Rotator cuff calcific tendinitis: another entity of rotator cuff problems

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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

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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.

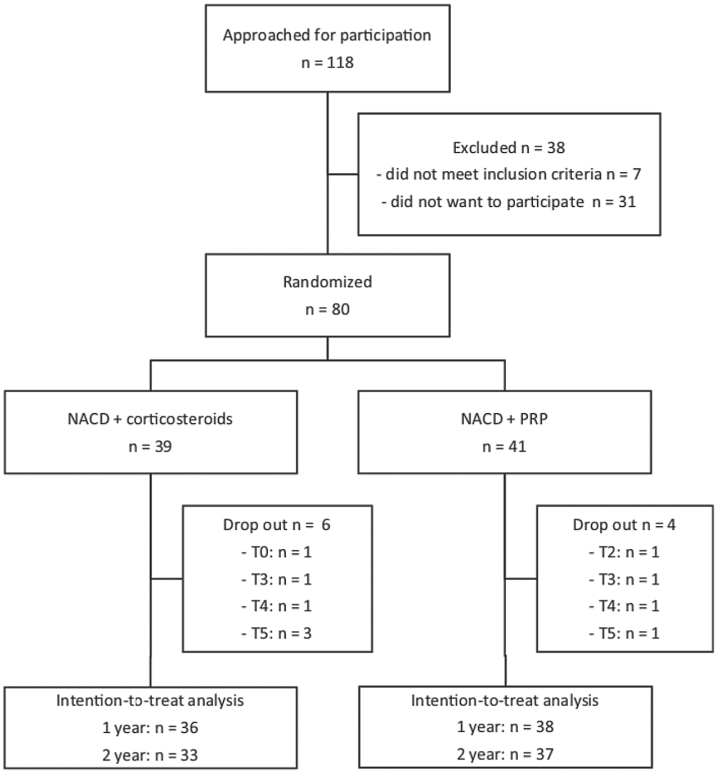

Figure 1: study flowchart. T0 = baseline; T2 = 3-month follow-up; T3 = 6-month follow-up; T4 = 1-year follow-up; T5 = 2-year follow-up. NACD: needle aspiration of calcific deposits; PRP: platelet-rich plasma.

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.

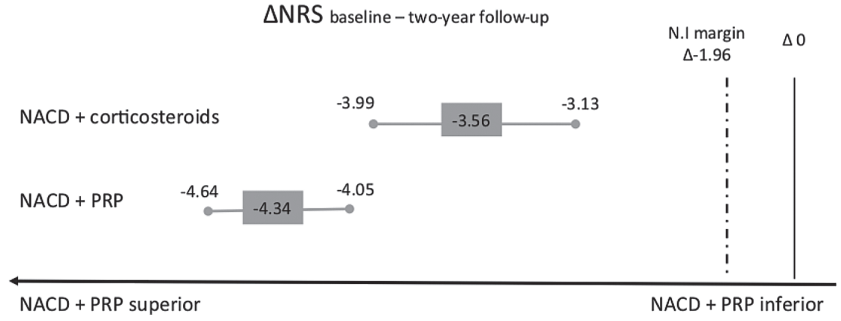

Figure 2: Results of the non-inferiority analysis of the decrease of the NRS score at two-year follow-up (ΔNRS baseline – NRS two years follow-up). Data are expressed as mean with 95% confidence interval. Dotted line indicates the non-inferiority lower boundary (mean ΔNRS NACDcorticosteroids - clinically 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 $p<0.001$).

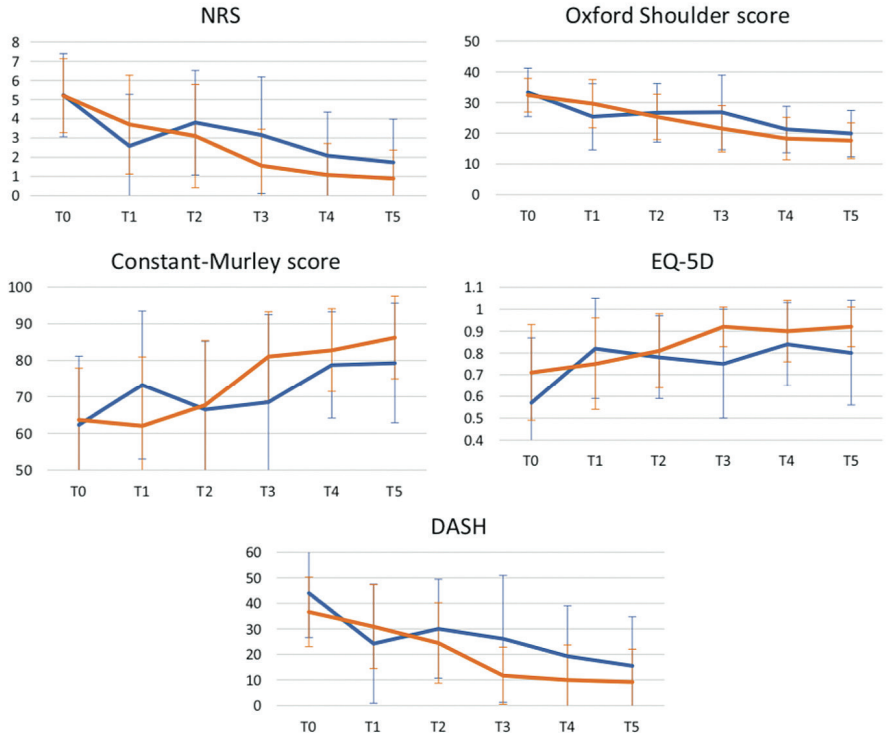

Figure 3: Clinical course of mean NRS (numeric rating scale for pain), Constant-Murley score, DASH (Disabilities of the Arm, Shoulder and Hand), Oxford Shoulder Score and EQ-5D scores with standard error after treatment for calcific tendinitis with either NACD+PRP (orange line) or NACD+corticosteroids (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.

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