 2018 Jul;46(8):2020-2032. doi: 10.1177/0363546517743746.
5. Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: a systematic review of randomised controlled trials. Lancet. 2010 Nov 20;376(9754):1751-67. doi: 10.1016/S0140-6736(10)61160-9.
6. Darrieutort-Laffite C, Varin S, Coiffier G, Albert JD, Planche L, Maugars Y, Cormier G, Le Goff B. Are corticosteroid injections needed after needling and lavage of calcific tendinitis? Randomised, double-blind, non-inferiority trial. Ann Rheum Dis. 2019 Jun;78(6):837-843. doi: 10.1136/annrheumdis-2018-214971.
7. de Witte PB, Kolk A, Overes F, Nelissen RGHH, Reijnierse M. Rotator Cuff Calcific Tendinitis: Ultrasound-Guided Needling and Lavage Versus Subacromial Corticosteroids: Five-Year Outcomes of a Randomized Controlled Trial. Am J Sports Med. 2017 Dec;45(14):3305-3314. doi: 10.1177/0363546517721686.
8. de Witte PB, Selten JW, Navas A, et al. Calcific tendinitis of the rotator cuff: a randomized controlled trial of ultrasound-guided needling and lavage versus subacromial corticosteroids. Am J Sports Med. 2013;41:1665-1673.
9. de Witte PB, van Adrichem RA, Selten JW, Nagels J, Reijnierse M, Nelissen RG (2016) Radiological and clinical predictors of long-term outcome in rotator cuff calcific tendinitis. Eur Radiol. 26(10):3401-11.
10. Diehl P, Gerdesmeyer L, Gollwitzer H, Sauer W, Tischer T.[Calcific tendinitis of the shoulder]. Orthopade. 2011;40:733-746.
11. Dupley L, Charalambous CP. Platelet-Rich Plasma Injections as a Treatment for Refractory Patellar Tendinosis: A Meta-Analysis of Randomised Trials. Knee Surg Relat Res. 2017 Sep 1;29(3):165-171. doi: 10.5792/ksrr.16.055.
12. Evans J, Dattani R, Ramasamy V, Patel V. Responsiveness of the EQ-5D-3L in elective shoulder surgery: Does it adequately represent patient experience?. J Orthop Surg (Hong Kong). 2018;26(2):2309499018774922. doi:10.1177/2309499018774922
13. Filardo G, Di Matteo B, Kon E, Merli G, Marcacci M. Platelet-rich plasma in tendon-related disorders: results and indications. Knee Surg Sports Traumatol Arthrosc. 2018 Jul;26(7):1984 1999. doi: 10.1007/s00167-016-4261-4.

14. Fitzpatrick J, Bulsara M, Zheng MH. The effectiveness of platelet-rich plasma in the treatment of tendinopathy: a meta-analysis of randomized controlled clinical trials. Am J Sports Med. 2017;45(1):226-233.
15. Gartner J, Heyer A (1995) Calcific tendinitis of the shoulder. Orthopade 24(3):284-302.
16. Gosens T, Hofstee DJ (2009) Calcifying tendinitis of the shoulder: Advances in imaging and management. Curr Rheumatol Rep 11(2):129-34.
17. Grambart ST. Sports medicine and platelet-rich plasma: nonsurgical therapy. Clin Podiatr Med Surg. 2015;32(1):99-107.
18. Hahn S. Understanding noninferiority trials. Korean J Pediatr. 2012;55(11):403-407. doi:10.3345/kjp.2012.55.11.403
19. Hao Q, Devji T, Zeraatkar D, Wang Y, Qasim A, Siemieniuk RAC, Vandvik PO, Lähdeoja T, Carrasco-Labra A, Agoritsas T, Guyatt G. Minimal important differences for improvement in shoulder condition patient-reported outcomes: a systematic review to inform a BMJ Rapid Recommendation. BMJ Open. 2019 Feb 20;9(2):e028777. doi: 10.1136/bmjopen-2018-028777.
20. Ilhanli I, Guder N, Gul M. Platelet-Rich Plasma Treatment With Physical Therapy in Chronic Partial Supraspinatus Tears. Iran Red Crescent Med J. 2015;17(9):e23732. Published 2015 Sep 28. doi:10.5812/ircmj.23732
21. Kesikburun S, Tan AK, Yilmaz B, Yaşar E, Yazicioğlu K. Platelet-rich plasma injections in the treatment of chronic rotator cuff tendinopathy: a randomized controlled trial with 1-year follow-up. Am J Sports Med. 2013 Nov;41(11):2609-16. doi: 10.1177/0363546513496542.
22. Kim SJ, Yeo SM, Noh SJ, et al. Effect of platelet-rich plasma on the degenerative rotator cuff tendinopathy according to the compositions. J Orthop Surg Res. 2019;14(1):408. Published 2019 Dec 2. doi:10.1186/s13018-019-1406-4
23. Kim YS, Lee HJ, Kim YV, Kong CG. Which method is more effective in treatment of calcific tendinitis in the shoulder? Prospective randomized comparison between ultrasound-guided needling and extracorporeal shock wave therapy. J Shoulder Elbow Surg. 2014;23:1640-1646.
24. Lädermann A, Zumstein MA, Kolo FC, Grosclaude M, Koglin L, Schwitzguebel AJ. In vivo clinical and radiological effects of platelet-rich plasma on interstitial supraspinatus lesion: Case series. Orthop Traumatol Surg Res. 2016 Dec;102(8):977-982. doi: 10.1016/j.otsr.2016.09.010.
25. Lam F, Bhatia D, van Rooyen K, de Beer JF. Modern management of calcifying tendinitis of the shoulder. Curr Orthop. 2006;20:446-452.
26. Lenza M, Buchbinder R, Takwoingi Y, Johnston RV, Hanchard NC, Faloppa F. Magnetic resonance imaging, magnetic resonance arthrography and ultrasonography for assessing rotator cuff tears in people with shoulder pain for whom surgery is being considered. Cochrane Database Syst Rev. 2013 Sep 24;(9):CD009020. doi: 10.1002/14651858.CD009020.pub2.
27. Lin MT, Chiang CF, Wu CH, Huang YT, Tu YK, Wang TG. Comparative Effectiveness of Injection Therapies in Rotator Cuff Tendinopathy: A Systematic Review, Pairwise and Network Meta-analysis of Randomized Controlled Trials. Arch Phys Med Rehabil. 2019 Feb;100(2):336-349.e15. doi: 10.1016/j.apmr.2018.06.028.

28. Louwerens JK, Veltman ES, van NA, van den Bekerom MP. The effectiveness of high-energy extracorporeal shockwave therapy ver- sus ultrasound-guided needling versus arthroscopic surgery in the management of chronic calcific rotator cuff tendinopathy: a system- atic review. Arthroscopy. 2016;32:165-175.

29. Maman E, Yehuda C, Pritsch T, Morag G, Brosh T, Sharfman Z, Dolkart O. Detrimental Effect of Repeated and Single Subacromial Corticosteroid Injections on the Intact and Injured Rotator Cuff: A Biomechanical and Imaging Study in Rats. Am J Sports Med. 2016 Jan;44(1):177-82. doi: 10.1177/0363546515591266.

30. Merolla G, Singh S, Paladini P, Porcellini G (2016) Calcific tendinitis of the rotator cuff: state of the art in diagnosis and treatment. J Orthop Traumatol. 17(1):7-14.

31. Mintken PE, Glynn P, Cleland JA. Psychometric properties of the shortened disabilities of the Arm, Shoulder, and Hand Questionnaire (QuickDASH) and Numeric Pain Rating Scale in patients with shoulder pain. J Shoulder Elbow Surg. 2009 Nov-Dec;18(6):920-6. doi: 10.1016/j.jse.2008.12.015.

32. Miranda I, Sanchez-Alepuz E, Lucas FJ, Carratala V, Gonzalez-Jofre CA. Use of platelet-rich plasma in the treatment of rotator cuff pathol- ogy: what has been scientifically proven? Rev Esp Cir Ortop Trauma- tol. 2017;61(4):249-258.

33. Mohamadi A, Chan JJ, Claessen FM, Ring D, Chen NC. Corticosteroid Injections Give Small and Transient Pain Relief in Rotator Cuff Tendinosis: A Meta-analysis. Clin Orthop Relat Res. 2017 Jan;475(1):232-243. doi: 10.1007/s11999-016-5002-1.

34. Ogon P, Suedkamp NP, Jaeger M, Izadpanah K, Koestler W, Maier D (2009) Prognostic factors in nonoperative therapy for chronic symptomatic calcific tendinitis of the shoulder. Arthritis Rheum 60(10):2978-84.

35. Oudelaar BW, Huis In 't Veld R, Schepers-Bok R, Ooms EM, Nelissen RGHH, Vochteloo AJH. Prognostic factors for the outcome of needle aspiration of calcific deposits for rotator cuff calcific tendinitis. Eur Radiol. 2020;30(7):4082-4090. doi:10.1007/s00330-020-06669-0

36. Oudelaar BW, Ooms EM, Huis In 't Veld R, Schepers-Bok R, Vochteloo AJ (2015) Smoking and morphology of calcific deposits affect the outcome of needle aspiration of calcific deposits (NACD) for calcific tendinitis of the rotator cuff. Eur J Radiol. 84(11):2255-60. doi: 10.1016/j.ejrad.2015.07.030

37. Oudelaar BW, Peerbooms JC, Huis In 't Veld R, Vochteloo AJH. Concentrations of Blood Components in Commercial Platelet-Rich Plasma Separation Systems: A Review of the Literature. Am J Sports Med. 2019 Feb;47(2):479-487. doi: 10.1177/0363546517746112.

38. Oudelaar BW, Schepers-Bok R, Ooms EM, Huis In 't Veld R, Vochteloo AJ (2016) Needle aspiration of calcific deposits (NACD) for calcific tendinitis is safe and effective: Six months follow-up of clinical results and complications in a series of 431 patients. Eur J Radiol. 85(4):689-94. doi: 10.1016/j.ejrad.2016.01.018

39. Pasin T, Ataoğlu S, Pasin Ö, Ankarali H. Comparison of the Effectiveness of Platelet-Rich Plasma, Corticosteroid, and Physical Therapy in Subacromial Impingement Syndrome. Arch Rheumatol. 2019 Mar 28;34(3):308-316. doi: 10.5606/ArchRheumatol.2019.7225.

40. Rha DW, Park GY, Kim YK, Kim MT, Lee SC. Comparison of the therapeutic effects of ultrasound-guided platelet-rich plasma injection and dry needling in rotator cuff disease: a randomized controlled trial. Clin Rehabil. 2013 Feb;27(2):113-22. doi: 10.1177/0269215512448388.

41. Rutten MJ, Jager GJ, Kiemeney LA. Ultrasound detection of rotator cuff tears: observer agreement related to increasing experience. AJR Am J Roentgenol. 2010 Dec;195(6):W440-6. doi: 10.2214/AJR.10.4526.

42. Salaffi F, Stancati A, Silvestri CA, Ciapetti A, Grassi W. Minimal clinically important changes in chronic musculoskeletal pain intensity measured on a numerical rating scale. Eur J Pain. 2004 Aug;8(4):283-91.

43. Saltzman BM, Jain A, Campbell KA, Mascarenhas R, Romeo AA, Verma NN, Cole BJ. Does the Use of Platelet-Rich Plasma at the Time of Surgery Improve Clinical Outcomes in Arthroscopic Rotator Cuff Repair When Compared With Control Cohorts? A Systematic Review of Meta-analyses. Arthroscopy. 2016 May;32(5):906-18. doi: 10.1016/j.arthro.2015.10.007.

44. Schwitzguebel AJ, Kolo FC, Tirefort J, Kourhani A, Nowak A, Gremeaux V, Saffarini M, Lädermann A. Efficacy of Platelet-Rich Plasma for the Treatment of Interstitial Supraspinatus Tears: A Double-Blinded, Randomized Controlled Trial. Am J Sports Med. 2019 Jul;47(8):1885-1892. doi: 10.1177/0363546519851097.

45. Shams A, El-Sayed M, Gamal O, Ewes W. Subacromial injection of autologous platelet-rich plasma versus corticosteroid for the treatment of symptomatic partial rotator cuff tears. Eur J Orthop Surg Traumatol. 2016 Dec;26(8):837-842.

46. Speed CA, Hazleman BL (1999) Calcific tendinitis of the shoulder. N Engl J Med 340(20):1582-4.

47. Uhthoff HK, Sarkar K. Calcifying tendinitis. Baillieres Clin Rheumatol. 1989;3:567-581.

48. Vavken P, Sadoghi P, Palmer M, Rosso C, Mueller AM, Szoelloesy G, Valderrabano V. Platelet-Rich Plasma Reduces Retear Rates After Arthroscopic Repair of Small- and Medium-Sized Rotator Cuff Tears but Is Not Cost-Effective. Am J Sports Med. 2015 Dec;43(12):3071-6. doi: 10.1177/0363546515572777.

49. von Wehren L, Blanke F, Todorov A, Heisterbach P, Sailer J, Majewski M. The effect of subacromial injections of autologous conditioned plasma versus cortisone for the treatment of symptomatic partial rotator cuff tears. Knee Surg Sports Traumatol Arthrosc. 2016 Dec;24(12):3787-3792.

50. Wölk T, Wittenberg RH (1997) Calcifying subacromial syndrome-clinical and ultrasound outcome of non-surgical therapy. Z Orthop Ihre Grenzgeb. 135(5):451-7.

51. Zhao JG, Zhao L, Jiang YX, Wang ZL, Wang J, Zhang P. Platelet-rich plasma in arthroscopic rotator cuff repair: a meta-analysis of randomized controlled trials. Arthroscopy. 2015 Jan;31(1):125-35. doi: 10.1016/j.arthro.2014.08.008.

Chapter 7

Summary, general discussion and future perspectives

Rotator cuff calcific tendinitis (RCCT) is a frequently diagnosed cause of shoulder pain that mainly affects patients of working age[1-5]. Although RCCT is believed to be a self-limiting disease, treatment is warranted for symptomatic patients as spontaneous resorption may take years[4, 6-14]. In **chapter 1** of this thesis, a comprehensive overview of the epidemiology, etiology, pathogenesis and current treatment options is provided. Needle aspiration of calcific deposits (NACD) is one of the most applied treatments for RCCT. The primary aim of this thesis was to optimize the outcome of NACD by investigating the outcome, defining prognostic factors for a favorable outcome and by investigating a novel therapy for the treatment of RCCT.

In this chapter, the findings of the studies that were conducted in this thesis are presented and the clinical implications of these findings and recommendations for future research are discussed.

Evaluating the outcome of needle aspiration of calcific deposits

In **chapter 2**, the effectiveness of NACD was retrospectively evaluated in a cohort of 431 patients with symptomatic RCCT. Results of this study show that 74% of patients had complete relief of symptoms six months after the NACD procedure. This percentage is comparable to the percentage found by Farin et al., which were the first to describe the outcome of ultrasound-guided NACD and the only other study to evaluate the outcome of NACD in terms of complete relief of symptoms[15]. Ever since, the outcome of NACD is mainly described in terms of improvement of functional shoulder questionnaires such as the Constant-Murley score[16-24]. Although these functional shoulder scores provide a more objective outcome, evaluating the outcome in terms of complete relief of symptoms is easier to interpret by patients as this is more tangible information.

Furthermore, chapter 2 shows that NACD provides quick relief of pain as the vast majority of patients (84%) had a clinically relevant decrease of pain during the first two weeks after the NACD procedure. Several authors have reported that symptoms will initially worsen during the first days following NACD but results of NACD during the first month are rarely reported[19,25]. The latter is important information in managing patient expectations prior to NACD.

Repeated NACD procedures, due to persistent or recurrent complaints, were necessary in 33% of patients, which is comparable to the percentages found in

previous studies (18-42%)[15,19]. The overall percentage of patients with complete relief of symptoms at six months post-treatment did not differ between patients undergoing a single, two or even three NACD procedures (complete symptom relief of respectively 52, 55 and 52%). This is in accordance with the findings by del Cura et al.[19], but in contrast to Farin et al., who found complete relief of pain in only 36% (4/14) of the patients who underwent a second procedure compared to 63% (40/63) after the primary procedure[15]. The association between the number of NACD procedures and the functional outcome of NACD is further discussed in chapter 4.

Complications were seen in 7.2% of patients. Chemical bursitis was the most common complication (4.9%), followed by frozen shoulder (1.6%). More importantly, three patients (0.9%) developed a septic bursitis as a result of the NACD procedure, this is a rare complication which has only been reported once in literature in a case report[26].

Clinical implications

- NACD provides clinically relevant relief of pain in the vast majority of patients within the first two weeks after the NACD procedure
- 74% of patients will have complete relief of symptoms following NACD
- Approximately one third of the patients will require multiple NACD procedures

Defining prognostic factors for the outcome of needle aspiration of calcific deposits

In **chapter 3**, prognostic factors for a successful clinical outcome and for the need for multiple NACD procedures were evaluated in a retrospective cohort study. Similar to the study in chapter 2, successful treatment outcome was defined as complete relief of symptoms at six-month follow-up. Previous studies suggest that successful outcome of NACD depend on the radiographic morphology of the calcific deposits (i.e. Gärtner and Heyer classification) prior to NACD[27]. The study in chapter 3 failed to find an association between the radiographic morphology of the calcific deposits and the success rate of NACD, i.e. no differences were found in the morphology of calcific deposits between patients in whom NACD was successful and in whom NACD failed (Gärtner and Heyer type 1: respectively 39 vs 42%; type 2: 41 vs 36% and type 3: 20 vs 22%). However, the radiographic morphology of the calcific deposits prior to NACD was associated with the number of NACD procedures that was required:

patients with Gärtner and Heyer type I deposits were over 3 times more likely to have multiple NACD procedures. Furthermore, smoking almost doubled the chance of failure of NACD. Other factors, such as the presence of partial rotator cuff tears, which were present in 16% of patients, did not seem to influence the outcome of NACD.

In **chapter 4**, a prospective study on prognostic factors for the outcome of NACD was conducted. Results of this study show that at one-year follow-up 70% of patients had a clinically relevant decrease of pain, 65% of patients had a clinically important improvement of shoulder function and 46% of patients had clinically relevant improvement of their QoL scores. The largest decrease in pain and improvement of shoulder function and QoL scores was seen at 3 months post-intervention after which the improvement plateaued. This again demonstrates that NACD provides quick relief of symptoms, which is in accordance with the findings in chapter 2. Comparable results were found in a large prospective study in which decrease of pain and improvement of shoulder function was found to up to three months after the intervention after which the improvement plateaued to up to the 10-year follow-up[23]. Interestingly, this initial response to NACD seems to be one of the most important prognostic factors for a good outcome of NACD at one-year follow-up.

A longer duration of symptoms prior to NACD was associated with inferior outcomes. This is a well-known negative prognostic factor which is supported by multiple studies[28,29]. Furthermore, the need for multiple NACD procedures was associated with inferior outcomes. This is in contrast to the findings of our retrospective study (chapter 2) which found no differences in outcome between shoulders that were treated once and those treated twice or even three times. The results of the study in chapter 2 are, however, more susceptible to bias, especially recall bias, which is inherent to the retrospective nature of this study, which might party explain the contradicting results. The contradicting results can furthermore be explained by the differences in outcome measures between the studies. The primary endpoint ‘successful treatment’ in the study in chapter 2 was defined as complete relief of symptoms, whereas in the prospective study shoulder-specific outcome scores were used. Literature on the effect of multiple procedure on the outcome of NACD is scarce and inconclusive. Farin et al. found the outcome of second and third NACD procedures to be inferior to the outcome after the primary NACD procedure[15]. In contrast, del Cura et al. found no difference in outcome between shoulders that were treated once

and those treated twice or even three times[19]. One might question whether the need for multiple NACD procedures is indeed a predictor for an inferior outcome or whether it represents the consequence of attempting the same procedure in a non-responding patient. As previous studies, including the one in chapter 2, show that at least a part of the patients that require repeated NACD procedures demonstrate clinical improvement, the latter does not apply to all patients who require multiple NACD procedures. Whether the lack of effect in patients who don't respond to repeated NACD procedures is due to a non-responding calcific tendinitis or due to non-responding patients remains to be evaluated. Nevertheless, physicians treating patients with RCCT should be aware of the possible inferior results of multiple NACD procedures and should manage patient expectations likewise prior to a second or even third NACD procedure.

Finally, chapter 4 shows that smaller-sized calcific deposits are associated with an inferior outcome. So, in the treatment of RCCT, size seems to matter with regard to the outcome of NACD. Size also seems to matter regarding the development of shoulder complaints in patients with RCCT. Louwerens et al. state that patients with calcific deposits of >1.5 cm in length had the highest chance of suffering from symptomatic RCTT whereas calcifications with a mean size of less than 0.5 cm were more frequently found in asymptomatic patients[30]. Shoulder complaints in patients with smaller-size calcific deposits could therefore be the result of another, perhaps more complex, inflammatory pathology which could require a treatment different than NACD. Unfortunately, the study in chapter 4 failed to identify a cut-off value for the size of calcific deposits likely to respond well to NACD. Regarding the long-term outcome of patients with RCCT, de Witte et al. found that the size of the initial calcific deposit did not affect the long-term outcome (mean follow-up of 14 years) irrespective of the treatment they received (conservative or NACD)[29]. The study furthermore showed that 42% of patients with RCCT had a severely impaired shoulder function (i.e. WORC score < 60 points) in the long-term. So, although RCCT is believed to be a self-limiting disease, a substantial percentage of patients will have an impaired shoulder function in the long term. This again shows that shoulder complaints of patients with RCCT in the long-term are probably due to other shoulder pathology than RCCT. Nevertheless, physicians should be aware of the inferior results of NACD for smaller-size calcific deposits and the necessity to exclude other causes of shoulder complaints in these patients prior to referring for NACD.

Clinical implications

- Patients with a good initial response to NACD have a higher likelihood of a good clinical outcome in the long term
- Smoking and a longer duration of symptoms prior to NACD are associated with inferior outcomes
- Patients with Gärtner and Heyer type I deposits are more likely to require multiple NACD procedures
- The success of NACD in terms of complete relief of symptoms is comparable between patients with a single and patients with multiple NACD procedures, but multiple NACD procedures are associated with less decrease of pain in the long term
- Smaller-sized calcific deposits are associated with a less favorable outcome

Evaluating the efficacy of platelet-rich plasma as a novel treatment for rotator cuff calcific tendinitis

What type of platelet-rich plasma should be used?

In chapter 6 of this thesis the effectiveness of the use of platelet-rich plasma (PRP) in patients with RCCT was investigated. It should be noted that comparison of studies investigating PRP is complex, if not impossible due to the multitude of commercially available PRP separation systems and processing procedures, as well as different concentration of bioactive products within PRP as the result of the multitude of separation systems and processing procedures. Therefore, a systematic review of literature was conducted to gain more insight in the differences in blood components in PRP produced by these different separation systems (**chapter 5**). Results of this study demonstrate that there is large heterogeneity among the various systems regarding concentrations of platelets and leukocytes and that, with regard to the concentrations of growth factors, there is large heterogeneity both between and within the different systems.

PRP separation systems can be divided into systems producing a high and a low concentration of platelets and systems producing a high and a low concentration of leukocytes (leukocyte-rich and leukocyte-poor PRP). Quite recently, a review investigating the optimal platelet concentrations for cell proliferation found that the optimal PRP/media ratio was PRP $\leq$ 10% while the optimal platelet concentration was 1.0–1.5 × 10^6/µL[31]. This review is, however, limited to in in-vitro studies and the authors note that other concentrations might be beneficial depending on cell type and tissue site. Thus, further in-vivo studies are needed to further investigate the actual objective effect and optimal concentration of platelets in PRP.

The concentration of leukocytes in PRP seems to be of more importance. There is increasing evidence that the concentration of leukocytes in PRP should be matched to the specific clinical field of application. In the treatment of chronic tendinopathy, for example, the use of leukocyte-rich PRP seems to be superior to leukocyte-poor PRP, whereas leukocyte-poor PRP seems to be more suitable for the treatment of articular cartilage lesions[32,33]. Furthermore, Kim et al. analyzed cut-off values for specific growth factors in PRP (IL-1β and TGF-β1) to predict meaningful improvement in patients with degenerative rotator cuff tendinopathy[34]. The study in chapter 5 of this thesis showed large heterogeneity both between and within the different PRP separation systems with regard to the concentration of TGF-β1. Interestingly, none of the TGF-β1 values for any of the studied commercial separation systems exceeded the cut-off value as proposed by Kim et al. This difference can to some extent be explained by the use of different ELISA kits. The assays of growth factors contained in the platelets may be influenced by the incomplete removal of platelets and red blood cells resulting in variable results, which makes comparison of growth factors between studies less reliable[35]. The latter also implies that research on dose-response relationships based on concentrations of growth factors in PRP are not (yet) valid. Future research should focus on determining the optimal concentrations of platelets and leukocytes in PRP for specific fields of application (e.g. cartilage, tendons, etc.).

Clinical implications

- Large heterogeneity exists between PRP separation systems with respect to concentrations of platelets, leukocytes and growth factors, making comparisons between studies difficult
- The choice for the most appropriate type of PRP should be based on the specific clinical field of application
- Leukocyte-rich PRP seems to be more suitable for the treatment of chronic tendinopathy

Does the application of platelet-rich plasma improve the outcome of NACD?

In **chapter 6**, the effectiveness of the use of PRP in patients with RCCT was investigated in a double-blind randomized controlled trial comparing the adjuvant application of PRP after NACD to conventional NACD with corticosteroids. It was concluded that conventional NACD with corticosteroids remains the treatment of choice for patients with RCCT as this provided an earlier effect on pain and function combined with less complications in comparison to NACD with PRP.

The early effect of conventional NACD is most probably the result of the injection of corticosteroids. In the study in chapter 6, the rapid improvement of clinical scores at the 6-week follow-up was followed by a worsening of clinical scores at the 3-month follow-up, a pattern that is typical for corticosteroid injections[36-38]. After the "wash-out period" of the corticosteroids (at the six-month follow-up), the patients who received PRP after the NACD procedure showed a clinically relevant larger decrease of pain and more improvement of shoulder function than the patients who underwent conventional NACD with corticosteroids. One could argue whether the superior results of PRP at the six-month follow-up are indeed the result of the application of PRP or that these are the result of the "wash-out" of the effect of corticosteroids. Ideally, a placebo-controlled trial should have been conducted comparing NACD with corticosteroids to NACD with saline and NACD with PRP and, even better, a control arm with a sham procedure. As for the latter, it has been shown by others that the "power" of contextual confounders can be large, sometimes even larger than the specific treatment effect of a treatment[39]. Whether the placebo effect exists or not is no longer a question, only its effect size remains unknown for most treatments. Some authors therefore advice to include a no-treatment arm to define the placebo effect as such[40]. However, such a controlled four-, or even five-arm study would make it a very complicated study. Besides, the addition of corticosteroids does not seem to negatively affect the outcome of NACD. In contrast, when compared to NACD with saline, NACD with corticosteroids showed a significantly greater reduction of pain six weeks after the NACD procedure and a significantly greater improvement of shoulder function three months after the NACD procedure as concluded by Darrieutort-Laffite et al.[41]. It therefore seems likely that the superior results of PRP at the six-month follow-up are indeed the result of the application of PRP. During further follow-up, at one- and two-year, no more differences between conventional NACD with corticosteroids and NACD with PRP were found. As both treatments are equally effective in the long term, the short-term results are decisive in which treatment is the most suitable. As we deem immediate results (6 weeks) more important than 6-month results in the treatment of RCCT, NACD with corticosteroids remains the treatment of choice for RCCT. The use of PRP may be indicated for a more specific group of RCCT patients, such as patients with persisting complaints after an initial conventional NACD with corticosteroids and with risk factors for an increased chance for repeated NACD procedures, such as Gärtner and Heyer type 1 calcifications. This must, however, be further evaluated in a new prospective study.

Besides the clinical outcome, the need for additional treatment could be used to evaluate the treatment effect. Chapter 6 showed that the use of PRP did result in less additional treatment: secondary NACD procedure were less often required and less patients eventually required surgery in patients who received PRP after the NACD procedure. With regard to surgery, five patients underwent an arthroscopic subacromial decompression and four patients underwent an arthroscopic distal clavicle excision. The latter is interesting as one could debate whether the initial diagnosis was correct in these cases. On the other hand, persistent complaints after NACD are not uncommon. Furthermore, it is still unknown what the incidence is of other shoulder pathology (e.g. (osteo)arthritis of the acromioclavicular joint) is in patients with persisting shoulder complaints after NACD. The latter, the origin of shoulder pathology in patients with persisting shoulder complaints after NACD, should be the focus of future research. Additionally, it should be noted that our clinical diagnosis is not accurate enough to differentiate between shoulder conditions causing symptoms as has also been acknowledged earlier by de Witte et al.[42,43]. The importance of this is also underscored by the fact that 36% of patients in the study required a secondary NACD procedure because of persisting shoulder complaints. Although in all patients who underwent a repeated NACD procedure no radiographic signs of resorption of the calcific deposit were seen at three months, which was the indication for the repeated NACD procedure, the pain in these patients may be caused by a more complex mechanism than “just” the calcific deposit. Earlier in this thesis it was concluded that multiple NACD procedures were associated with less decrease of pain at one year after the NACD procedure. In the study in chapter 6 there was a significant difference in the need for a secondary NACD procedure between groups (49% in the conventional NACD group vs. 24% in the NACD with PRP group). Interestingly, a post-hoc analysis of the results of the study in chapter 6 shows that, irrespective of the treatment, patients that required multiple NACD procedure had significantly less decrease of pain and significantly less improvement of shoulder function and quality of life at one-year follow-up. Although, this did not result in a significant difference of clinical scores between both groups at one-year follow-up, it does further support the earlier finding that multiple NACD procedures negatively affect the outcome of NACD. The difference in the need for secondary NACD procedure between groups might be pure chance, since the study was not powered to find differences in secondary procedures, but it could also possibly be explained by the pro-inflammatory properties of PRP. The latter may enhance

removal of residual calcium after aspiration or fragmentation of the calcific deposit during the NACD procedure. This is supported by the post-hoc analysis finding that the rate of total resorption of calcific deposits is higher in patients who received PRP after NACD (84% vs. 66%). A confounder might be the difference in the post-procedural pain by patients. In a post-hoc analysis, significantly more supplemental pain medication was needed during the first week after the NACD procedure in the PRP group. This might again be associated with the pro-inflammatory properties of PRP which triggers a local inflammatory response increasing pain. The latter may result in reluctance of having a secondary NACD procedure in patients in the NACD with PRP group.

The pro-inflammatory properties of PRP are probably also related to the higher complication rate in patients who received PRP after the NACD procedure: 12% of the patients developed a frozen shoulder compared to none of the patients in the conventional NACD group. Comparable findings have been demonstrated by Schwitzguebel et al. who reported that 20% of patients who received PRP developed a frozen shoulder in a study comparing the effects of infiltration of PRP and a placebo in the treatment interstitial supraspinatus tears[44]. The development of a frozen shoulder seems therefore a concern in the use of PRP in the treatment of chronic rotator cuff tendinopathy.

Clinical implications

- In comparison with NACD with PRP, conventional NACD with corticosteroids results in earlier improvement of pain and shoulder function
- NACD with PRP seems to reduce the need for secondary NACD procedures
- More frozen shoulders were seen after the use of PRP

Future perspectives

Elaborating on persistent complaints after NACD

In the second part of this thesis, prognostic factors for the outcome of NACD were identified. Besides these prognostic factors for persistent complaints after NACD, reasons why some patients develop persistent complaints after NACD, despite resorption of the calcific deposit, is of interest. The persistent complaints may be due to misinterpreted symptoms, physical examination and/or imaging studies, but are more likely the result of a more complex inflammatory or degenerative entity

than “just” the calcific deposit, whilst central sensitization as a cause for persisting complaints should also be considered.

Future research focusing on the (concomitant) occurrence of other structural causes for shoulder complaints after NACD, such as (partial) rotator cuff tears, biceps tendinitis or (osteo)arthritis of the acromioclavicular joint, which will not respond to NACD and thus effect the results of NACD, could perhaps explain persisting complaints after NACD partly. However, our clinical diagnosis is not accurate enough to differentiate between the origin of shoulder pathology as has been discussed by our group[42,43]. As also discussed in these papers, relying on imaging as the holy grail for the diagnosis in these shoulder patients is too simple. It is known that certain imaging ‘abnormalities’ of the shoulder are also found in asymptomatic patients. Acromioclavicular osteoarthritis for example, is found on MRI’s in over 80% of asymptomatic patients[45]. Local injection of analgesics (marcainisation) might help to further differentiate between possible causes of shoulder complaints, but it is known that the effect of certain diagnostic (as well as therapeutic) modalities is also largely dependent on contextual factors (i.e. the placebo effect), adding to the complexity of the ultimate diagnosis[39].

Furthermore, the possibility of central sensitization as an explanation for the “chronification” of shoulder pain should be considered. Central sensitization is defined as “an amplification of neural signaling within the central nervous system that elicits pain hypersensitivity”[46]. Research on the role of central sensitization in chronic shoulder pain is emerging but is still in its infancy. However, previous studies concluded that the involvement of the central nervous system is likely in a subgroup of patients with shoulder pain and that it is likely that there is an association between persistent tendon pain and sensitization of the nervous system[47,48]. Furthermore, premorbid and acute stage high sensory sensitivity and/or somatization and low expectation of recovery at the acute stage of pain are predictors for central sensitization in patients with chronic musculoskeletal pain[49]. Interestingly, expectations of treatment effect have been established as a key process behind the placebo effect[50]. All these factors add to the heterogeneity of the disease, making it challenging to determine the exact cause of persisting complaints after NACD, but it also stresses the importance of uniform large multicenter data collection and further research investigating the role of central sensitization and contextual factors in this matter.

The future of the treatment of rotator cuff calcific tendinitis

As also stated in chapter 6 of this thesis, future research is warranted to further investigate whether PRP is indicated for a more specific type of patient, such as patients who require repeated NACD procedures. More importantly, further research should focus on the cost-effectiveness of all treatment modalities used for RCCT, including the need for reinterventions as well as the burden to society (e.g. sick-leave, extra medical care, etc.). Conservative therapies such as specific physical therapy focused on training shoulder depressors combined with short duration of non-steroidal anti-inflammatory drugs (NSAIDs) demonstrate good results in about 70% of patients and are therefore regarded as the first line of treatment in patients with symptomatic RCCT[4,7,9-11]. It is debatable whether patients with persistent complaints despite adequate conservative therapy should immediately be referred for NACD or whether a subacromial injection with corticosteroids (SAI) should first be given to these patients. Although previous studies comparing both treatments concluded that NACD is associated with faster improvement and a lower number of patients requiring additional treatment[18,51], SAI is less time consuming, can immediately be performed during the consultation and might therefore be cheaper. Cost-effectiveness analysis of both treatments in patients with RCCT has never been performed but might alter the current opinion on the most suitable treatment for patients with RCCT who are unresponsive to conservative treatment. Furthermore, an analysis into predictors for successful SAI treatment is important to gain more insight into which patients are most suitable for SAI treatment. More insights into predictors for successful treatment for all the different treatment modalities for RCCT could lead to a more individualized approach to the treatment of patients with RCCT based on a patient's specific clinical and radiological characteristics. This would make the treatment of RCCT more efficient as well as more cost-effective.

Another frequently applied treatment for RCCT is extracorporeal shockwave therapy (ESWT). Louwerens et al. recently showed that ESWT is equally effective as NACD in improving function and pain[52]. NACD was, however, more effective in eliminating the calcific deposit and less additional treatments were necessary in patients who underwent NACD. Interestingly, larger size calcific deposits seem to be a negative predictor for the outcome of ESWT whereas for the outcome of NACD it was found that smaller size calcific deposits show inferior results[28]. NACD could therefore be the treatment of choice for larger size calcific deposits, whereas EWST should

be applied in patients with smaller size calcific deposits. Further research should however investigate this hypothesis, as the difference might also be due to the heterogeneity between patient groups labelled as RCCT, which again adds to the need for more uniform large multicenter data collection[53].

Recommendations for future research

- Uniform data collection of RCCT patients, including objective physical examination results, imaging data (x-ray and ultrasound) and pain sensitization scores
- Analysis of the role of central sensitization and contextual factors in persisting shoulder complaints after NACD
- Cost-effectiveness analysis of all treatment modalities used for RCCT (shoulder specific physical therapy, NSAIDs, subacromial injections, ESWT, conventional NACD with corticosteroids, NACD with PRP)
- Creating an algorithm for the treatment of RCCT based on predictors for a good outcome in order to individualize the treatment of RCCT

References

1. Welfling J, Kahn MF, Desroy M, Paologgi JB, Seze SD. Calcification of the shoulder. The disease of multiple tendinous calcifications. Rev Rheumatology 1965;32:325–334
2. Uhthoff HK, Sarkar K. Calcifying tendinitis. Baillieres Clin Rheumatol. 1989;3:567-581.
3. Speed CA, Hazleman BL. Calcific tendinitis of the shoulder. N Engl J Med 1999;20;340(20):1582-4.
4. Diehl P, Gerdesmeyer L, Gollwitzer H, Sauer W, Tischer T. Calcific tendinitis of the shoulder. Orthopade 2011;40(8):733-46.
5. Sansone V, Maiorano E, Galluzzo A, Pascale V. Calcific tendinopathy of the shoulder: clinical perspectives into the mechanisms, pathogenesis, and treatment. Orthop Res Rev. 2018;10:63-72.
6. Uhthoff HK, Loehr JW. Calcific Tendinopathy of the Rotator Cuff: Pathogenesis, Diagnosis, and Management. J Am Acad Orthop Surg. 1997;5(4):183-191.
7. Gosens T, Hofstee DJ. Calcifying tendinitis of the shoulder: advances in imaging and management. Curr Rheumatol Rep. 2009;11(2):129-34.
8. Uhthoff HK. Anatomopathology of calcifying tendinitis of the cuff. In: Gazielly DF, Gleyze P, Thomas T. The Cuff. Paris: Elsevier; 1997. pp. 144–147.
9. Cho NS, Lee BG, Rhee YG. Radiologic course of the calcific deposits in calcific tendinitis of the shoulder: does the initial radiologic aspect affect the final results? J Shoulder Elbow Surg. 2010;19(2):267-72.
10. Ogon P, Suedkamp NP, Jaeger M, Izadpanah K, Koestler W, Maier D. Prognostic factors in nonoperative therapy for chronic symptomatic calcific tendinitis of the shoulder. Arthritis Rheum. 2009;60(10):2978-84.
11. Wolk T, Wittenberg RH. Calcifying subacromial syndrome--clinical and ultrasound outcome of non-surgical therapy. Z Orthop Ihre Grenzgeb. 1997;135(5):451-7.
12. Lam F, Bhatia D, van Rooyen K, de Beer JF. Modern management of calcifying tendinitis of the shoulder. Curr Orthop. 2006;20:446-452.
13. Louwerens JK, Veltman ES, van NA, van den Bekerom MP. The effectiveness of high-energy extracorporeal shockwave therapy versus ultrasound-guided needling versus arthroscopic surgery in the management of chronic calcific rotator cuff tendinopathy: a systematic review. Arthroscopy. 2016;32:165-175.
14. Merolla G, Singh S, Paladini P, Porcellini G (2016) Calcific tendinitis of the rotator cuff: state of the art in diagnosis and treatment. J Orthop Traumatol. 17(1):7-14.
15. Farin PU, Rasanen H, Jaroma H, Harju A. Rotator cuff calcifications: treatment with ultrasound-guided percutaneous needle aspiration and lavage. Skeletal Radiol. 1996;25(6):551-4.
16. Aina R, Cardinal E, Bureau NJ, Aubin B, Brassard P. Calcific shoulder tendinitis: treatment with modified US-guided fine-needle technique. Radiology. 2001;221(2):455-61.
17. De Conti G, Marchioro U, Dorigo A, Boscolo N, Vio S, Trevisan M, et al. Percutaneous ultrasound-guided treatment of shoulder tendon calcifications: Clinical and radiological follow-up at 6 months. J Ultrasound. 2010;13(4):188-98.
18. de Witte PB, Selten JW, Navas A, Nagels J, Visser CP, Nelissen RG, et al. Calcific tendinitis of the rotator cuff: a randomized controlled trial of ultrasound-guided needling and lavage versus subacromial corticosteroids. Am J Sports Med. 2013;41(7):1665-73.

19. del Cura JL, Torre I, Zabala R, Legorburu A. Sonographically guided percutaneous needle lavage in calcific tendinitis of the shoulder: short- and long-term results. AJR Am J Roentgenol. 2007;189(3):W128-34.
20. Fusaro I, Orsini S, Diani S, Saffioti G, Zaccarelli L, Galletti S. Functional results in calcific tendinitis of the shoulder treated with rehabilitation after ultrasonic-guided approach. Musculoskelet Surg. 2011;95 Suppl 1:S31-6.
21. Kim YS, Lee HJ, Kim YV, Kong CG. Which method is more effective in treatment of calcific tendinitis in the shoulder? Prospective randomized comparison between ultrasound-guided needling and extracorporeal shock wave therapy. J Shoulder Elbow Surg. 2014;23(11):1640-6.
22. Lin JT, Adler RS, Bracilovic A, Cooper G, Sofka C, Lutz GE. Clinical outcomes of ultrasound-guided aspiration and lavage in calcific tendinosis of the shoulder. HSS J. 2007;3(1):99-105.
23. Serafini G, Sconfienza LM, Lacelli F, Silvestri E, Aliprandi A, Sardanelli F. Rotator cuff calcific tendonitis: short-term and 10-year outcomes after two-needle us-guided percutaneous treatment--nonrandomized controlled trial. Radiology. 2009;252(1):157-64.
24. Yoo JC, Koh KH, Park WH, Park JC, Kim SM, Yoon YC. The outcome of ultrasound-guided needle decompression and steroid injection in calcific tendinitis. J Shoulder Elbow Surg. 2010;19(4):596-600.
25. Pfister J, Gerber H. Chronic calcifying tendinitis of the shoulder-therapy by percutaneous needle aspiration and lavage: a prospective open study of 62 shoulders. Clin Rheumatol. 1997;16(3):269-74.
26. Sconfienza LM, Randelli F, Sdao S, Sardanelli F, Randelli P. Septic bursitis after ultrasound-guided percutaneous treatment of rotator cuff calcific tendinopathy. PM R. 2014 Aug;6(8):746-8.
27. Gartner J, Heyer A. Calcific tendinitis of the shoulder. Orthopade 1995;24(3):284-302.
28. Chou WY, Wang CJ, Wu KT, Yang YJ, Ko JY, Siu KK. Prognostic factors for the outcome of extracorporeal shockwave therapy for calcific tendinitis of the shoulder. Bone Joint J. 2017;99-B(12):1643-1650.
29. de Witte PB, van Adrichem RA, Selten JW, Nagels J, Reijnierse M, Nelissen RG. Radiological and clinical predictors of long-term outcome in rotator cuff calcific tendinitis. Eur Radiol. 2016;26(10):3401-3411.
30. Louwerens JK, Sierevelt IN, van Hove RP, van den Bekerom MP, van Noort A (2015) Prevalence of calcific deposits within the rotator cuff tendons in adults with and without subacromial pain syndrome: clinical and radiologic analysis of 1219 patients. JSES 24(10):1588-93.
31. Gentile P, Garcovich S. Systematic Review-The Potential Implications of Different Platelet-Rich Plasma (PRP) Concentrations in Regenerative Medicine for Tissue Repair. Int J Mol Sci. 2020;21(16):5702.
32. Fitzpatrick J, Bulsara M, Zheng MH. The effectiveness of platelet-rich plasma in the treatment of tendinopathy: a meta-analysis of randomized controlled clinical trials. Am J Sports Med. 2017;45(1):226-233.
33. Riboh JC, Saltzman BM, Yanke AB, Fortier L, Cole BJ. Effect of Leukocyte Concentration on the Efficacy of Platelet-Rich Plasma in the Treatment of Knee Osteoarthritis. Am J Sports Med. 2016;44(3):792-800.

34. Kim SJ, Yeo SM, Noh SJ, et al. Effect of platelet-rich plasma on the degenerative rotator cuff tendinopathy according to the compositions. J Orthop Surg Res. 2019;14(1):408.
35. Mazzocca AD, McCarthy MB, Chowaniec DM, et al..Platelet-rich plasma differs according to preparation method and human variability.J Bone Joint Surg Am. 2012;94:308–316.
36. Coombes BK, Bisset L, Vicenzino B. Efficacy and safety of corticosteroid injections and other injections for management of tendinopathy: a systematic review of randomised controlled trials. Lancet. 2010;376(9754):1751-67.
37. Lin MT, Chiang CF, Wu CH, Huang YT, Tu YK, Wang TG. Comparative Effectiveness of Injection Therapies in Rotator Cuff Tendinopathy: A Systematic Review, Pairwise and Network Meta-analysis of Randomized Controlled Trials. Arch Phys Med Rehabil. 2019;100(2):336-349.e15.
38. Mohamadi A, Chan JJ, Claessen FM, Ring D, Chen NC. Corticosteroid Injections Give Small and Transient Pain Relief in Rotator Cuff Tendinosis: A Meta-analysis. Clin Orthop Relat Res. 2017;475(1):232-243.
39. Zhang W. The powerful placebo effect in osteoarthritis. Clin Exp Rheumatol. 2019 Sep-Oct;37 Suppl 120(5):118-123..
40. Colloca L, Barsky AJ. Placebo and Nocebo Effects. N Engl J Med. 2020;382(6):554-561.
41. Darrieutort-Laffite C, Varin S, Coiffier G, Albert JD, Planche L, Maugars Y, Cormier G, Le Goff B. Are corticosteroid injections needed after needling and lavage of calcific tendinitis? Randomised, double-blind, non-inferiority trial. Ann Rheum Dis. 2019;78(6):837-843.
42. de Witte PB, Overbeek CL, Navas A, Nagels J, Reijnierse M, Nelissen RG. Heterogeneous MR arthrography findings in patients with subacromial impingement syndrome - Diagnostic subgroups? J Electromyogr Kinesiol. 2016;29:64-73.
43. de Witte PB, Nagels J, van Arkel ER, Visser CP, Nelissen RG, de Groot JH. Study protocol subacromial impingement syndrome: the identification of pathophysiologic mechanisms (SISTIM). BMC Musculoskelet Disord. 2011;14;12:282.
44. Schwitzguebel AJ, Kolo FC, Tirefort J, Kourhani A, Nowak A, Gremeaux V, Saffarini M, Lädermann A. Efficacy of Platelet-Rich Plasma for the Treatment of Interstitial Supraspinatus Tears: A Double-Blinded, Randomized Controlled Trial. Am J Sports Med. 2019;47(8):1885-1892.
45. Frigg A, Song D, Willi J, Freiburghaus AU, Grehn H. Seven-year course of asymptomatic acromioclavicular osteoarthritis diagnosed by MRI. J Shoulder Elbow Surg. 2019;28(10):e344-e351.
46. Kuppens K, Hans G, Roussel N, Struyf F, Fransen E, Cras P, Van Wilgen CP, Nijs J. Sensory processing and central pain modulation in patients with chronic shoulder pain: A case-control study. Scand J Med Sci Sports. 2018;28(3):1183-1192.
47. Noten S, Struyf F, Lluch E, D'Hoore M, Van Looveren E, Meeus M. Central Pain Processing in Patients with Shoulder Pain: A Review of the Literature. Pain Pract. 2017;17(2):267-280.
48. Plinsinga ML, Brink MS, Vicenzino B, van Wilgen CP. Evidence of Nervous System Sensitization in Commonly Presenting and Persistent Painful Tendinopathies: A Systematic Review. J Orthop Sports Phys Ther. 2015;45(11):864-75.
49. Clark J, Nijs J, Yeowell G, Goodwin PC. What Are the Predictors of Altered Central Pain Modulation in Chronic Musculoskeletal Pain Populations? A Systematic Review. Pain Physician. 2017;20(6):487-500.

50. Brown WA. Expectation, the placebo effect and the response to treatment. R I Med J (2013). 2015;98(5):19-21.

51. de Witte PB, Kolk A, Overes F, Nelissen RGHH, Reijnierse M. Rotator Cuff Calcific Tendinitis: Ultrasound-Guided Needling and Lavage Versus Subacromial Corticosteroids: Five-Year Outcomes of a Randomized Controlled Trial. Am J Sports Med. 2017;45(14):3305-3314.

52. Louwerens JKG, Sierevelt IN, Kramer ET, Boonstra R, van den Bekerom MPJ, van Royen BJ, Eygendaal D, van Noort A. Comparing Ultrasound-Guided Needling Combined With a Subacromial Corticosteroid Injection Versus High-Energy Extracorporeal Shockwave Therapy for Calcific Tendinitis of the Rotator Cuff: A Randomized Controlled Trial. Arthroscopy. 2020;36(7):1823-1833.e1.

53. McCulloch P, Altman DG, Campbell WB, et al. No surgical innovation without evaluation: the IDEAL recommendations. Lancet. 2009 Sep 26;374(9695):1105-12.

Chapter 8

Samenvatting (layman's summary in Dutch)

Schouderklachten zijn een van de meest voorkomende klachten van het bewegingsapparaat. Tendinitis calcarea (vorming van kalk in een of meerdere pezen rond het schoudergewricht) is een veel voorkomende oorzaak van schouderklachten. De oorzaak van de formatie van deze verkalkingen is onduidelijk. Er zijn verschillende hypothesen over zoals overbelasting of veroudering van de pees.

Tendinitis calcarea komt voornamelijk voor bij mensen tussen de 30 en 60 jaar en 1.5-2x vaker bij vrouwen. 10 tot 25% van de patiënten ontwikkelt de aandoening in beide schouders.

Pijn is de meest voorkomende klacht bij tendinitis calcarea. Verder kunnen patiënten verlies van beweeglijkheid en kracht van de schouder ervaren. Het beloop van tendinitis calcarea kan worden opgedeeld in 3 fasen: de formatie-, rust- en resorptiefase. In de resorptiefase lost de calcificatie op wat vaak een lokale ontstekingsreactie teweegbrengt die gepaard gaat met forse toename van schouderklachten die vaak enkele weken aanhoudt.

Uiteindelijk zal de verkalking dus vanzelf oplossen. Dit natuurlijk beloop kan echter jaren duren, daarom is behandeling van deze aandoening bij patiënten met klachten vaak noodzakelijk. De eerste stap van de behandeling bestaat uit fysiotherapie, ontstekingsremmende pijnstillers (NSAIDs) en eventueel een injectie van een ontstekingsremmer (corticosteroïd) in de slijmbeurs van de schouder. Deze behandelingen zijn succesvol bij 70-90% van de patiënten. Bij patiënten die ondanks deze behandelingen klachten blijven houden zijn meer invasieve behandelingen nodig zoals barbotage of shockwave (hoogfrequente geluidsgolven). Bij een barbotage wordt de kalk echografisch in beeld gebracht en vervolgens met een holle naald aangeprikt en opgezogen. Na dit verwijderen van de kalk wordt een ontstekingsremmer (corticosteroïd) in de slijmbeurs gespoten. Vergelijkende studies tussen beide behandelingen zijn er niet veel, maar de aanwezige studies laten zijn dat barbotage waarschijnlijk effectiever is dan shockwave voor pijnverlichting en in het herstellen van de schouderfunctie.

Ondanks dat barbotage de meest effectieve behandeling voor tendinitis calcarea lijkt te zijn, laten de huidige onderzoeken naar de effectiviteit van barbotage zien dat ongeveer 30% van de patiënten schouderklachten blijft houden na de barbotage. Hierbij dient opgemerkt te worden dat deze onderzoeken vaak gedaan zijn onder relatief kleine groepen patiënten. Verder is het onduidelijk of er bepaalde factoren zijn

die die effectiviteit van barbotage positief dan wel negatief beïnvloeden. Daarnaast is er tot op heden weinig onderzoek gedaan naar andere behandelmogelijkheden voor tendinitis calcarea. Een van die mogelijke andere behandelmogelijkheid is de injectie van platelet-rich plasma (PRP). Dit is een geconcentreerde hoeveelheid bloedplaatjes die wordt bereid uit het bloed van de patiënt zelf. Theoretisch zou PRP gunstige effecten hebben op het genezingsproces door de groeifactoren die bloedplaatjes bevatten. Verschillende studies naar de effectiviteit van PRP hebben mogelijk gunstige effecten van PRP laten zien voor aandoeningen als een tenniselleboog (epicondylitis lateralis) of een ontstoken knieschijfpees (apexitis patellae of tendinitis van de patellapees). Ook bij de niet-operatieve behandeling van gedeeltelijke scheuren van de pezen van de schouder lijkt het gebruikt van PRP effectief te zijn. Het gebruik van PRP voor de behandeling van tendinitis calcarea is tot dusver nog niet onderzocht.

Het doel van dit proefschrift is de effectiviteit van de behandeling van tendinitis calcarea te onderzoeken en zodoende te optimaliseren. In verschillende onderzoeken is de effectiviteit van barbotage onderzocht en is gekeken naar welke factoren van invloed zijn op de afname van schouderklachten na barbotage. Daarnaast is onderzocht of het injecteren van PRP na de barbotage leidt tot betere uitkomsten (zowel op pijn als schouderfunctie) voor de patiënt.

In **hoofdstuk 2** van dit proefschrift worden de uitkomsten van een onderzoek naar de effectiviteit van barbotage onder 431 patiënten met tendinitis calcarea beschreven. Uit deze studie bleek dat na zes maanden 74% van de patiënten klachtenvrij is. Verder toonde dit onderzoek aan dat de overgrote meerderheid van patiënten (84%) na twee weken al een klinisch belangrijke afname van pijnklachten had. Barbotage zorgt dus voor een snelle afname van klachten bij de meeste patiënten. Wel bleek uit dit onderzoek dat een derde van de patiënten meerdere barbotages nodig had om uiteindelijk klachtenvrij te zijn. Complicaties werden gezien bij 7% van de patiënten. Drie patiënten ontwikkelden een bacteriële slijmbeursontsteking, een serieuze complicatie die behandeling met antibiotica en soms zelf een operatie tot gevolg heeft.

In **hoofdstuk 3** werd onderzocht welke factoren van invloed zijn op de effectiviteit van barbotage. Uit dit onderzoek bleek dat patiënten die roken een bijna tweemaal zo grote kans hebben op het niet slagen van de behandeling. Verder bleek dat patiënten waarbij de calcificatie op de röntgenfoto een hoge dichtheid had en scherp

begrenst is vaker een tweede barbotage nodig hebben. Het onderzoek in hoofdstuk 3 is een retrospectieve studie. Dit betekent dat de gegevens waarvan gebruik gemaakt is, in het verleden zijn verzameld, waardoor dus alleen de factoren waar “toevallig” informatie over beschikbaar is, onderzocht kunnen worden. Om meer inzicht te krijgen in alle mogelijke factoren waarvan wij denken dat ze relevant zijn voor de uitkomst van barbotage, hebben wij in **hoofdstuk 4** een prospectief onderzoek gedaan naar de uitkomst van barbotage en naar welke factoren van invloed zijn op de uitkomst. Uit dit onderzoek bleek dat een jaar na de barbotage ongeveer twee derde van de patiënten een klinisch belangrijke afname van pijnklachten en toename van schouderfunctie heeft. De grootste afname van pijn en toename van schouderfunctie werd gezien in de eerste drie maanden na de barbotage. Een snelle afname van klachten na barbotage bleek tevens de belangrijkste voorspeller te zijn voor een goed resultaat van de barbotage. Verder bleek dat patiënten met een langere duur van klachten voorafgaand aan de barbotage en patiënten die meerdere barbotages nodig hadden een grotere kans hebben op een slechtere uitkomst. Ook toonde deze studie aan dat patiënten met kleinere verkalkingen een grotere kans hebben op een slechtere uitkomst. Een mogelijke verklaring hiervoor is dat de schouderklachten bij deze patiënten niet veroorzaakt worden door de verkalking, maar door een andere aandoening. Het is namelijk bekend dat kleine verkalkingen ook bij mensen zonder schouderklachten aanwezig kunnen zijn, deze kleine verkalkingen hoeven dus niet altijd klachten te geven. Het is daarom zinvol om bij patiënten met kleinere verkalkingen ook altijd te zoeken naar een andere verklaring voor de schouderklachten om zo te voorkomen dat patiënten de verkeerde behandeling krijgen.

Vervolgens is in hoofdstuk 5 en 6 onderzocht of het gebruik van PRP bij de barbotage bij kan dragen aan een beter resultaat van de barbotage. Er zijn veel verschillende firma’s die apparatuur leveren voor de bereiding van PRP. Doordat de methode waarop PRP geproduceerd wordt verschilt tussen deze firma’s, kunnen er ook verschillen in de samenstelling van de PRP ontstaan. Deze verschillen hebben met name betrekking op de concentratie van bloedplaatjes en witte bloedcellen in PRP. Om inzichtelijk te krijgen wat de verschillen in samenstelling van PRP tussen de fabrikanten precies zijn, is in **hoofdstuk 5** een literatuurstudie gedaan waarin alle beschikbare onderzoeken hierover beoordeeld zijn. Deze literatuurstudie toonde aan dat er grote verschillen zijn in de concentratie bloedplaatjes en witte bloedcellen tussen de PRP van de verschillende fabrikanten maar dat de concentratie

bloedplaatjes en witte bloedcellen wel betrouwbaar is per fabrikant. Dit in tegenstelling tot de concentratie groeifactoren, die laat zowel tussen de verschillende fabrikanten grote verschillen zien maar ook tussen verschillende onderzoeken over dezelfde fabrikant. De verschillende soorten PRP kunnen grofweg worden ingedeeld in PRP met veel of weinig bloedplaatjes en PRP met veel of weinig witte bloedcellen. De ideale concentratie van bloedplaatjes in PRP is nog onbekend. Over de ideale concentratie witte bloedcellen is meer bekend en deze lijkt af te hangen van het specifieke toepassingsgebied. Zo lijkt PRP met weinig witte bloedcellen geschikter voor het gebruik in gewrichten en lijkt PRP met witte bloedcellen geschikter voor het gebruik bij peesaandoeningen zoals dus bijvoorbeeld tendinitis calcarea.

In **hoofdstuk 6** van dit proefschrift is onderzocht of het gebruik van PRP bij de barbotage daadwerkelijk tot beter resultaten leidt. In een zogenaamde dubbelblind gerandomiseerde gecontroleerde trial (RCT) is onderzocht of het toevoegen van PRP rond de aangedane pees na de barbotage effectiever is dan de gebruikelijke barbotage waarbij na de barbotage corticosteroïden in de slijmbeurs worden geïnjecteerd. Een dubbelblinde RCT houdt in dat het lot bepaalt welke behandeling patiënten krijgen. Het dubbelblinde karakter van de studie betekent dat noch de onderzoeker, noch de patiënt gedurende de duur van het onderzoek weet welke behandeling is gegeven. Uit dit onderzoek bleek dat de gebruikelijk barbotage met corticosteroïden sneller verlichting van pijn en verbetering van de functie van de schouder geeft. Daarnaast is de kans op complicaties ook kleiner bij de barbotage met corticosteroïden, met name frozen shoulders (stijve schouder) kwamen minder vaak voor in deze groep. Het gebruik van PRP na barbotage leek wel de kans op het nodig zijn van meerdere behandelingen te verkleinen. Uiteindelijk was de conclusie dat, op basis van onze data, barbotage met corticosteroïden de behandeling van keus moet blijven voor patiënten met tendinitis calcarea van de rotator cuff.

Met het oog op toekomstig onderzoek stelt dit proefschrift dat verder onderzoek nodig is om te analyseren wat de reden van aanhoudende klachten na barbotage is. Dit kan een structurele anatomische oorzaak hebben, zoals bijvoorbeeld een scheur van een van de pezen van de rotatormanchet van de schouder of slijtage van het gewricht tussen het sleutelbeen en het acromion (bot dat het "dak" van de schouder vormt), de zogeheten AC-artrose, of een samenspel van deze factoren. Anderzijds zouden deze klachten ook het gevolg kunnen zijn van centrale pijnsensitisatie (CS), waardoor andere beweegpatronen ontstaan, met secundair overbelasting en dus

pijn, waardoor een vicieuze cirkel ontstaat voor de patiënt. Centrale sensitisatie kan worden gedefinieerd als een versterkt pijnsignaal binnen het centrale zenuwstelsel, terwijl er geen sprake meer is van een lichamelijke oorzaak van de pijnklachten. Met andere woorden, het pijnsysteem is overgevoelig geworden. Er zijn al een aantal onderzoeken gedaan naar de rol van CS bij schouderklachten maar het is nog onbekend of dit ook een rol speelt bij aanhoudende klachten bij patiënten met tendinitis calcarea.

Uiteindelijk is voor alle diagnostiek en behandeling doelmatigheid evaluatie nodig, niet alleen voor wat betreft het effect voor de patiënt, maar ook een kosteneffectiviteit analyse voor de verschillende patiëntgroepen. Het systematisch analyseren volgens de IDEAL-principes is dan een voorwaarde: Idea development, exploration, assessment, long-term follow-up. Dit geldt ook voor de evaluatie van de behandeling van tendinitis calcarea. Ook deze zal zich moeten richten op de effectiviteit en kosteneffectiviteit van alle mogelijke behandelingen. Als uiteindelijk bekend is welke behandelingen het meest geschikt zijn voor de specifieke patiëntencategorieën, kan de behandeling van patiënten met tendinitis calcarea geïndividualiseerd worden.

Appendix

Publications and presentations

Acknowledgements

Curriculum Vitae

Publications and presentations

Publications related to this thesis

Oudelaar BW, Huis In 't Veld R, Ooms EM, Schepers-Bok R, Nelissen RGHH, Vochteloo AJH. Efficacy of Adjuvant Application of Platelet-Rich Plasma after Needle Aspiration of Calcific Deposits for the Treatment of Rotator Cuff Calcific Tendinitis: A Double-Blinded, Randomized Controlled Trial with 2-year Follow-up. Am J Sports Med. 2021 Mar;49(4):873-882.

Oudelaar BW, Huis In 't Veld R, Schepers-Bok R, Ooms EM, Nelissen RGHH, Vochteloo AJH. Prognostic Factors for the Outcome of Needle Aspiration of Calcific Deposits for Calcific Tendinitis of the Rotator Cuff. Eur Radiol. 2020;30(7):4082-4090.

Oudelaar BW, Peerbooms JC, Huis In 't Veld R, Vochteloo AJH. Concentrations of Blood Components in Commercial Platelet-Rich Plasma Separation Systems: A Review of the Literature. Am J Sports Med. 2019 Feb;47(2):479-487.

Oudelaar BW, Schepers-Bok R, Ooms EM, Huis In 't Veld R, Vochteloo AJ. Needle aspiration of calcific deposits (NACD) for calcific tendinitis is safe and effective: Six months follow-up of clinical results and complications in a series of 431 patients. Eur J Radiol. 2016;85(4):689- 94.

Oudelaar BW, Ooms EM, Huis In 't Veld R, Schepers-Bok R, Vochteloo AJ. Smoking and morphology of calcific deposits affect the outcome of needle aspiration of calcific deposits (NACD) for calcific tendinitis of the rotator cuff. Eur J Radiol. 2015 Nov;84(11):2255-60.

Other publications

Oudelaar BW, van Liebergen MR, van Arkel ERA. Een vrouw met acuut ontstane schouderklachten Nederlands Tijdschrift voor Geneeskunde. 2021 18;165:D6056.

Hoogeslag RA, **Oudelaar BW**, Huis In't Veld R, Brouwer RW. Double-Bundle, All-Inside Posterior Cruciate Ligament Reconstruction: A Technique Using 2 Separate Autologous Grafts. Arthrosc Tech. 2016 Sep 26;5(5):1095-1103.

Oudelaar BW, Peters A, Peters-Veluthamaningal C, Huis In 't Veld R. Een man met knieklachten door een heupafwijking. Huisarts en wetenschap 59(1):32-34

Oudelaar BW, Peters A, Kerkhoffs GMMJ, Vochteloo AJH, Huis in 't Veld R. Een man met een zeldzame fractuur van de talus. Nederlands Tijdschrift voor Traumachirurgie. 2014;6:158

Braun SM, Beurskens AJ, Kleynen M, **Oudelaar BW**, Schols JM, Wade DT. A multicenter randomized controlled trial to compare subacute 'treatment as usual' with and without mental practice among persons with stroke in Dutch nursing homes. J Am Med DirAssoc. 2012;13:851-7

Presentations

Oudelaar BW, Huis In 't Veld R, Ooms EM, Schepers-Bok R, Nelissen RGHH, Vochteloo AJH. Efficacy of Adjuvant Application of Platelet-Rich Plasma after Needle Aspiration of Calcific Deposits for the Treatment of Rotator Cuff Calcific Tendinitis: A Double-Blinded, Randomized Controlled Trial with 2-year Follow-up. 1st Virtual SECEC Congress, 2020

Oudelaar BW, Huis in 't Veld R, Ooms EM, Vochteloo AJH. Prognostic factors for the outcome of needle aspiration of calcific deposits for calcific tendinitis of the rotator cuff. SECEC-ESSSE Congress, 21 september 2018, Geneve

Oudelaar BW, Ooms EM, Huis in 't Veld R, Schepers-Bok R, Vochteloo AJH. Needle aspiration of calcific deposits (NACD) for calcific tendinitis is safe and effective: six-month follow-up of clinical results and complications in a series of 431 patients. NOV jaarcongres, 28 januari 2016, 's Hertogenbosch.

Oudelaar BW, van der Valk S, Vochteloo AJH, Huis in 't Veld R, Ooms EM, Schepers-Bok R. Prognostic factors in needle aspiration of calcific deposits (NACD) for calcific tendinitis of the rotator cuff. ECR, maart 2015, Wenen

van der Valk SBA, **Oudelaar BW**, Vochteloo AJH, Huis in 't Veld R, Ooms EM, Schepers-Bok R. Keynote lecture: Wat zijn prognostische factoren voor de effectiviteit van barbotage bij tendinits calcarea van de rotatorcuff? Radiologendagen, 11 september 2014, 's- Hertogenbosch

Oudelaar BW, Schepers R, Vochteloo AJH, Huis in 't Veld R, Ooms EM. Wat is de invloed van partiële rotatorcuff rupturen op het effect van barbotage bij patiënten met tendinitis calcarea? NOV Voorjaarsvergadering, 23 mei 2014, Utrecht

Ooms EM, **Oudelaar BW**, Vochteloo AJH, Schepers R, Huis in 't Veld R. Do partial rotator cuff tears diminish the outcome of ultrasound-guided needle aspiration of calcific deposits (NACD) in patients with calcific tendinitis? SECEC Annual Congress, September 2014, Istanbul (poster)

Acknowledgements

Graag wil ik iedereen bedanken die betrokken is geweest bij de totstandkoming van dit proefschrift, zonder jullie hulp was dit nooit mogelijk geweest.

In het bijzonder wil ik Edwin Ooms, Anne Vochteloo, Rianne Huis in ’t Veld en Rob Nelissen bedanken. Edwin, dank dat je mij een plek als wetenschapsstudent hebt aangeboden en inzag dat er een promotietraject van te maken was. Anne, dank voor je altijd snelle en scherpe feedback, het heeft ontzettend veel bijgedragen aan dit proefschrift. Rianne, voor mijn idee heb jij evenveel tijd in dit proefschrift gestoken als ik, dank dat jij altijd beschikbaar was om even te discussiëren en mij weer de goede richting op te sturen. Rob, dank dat je mij uiteindelijk onder je hoede hebt genomen als promovendus en van mij een veel kritischere onderzoeker hebt gemaakt. Jouw Leidse inbreng heeft dit proefschrift echt afgemaakt.

Ook Jordy Mongula en mijn zusje, Marieke Oudelaar, ben ik veel dank verschuldigd voor hun relativeringsvermogen en motiverende woorden op momenten dat ik door het gerommel in de marge het zicht op het uiteindelijke doel verloor.

Natuurlijk was dit alles niet mogelijk geweest zonder mijn ouders. Dank voor jullie onvoorwaardelijke steun en interesse.

En tot slot natuurlijk mijn vriendin, Margo. Bedankt voor jouw steun, geduld en begrip, dit heeft mij ontzettend geholpen bij het afronden van dit proefschrift.

Curriculum vitae

Bart Oudelaar was born on November 18th 1986 in Naarden and spent most of his youth in Huizen. At the age of sixteen he moved to Gronsveld. In 2005 he graduated from secondary school (Porta Mosana College, Maastricht). After studying engineering (2005-2006; Eindhoven University) and physiotherapy (2006-2010; Zuyd University of Applied Sciences), he was admitted to the pre-master Medicine in 2010 (Rijksuniversiteit Groningen). In 2014 he obtained his medical degree after which he started working as a resident not-in-training (ANIOS) in orthopedic surgery in the OCON in Hengelo. The OCON is also the place where the foundation of this thesis was laid under the supervision of dr. Vochteloo, dr. Ooms and dr. Huis in 't Veld. In 2016 he started his orthopedic surgery residency. He was trained at the department of General Surgery of the Hagaziekenhuis (supervisor dr. Wever), the department of Orthopedic Surgery of the Hagaziekenhuis (supervisor dr. Deijkers) and the department of Orthopedic Surgery of the Leiden University Medical Center (supervisor prof. dr. Nelissen). He currently works in the department of Orthopedic Surgery of the Haaglanden MC under the supervision of dr. van Arkel, where he will finish his residency in December 2022.

Bart is living in the Hague with his partner Margo and daughter Fien.