Rotator cuff calcific tendinitis: another entity of rotator cuff problems

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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

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