Prospective Study

Prevalence and Risk Factors of Neuropathic Pain in Patients with a Rotator Cuff Tear

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Background: Until now, few studies had investigated the neuropathic pain component in patients with a rotator cuff tear (RCT).

Objectives: The aim of the study was to identify the neuropathic pain component in patients with RCT and to determine the factors correlated with neuropathic pain in patients with RCT.

Study Design: Prospective, cohort, prognostic study.

Setting: Study patients who required arthroscopic rotator cuff repair were analyzed in a hospital setting.

Methods: We prospectively studied 101 patients who were less than 60 years old with full-thickness tears requiring arthroscopic rotator cuff repair and met the inclusion and exclusion criteria. Multiple regression analysis was performed to identify variables that independently affected neuropathic pain in patients with a RCT. We use Douleur neuropathique 4 questionnaire (DN4) to assess neuropathic pain, which was ≥ 4 points of the DN4 questionaire. The visual analog scale (VAS) for the most severe pain within 4 weeks before admission and mean pain level during the last 4 weeks were checked. The atrophy grades of the rotator cuff muscles were classified on magnetic resonance images according to the Goutallier classification. The size and medial retraction of the RCT were measured during arthroscopic repair for RCT.

Results: Sixteen (15.8%) of the 101 patients had neuropathic pain according to the cut-off values on the DN4 questionnaire for diagnosing neuropathic pain. The neuropathic pain group had significantly higher prevalence of smoking ($P = 0.042$), more mean VAS during last 4 weeks ($P = 0.008$), larger cuff tear ($P = 0.003$), more medial retraction of cuff ($P = 0.016$), and severe fatty degeneration of rotator cuff muscles (supraspinatus, $P < 0.001$; subscapularis, $P < 0.001$; and infraspinatus, $P = 0.003$) than the nonneuropathic pain group. The multiple logistic regression analyses showed that more mean VAS during the last 4 weeks and tear size of a rotator cuff were independent of other factors for the neuropathic pain of the patients with a full-thickness RCT.

Limitations: Small sample size is the first limitation of this study.

Conclusions: The prevalence of neuropathic pain in patients with a full-thickness RCT requiring arthroscopic rotator cuff repair was 15.8 % according to the DN4 questionnaire. The neuropathic pain component was more relevant to the severity of pain and tear size in the patients with a full-thickness RCT. It is important to be aware of the existence of neuropathic pain when treating a patient presenting with pain due to a RCT because accompanying neuropathy with a RCT could have a worse effect on repair of a RCT.

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Key words: Shoulder, rotator cuff tear, arthroscopic rotator cuff repair, neuropathic pain

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Neurologic structures are concentrated around the shoulder and abundant neural elements are identified within the subacromial bursa, rotator cuff tendon, biceps tendon and tendon sheath, and transverse humeral ligament (1). Neurologic injuries or neuropathy in the shoulder could result from nerve entrapment (2,3), trauma (4,5), excessive motion (6), and rotator cuff injuries (7-9). Therefore, neuropathic pain could occur in the patients with rotator cuff lesions.

Some reports have shown a correlation between neuropathic pain and rotator cuff lesions (10,11). Gwilym et al (11) reported that patients awaiting subacromion decompression had referred pain radiating down the arm and significant hyperalgesia to a punctuated stimulus of the skin compared to those of the controls. Fabis and Bgucki (10) reported that 33 (34%) of 97 patients with a rotator cuff tear (RCT) had radiating pain, which disappeared completely in 26 cases, partially in six, and persisted in one after an intra-articular lidocaine injection. Bachasson et al (12) reviewed a large number of neural structures and mechanisms that contribute to pain and shoulder dysfunction in patients with a RCT. They revealed that the neural factor around the shoulder may contribute to pain generation and persistence of pain in the patients with a RCT. Namely, the background and mechanisms of RCT pain are unknown, but pain from a RCT is supposed to include nociceptive and neuropathic pain components.

Simple questionnaires have been developed to help distinguish neuropathic from nociceptive pain, including the Leed assessment of neuropathic pain symptoms and signs pain scale, neuropathic pain questionnaire, painDETECT, and the Douleur neuropathique 4 questionnaire (DN4) (13-16). The DN 4 questionnaire is a useful tool for the diagnosis of neuropathic pain using a clinician-administered questionnaire. The DN4 questionnaire consists of 10 items, of which 7 items are related to pain quality (i.e., sensory and pain descriptors) based on interviews with patients and 3 items are related to the presence or absence of touch or pinprick hypoesthesia and tactile allodynia on the base of the bedside clinical examination (16,17). Each positive item is 1 point and each negative item scored zero. The cut-off value for diagnosing neuropathic pain is a total score of 4/10 with sensitivity of 82.9% and specificity of 89.9% (17).

Until now, no study has investigated the neuropathic pain component in patients with a RCT. The aim of this study was to identify the neuropathic pain component in patients with a full-thickness RCT requiring surgery and determine the factors correlated with neuropathic pain in these patients using the DN4 questionnaire.

Methods

Patient Population

Among 580 patients who visited our clinic from January 2015 to June 2015 due to shoulder pain or disability, 328 patients were diagnosed with a RCT by magnetic resonance image (MRI). The 117 patients met the following inclusion criteria: (1) required surgery for a full-thickness RCT because symptoms were not alleviated after conservative management and standardized rehabilitation; (2) duration of shoulder pain > 3 months; (3) no trauma history; and (4) younger than 60 years old to reduce the possibility that neuropathic pain relates to geriatric process. Exclusion criteria included: (1) previous ipsilateral shoulder surgery; (2) any other lesion of the contralateral shoulder; (3) other extra- or intraarticular lesion at the glenohumeral joint, including space occupying lesions; (4) previous injection therapy on the affected shoulder within 3 months before surgery; (5) previous trauma, shoulder infection, or other inflammatory disease; (6) possible cervical spine lesion confirmed by a specialized spine surgeon (SBK); and (7) previously diagnosed diabetes or other neurologic disorder, such as thoracic outlet syndrome, Parsonage and Turner syndrome, or cerebral infarction. All patients underwent plain radiography on the cervical spine and their blood sugar level was checked preoperatively to confirm a cervical spine lesion and diabetes. A total of 101 patients (53 men and 48 women) were enrolled. The mean age of the patients was 53.2 years (range: 43-59 years).

The ethics committee of our institution approved this protocol for the human procedures used in this study. The protocol and the manuscript describing the study were approved by our institutional review board, and informed consent was obtained from all patients.

All patients completed a questionnaire about their pain duration, pain intensity, and other epidemiological characteristics, as well as a neuropathic pain questionnaire 1 day before surgery.

The demographic factors included in this study were gender, age, and symptom duration from pain onset to the operation. All patients were questioned whether the affected shoulder was the dominant arm and whether they smoked or not. Ranges of motion

(ROM), visual analog scale (VAS) for pain score, the DN4 questionnaire for the neuropathic pain, tear size, tear retraction, fatty degeneration of rotator cuff muscles (supraspinatus, infraspinatus, subscapularis) were investigated (Table 1).

ROM were recorded for shoulder flexion, external rotation at the side, and internal rotation with a goniometer. Shoulder flexion and external rotation were recorded in degrees, whereas internal rotation at the back was measured by the vertebral level that was possible for the patient to reach with the thumb. The vertebral levels were numbered serially as 1 to 12 for the first to the twelfth thoracic vertebrae, 13 to 17 for the first to fifth lumbar vertebrae, and 18 for any level below the sacral vertebrae.

Pain Measurements

The authors expect that the pain or discomfort will be greatest when the patient decided to undergo surgery, and because the preoperative period lasts about two weeks, the most severe pain within the 4 weeks before admission and the mean pain level during the last 4 weeks were determined by the visual analog score (VAS). Each patient was evaluated with the DN4 questionnaire (7) to assess neuropathic pain. The cut-off value on the DN4 questionnaire for diagnosing neuropathic pain is ≥ 4 points (16). The patients were divided into the neuropathic pain group who scored ≥ 4 points in the DN4 questionnaire and the nonneuropathic pain group who scored < 4.

The Rotator Cuff Factors

The patients underwent arthroscopic rotator cuff repair by one specialized shoulder surgeon. The size of the RCT was measured with a probe for anteroposterior size of the tear at the lateral edge of the footprint. Tear grade of the RCT was classified according to anteroposterior size of the tear at the footprint as described by DeOrio and Cofield (18): small (< 1 cm), medium (1–3 cm), large (3–5 cm), and massive (> 5 cm). Retraction of the RCT was measured as the distance from the lateral margin of torn cuff to the lateral end of the footprint (19). The degree of fatty degeneration of the rotator cuff muscles was determined on a 1.5-T unit magnetic resonance imaging (MRI) evaluation (Signa, GE Medical Systems, Milwaukee, WI, USA) using routine pulse sequences according to the classification established by Goutallier et al (18): grade 0 (no fatty infiltration), grade 1 (some fatty streaks), grade 2 (< 50% fatty muscle atrophy), grade 3 (equal fat and muscle), and grade 4 (> 50% fatty muscle atrophy). Scans were evaluated at the level where the scapular spine and body form a Y-shape in the oblique sagittal view. To determine the effect of fatty degeneration of each rotator cuff muscle, the study population were trichotomized according to the modification by Fuchs et al (20) to Goutallier

Table 1. *Epidemiological characteristics of the patients.*

Number of Patients	101
Gender (Number of patients)(percentage)	
Men	53 (52.5%)
Women	48 (47.5%)
Age (mean ± SD yrs) (range)	53.2 ± 3.3 (43-59)
The mean symptom duration from pain onset to the operation (mean ± SD months) (range)	10.6 ± 3.4 (3-16)
The dominant arm (Number of patients) (percentage)	54 (53.5%)
Smoking (Number of patients) (percentage)	22 (21.8%)
Range of shoulder motion (mean ± SD degree) (range)	
Forward flexion	158.6 ± 16.6 (80-170)
External rotation at the side	55.3 ± 14.2 (20-70)
Internal rotation	12.3 ± 2.4(8-18)
Pain Scores (mean ± SD) (range)	
Severest pain during 4 weeks	6.3 ± 1.1(4-9)
Average pain during 4 weeks	5.0 ± 1.2(2-7)
DN 4 (mean ± SD) (range)	2.1 ± 1.3(0-5)
Tear size (mean ± SD cm) (range)	2.0 ± 1.1(0.7-5.5)
Small	18 (17.8%)
Medium	55 (54.5%)
Large	25 (24.8%)
Massive	3 (3.0%)
Extent of retraction (mean ± SD cm) (range)	2.1 ± 0.9 (0.8-4.5)
Fatty degeneration (mean ± SD)	
Suprasupinatus	1.7 ± 1.1
I	39 (38.6%)
II	43 (42.6%)
III	19 (18.8%)
Subscapularis	0.3 ± 0.6
I	95 (94.1%)
II	6 (59%)
Infrascapularis	1.0
I	68 (67.3%)
II	24 (23.8%)
III	9 (8.9%)

classification: stage 1 (normal muscle ; Goutallier grade 0-1), stage 2 (moderately pathologic muscle: Goutallier grade 2), and stage 3 (advanced degeneration: Goutallier grade 3-4) for the supraspinatus, the subscapularis, and the infraspinatus, respectively.

Statistical Analysis

The statistical analysis was performed using SPSS software ver. 19.0 (IBM SPSS, Inc., Armonk, NY, USA). In the univariate analysis, the student t test or Mann-Whitney U test were used for analysis of continuous variables, and the chi-square test or Fisher exact test was used for categorical variables between the neuropathic pain group and the nonneuropathic pain group. The Mantel-Haenszel chi-square test was used for fatty degeneration of rotator muscles. Multiple logistic regression analysis with a forward stepwise technique was performed on variables thought to be associated with neuropathic pain according to the univariate analyses (entry criterion, $P < 0.05$). A P-value ≤ 0.05 was considered as significant. Two of the authors independently reviewed fatty degeneration of the rotator cuff muscles and the reliability of measurements was evaluated using interclass correlation coefficient (ICC). The inter-observer ICC for the grade of fatty degeneration of the rotator cuff muscles were 0.802, 0.867, and 0.876 for supraspinatus, infraspinatus, and subscapularis, respectively. If there was grading incongruity of the evaluation on the grade of fatty degeneration of the rotator cuff muscles between 2 observers, the grade was determined by common consent.

Results

Prevalence and Risk Factors of Neuropathic Pain

Sixteen (15.8%) of the 101 patients had neuropathic pain according to the cut-off values on the DN4 questions for diagnosing neuropathic pain. Univariate analysis of variables between the neuropathic pain group and the nonneuropathic pain group is summarized in Table 2. The neuropathic pain group had significantly higher prevalence of smoking ($P = 0.042$), more mean VAS during last 4 weeks ($P = 0.008$), larger cuff tear ($P = 0.003$), more medial retraction of cuff ($P = 0.016$), and severe fatty degeneration of rotator cuff muscles (supraspinatus, $P < 0.001$; subscapularis, $P < 0.001$; and infraspinatus, $P = 0.003$) than the nonneuropathic pain group. No difference was observed for gender, age, symptom duration from pain onset to the operation, the dominant arm, the severest VAS in the last 4 weeks, and ROM of shoulder between neuropathic pain group and nonneuropathic pain group.

Forward stepwise logistic regression modeling showed that more mean VAS during the last 4 weeks and tear size of a rotator cuff were independent of other factors for the neuropathic pain of the patients with a full-thickness RCT (Table 3).

Discussion

Neuropathic pain is characterized by spontaneous pain with abnormal sensory symptoms as ongoing or paroxysmal pain and evoked types of pain as hyperalgesia or allodynia (21). There is a variety of pathophysiological mechanisms in the peripheral and central nervous system to generate neuropathic pain. The peripheral neural lesions trigger pathologic activity and sensitization processes in peripheral nociceptors that is peripheral sensitization, leading to neuropathic pain such as spontaneous burning pain, static mechanical, and heat hyperalgesia (22). This peripheral sensitization occurs in patients with rotator cuff disease, which releases a variety of substances that sensitize nociceptors by decreasing their activation threshold in the shoulder because RC disease is associated with local tissue damage and inflammation within the RC and surrounding structures (12). The spontaneous activity of nociceptors in turn induces secondary changes in the central sensory processing, leading to spinal cord hyperexcitability, which generates dynamic and punctate mechanical allodynia (22). The patients with central sensitization had worse clinical results than the patients without central sensitization after surgery to rotator cuff disease (11,12). In this present study, we confirmed that some patients with a full-thickness RCT had neuropathic pain in the shoulder.

We have presented the first evidence of the prevalence and risk factors of neuropathic pain in patients with a RCT using DN4 questionnaire, which had been found to be reliable and valid with good sensitivity, specificity, and positive predictive value for neuropathic pain. The prevalence of neuropathic pain in patients with a full-thickness RCT was 16 (15.8%) of the 101 patients based on the DN4 questionnaire. Some reports revealed the peripheral and central sensitization which could give rise to neuropathic pain occurred in the patients with shoulder pain, including shoulder impingement, rotator cuff tear (RCT), adhesive capsulitis, or labral lesion (11,23-25). Hidalgo-Lozano et al (24) revealed that 12 patients with chronic shoulder

Table 2. *Clinical Factors for neuropathic pain from RCT in univariate analysis.*

	Neuropathic pain group	Nonneuropathic pain group	*P*-value
Number of Patients	16 (15.8%)	85 (84.2%)	
Gender (Number of patients) (percentage)			
Men	10 (62.5%)	43(50.6%)	0.381
Women	6 (37.5%)	42(49.4%)	
Age (mean ± SD yrs) (range)	52.8 ± 3.5 (45-58)	53.3 ± 3.2 (43-59)	0.427
The mean symptom duration from pain onset to the operation (mean ± SD months) (range)	11.0 ± 3.7 (6-16)	10.5 ± 3.4 (3-16)	0.528
The dominant arm (Number of patients) (percentage)	11 (68.8%)	43 (50.6%)	0.182
Smoking (Number of patients) (percentage)	7 (43.8 %)	15 (17.6 %)	0.042
Range of shoulder motion (mean ± SD degree) (range)			
Forward flexion	160.0 ± 8.9 (150-170)	158.4 ± 17.7 (80-170)	0.751
External rotation at the side	49.4 ± 20.5 (20-70)	56.5 ± 12.5 (20-70)	0.337
Internal rotation	12.6 ± 1.7 (10-15)	12.3 ± 2.5 (8-18)	0.633
Pain Scores (mean ± SD) (range)			
Severest pain during 4 weeks	6.9 ± 0.8 (6-8)	6.4 ± 1.1 (4-9)	0.068
Average pain during 4 weeks	5.9 ± 1.1 (3-7)	5.1 ± 1.2 (2-7)	0.008
DN 4 (mean ± SD) (range)	4.3 ± 0.4 (4-5)	1.8 ± 1.1 (0-3)	< 0.001
Tear size (mean ± SD cm) (range)	3.0 ± 1.4 (0.8-5.5)	1.8 ± 1.0 (0.7-5.3)	0.003
Small	2 (12.5%)	16 (18.8%)	
medium	6 (37.5%)	49 (57.6%)	
large	6 (37.5%)	19 (22.4%)	
massive	2 (12.5%)	1 (1.2%)	
Extent of retraction (mean ± SD cm) (range)	2.7 ± 1.0 (0.8-4.5)	1.9 ± 0.9 (0.8-4.5)	0.016
Fatty degeneration (mean ± SD)			
Suprasupinatus	2.6 ± 1.0	1.5 ± 1.0 (75:10)	< 0.001
I	1 (6.3%)	38 (44.7%)	
II	8 (18.6%)	35 (41.2%)	
III	7 (43.8%)	12 (14.1%)	
Subscapularis	0.8 ± 0.8	0.2 ± 0.4 (84:1)	< 0.001
I	13 (81.3%)	82 (96.5%)	
II	3 (18.8%)	3 (3.5%)	
Infrascapularis	1.8 ± 1.0	0.7 ± 0.7 (75:10)	0.003
I	6 (37.5%)	62 (72.9%)	
II	6 (37.5%)	18 (21.2%)	
III	4 (15.8%)	5 (5.9%)	

impingement had a greater number of active and latent trigger points and significant lower pressure pain thresholds compared to 10 controls. Because the trigger points constitute a focus of peripheral nociceptive sensitization and the presence of widespread hyperalgesia and lower pressure pain thresholds reflect of the central sensitization, the authors suggested there were both the presence of both peripheral and central sensitization mechanisms in the patients with shoulder impingement syndrome. Coronado et al (23) examined the pattern of experimental pain responses in the affected and nonaffected extremities in patients with shoulder pain compared to the healthy volunteers, including pressure pain threshold, thermal pain threshold

Table 3. *Clinical factors for neuropathic pain from RCT in multivariate analysis using logistic regression (stepwise forward: conditional).*

	Exp (B)	95% CI	*P*-Value
Mean VAS in the last 4 weeks	2.024	1.065-3.846	0.031
Tear size of a rotator cuff	2.205	1.328-3.662	0.002

and tolerance, and supra-threshold heat pain response. The authors found the patients with shoulder pain showed pressure hypersensitivity at affected shoulder compared to nonaffected shoulder, supporting a peripherally sensitized status and bilateral hypersensitivity to pressure, and thermal stimuli at local and remote regions compared to healthy patients, indicating central sensitization. Gwilym et al (11) reported that 65 % of patients awaiting subacromion decompression had central sensitization in form of referred pain radiating down the arm, significant hyperalgesia to a punctuated stimulus of the skin, and lower mechanical pain threshold compared to those of the controls. The incidence of central sensitization in the patients with shoulder impingement syndrome was higher than the prevalence of neuropathic pain in the patients with a RCT in the presents study. We suppose that this disagreement on the prevalence was caused by the difference in sensitivity of the experimental items, which were performed in two studies. Because DN4 questionnaire consists of 10 items, including response to mechanical stimuli, which was similar to the experiment in the previous study and the cut-off value for diagnosing neuropathic pain is ≥ 4 points, the sensitivity of DN4 questionnaire would be lower than the previous study.

Mean VAS in the last 4 weeks and tear size of rotator cuff were independent factors for the neuropathic pain in the patients with a full-thickness RCT in the present study. In the systematic review by Boogaard et al (26) to summarize finding of predictors of persistent neuropathic pain in high-quality studies, higher acute pain severity was one of the predictors of persistent neuropathic pain, although there are risk factors that had been identified for neuropathic pain. Torrance et al (27) found the patient with chronic pain of predominantly neuropathic origin had significantly greater pain intensity than other chronic pain sufferers. Recent studies have suggested an association between tendon tear size and peripheral neuropathy in the patients with a RCT (9,28). Vad et al (9) reported 7 cases (28%) of 25 patients with a full-thickness RCT and shoulder atrophy had abnormal electromyographic results. In their study, 4 (50%) of 8 large cuff tears were found neuropathies, as compared with 3 (18%) of 17 small tears. Shi et al (28) examined the patients suspected of having suprascapular neuropathy with electromyography (EMG) and nerve conduction velocity (NCV) study and MRI for their shoulders. The authors reported suprascapular neuropathy is correlated to tendon tear size, but it does not have significant influence on fatty degeneration of either supraspinatus or infraspinatus.

Accompanying neuropathy with a RCT may prolong postsurgical recovery or result in a poor outcome after repair of a RCT (29). Therefore, identifying the neuropathic components is crucial for therapeutic management, given the differential response of neuropathic pain to analgesic treatment (16). However, it is difficult to diagnose neuropathies of the shoulder in the patients with a RCT. In addition, there is the lack of a recognized "gold standard" for diagnosing neuropathic pain (27). In these cases, EMG and NCV exam are used to identify shoulder neuropathy but this procedure could not be used in all the patients with a RCT because of its invasiveness and economic problem. Moreover, the neuropathic pain resulted from the peripheral sensitization by inflammation or mechanical irritation of a cuff tear could not be identified on the EMG and NCV exam. In those regards, the DN4 questionnaire could be useful tool to diagnose neuropathies of the shoulder in the patients with a RCT because this simple questionnaire has been known for being reliable and valid with good sensitivity, specificity, and positive predictive value for neuropathic pain (17).

Several limitations of this study should be discussed. First, we just included the patients with a RCT required surgery, not all patients with a RCT, indicating selection bias. We could not exclude all patients with cervical radiculopathy and other neuropathies. However, this study remains clinically relevant because the patients with possible cervical radiculopathy were excluded by a specialized spine surgeon, considering that a neuropathy diagnosis is mainly based on the patient's history and clinical symptoms and there is no specific that can confirm its presence (30). Second, the number of the patients with neuropathic pain was not enough to confirm the risk factors about neuropathic pain related to a RCT. Another study using a larger population is probably needed to clarify this issue. Third, we did not conduct EMG and NCV exam to diagnose neurologic abnormality in the patients with neuropathic pain and the reliability of the DN4 questionnaire to determine neuropathic pain in patients with a RCT has not been confirmed; therefore, further study is needed to clarify

this to overcome the bias. Fourth, testing parameter (DN4 questionnaire) is highly subjective which is filled a day before surgery. Finally, there is no comparative study with the control group.

Conclusion

The prevalence of neuropathic pain in patients with a full-thickness RCT requiring arthroscopic rotator cuff repair was 15.8 % according to the DN4 questionnaire. The neuropathic pain component was more relevant to the severity of pain and tear size in the patients with a full-thickness RCT. It is important to be aware of the existence of neuropathic pain when treating a patient presenting with pain due to a RCT because accompanying neuropathy with a RCT could have worse effect on repair of a RCT.

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