Shoulder disorder treatment : efficacy of ultrasoundtherapy and electrotherapy

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Shoulder disorder treatment

Efficacy of ultrasoundtherapy and electrotherapy

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Shoulder disorder treatment

Efficacy of ultrasoundtherapy and electrotherapy

Proefschrift

ter verkrijging van de graad van doctor
aan de Universiteit Maastricht,
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door

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Chapter 1

Introduction

Shoulder disorders

Pain and stiffness in the deltoid region are the main symptoms of patients with shoulder disorders. In about 30% of all cases in general practice these symptoms limit daily activities¹. Many patients have paraesthesia or pain that radiates to below the elbow. Pain during movement usually limits the active range of motion, while in severe cases the passive range of motion is also restricted. Pain when lying on the impaired shoulder is a common complaint that often results in problems with sleeping²⁻⁴. Up to 20% of all cases originate from neurological or generalized musculoskeletal conditions, neoplasms or referred pain from the neck or from internal organs⁵. The remainder of all shoulder disorders is reported to originate from entesopathies within the shoulder girdle, such as tendinitis, bursitis and capsulitis^{4,5}. An inflammatory reaction of soft tissue, due to subacromial impingement of articular and peri-articular structures, appears to be the common pathological mechanism behind these entesopathies^{3,4}.

Occurrence

Shoulder disorders constitute a frequently occurring health problem. About 10% of the general population suffer from one or more episodes of shoulder disorders in the course of their life². The annual cumulative incidence is estimated at about 2%. The one-year period prevalence is highest at about 25% during the 4th decade of life⁶. Little is known about the magnitude of the socio-economic impact, e.g. cost of health care and sick leave, but working capacity is reported to be reduced in more than 50% of all working patients^{1,7}.

The majority of all new episodes that occur disappear within a few weeks, and therefore shoulder disorders are usually considered to be self-limiting^{2,6-9}. A good short-term outcome is reported to be associated with the acute onset of symptoms or with an antecedent trauma of the upper extremity^{10,11}, short duration of symptoms before first presentation to the general practitioner¹¹⁻¹³ and overuse during leisure or sports activities¹². A poor long-term prognosis is reported to be associated with involvement of the non-dominant side or both sides^{12,14}, being female¹⁵, co-existent diabetes mellitus^{16,17}, a prolonged immobility and passive abduction range of less than 90°¹⁸, co-existent cervical spine disorders and radiating pain below the elbow^{16,19}, an increasing number of prior episodes²⁰ and advanced age^{10,21}.

Treatment

About 50% of all patients with shoulder disorders consult a physician²². After low back and neck disorders, they constitute the third most largest group of patients with locomotor disorders in primary care²³⁻²⁶. Approximately 5% of all consultations of general practitioners concern shoulder disorders^{2,8,23-26}. Yet, in spite of their frequent presentation, there is no consensus about the optimal management of either acute or persistent shoulder disorders. A variety of therapies is provided in primary care, such as rest, a sling, analgesics, NSAIDs, steroid injections, thermotherapy, exercises, electrotherapy, ultrasoundtherapy, short-wave diathermia and advice about daily living. Many patients who consult their general practitioner for a new episode of shoulder disorders recover within a few weeks^{18,19,22}. About half of all newly presented episodes are reported to last for 6 months, but a considerable number may even last over a year^{18,19,22}. In addition, the recurrence rate is reported to be high^{9,22}. When the course of the complaints is protracted, general practitioners tend to refer patients to other health care workers. Consequently, about 1% of all referrals to orthopaedic surgeons and about 10% of all referrals for physiotherapy concern shoulder disorders^{8,12,22-26}.

Efficacy of treatment

The purpose of treatment of patients with shoulder disorders is to increase the extent and speed of recovery. In spite of the wide variety of existing therapies, many patients suffer from persistent or recurrent symptoms. Randomized clinical trials offer the best possibility for a valid evaluation of treatment effects²⁷. Although to date many trials of common primary care treatments such as analgesics, NSAIDs, steroid injections and physiotherapy for shoulder disorders have been published, conclusive evidence on their efficacy is still lacking. Therefore, there is a need for systematic reviews on the efficacy of these frequently applied primary care treatments.

Ultrasoundtherapy and electrotherapy are believed to promote recovery of soft tissue shoulder disorders. Their frequent use in physiotherapy, usual as adjuvants to exercise therapy, has been reported for the Netherlands, but also for the United Kingdom, Canada, United States, Australia and New Zealand²⁸⁻³². Biological studies report promising effects of ultrasoundtherapy and electrotherapy, such as pain threshold elevation and promotion of muscle relaxation³³⁻³⁵. However, controversy over their efficacy persists³⁶. Therefore, there is a need for a new trial in primary care on the efficacy of ultrasoundtherapy and electrotherapy for shoulder disorders.

Content of thesis

This thesis reports on the design and results of studies about the treatment of soft-tissue shoulder disorders in primary care. Chapters 2 through 4 contain systematic reviews of randomized clinical trials on the efficacy of common approaches in physiotherapy, and of steroid injections and non-steroidal anti-inflammatory drugs (NSAIDs) for shoulder disorders. Chapter 5 presents the design and results of a randomized placebo-controlled clinical trial on the efficacy of ultrasoundtherapy and electrotherapy as adjuvants to exercise therapy for patients with soft-tissue shoulder disorders in primary care physiotherapy. The research question is whether these therapies contribute to the extent and speed of recovery from shoulder disorders. We compare the effect of active versus dummy treatments in a two by two factorial design. In order to estimate the placebo effect of the adjuvant treatments, an extra control group is added which only receives exercise therapy.

Chapter 6 describes the design of the shoulder disability questionnaire (SDQ). This chapter also includes an evaluation of the SDQ responsiveness compared with four other outcome measures that were used simultaneously.

Chapter 7, the general discussion, provides a critical review of the principles of design and conduct of our clinical trial. Furthermore, the results of the systematic reviews and the performance of the outcome measures are discussed. The general discussion concludes with recommendations for clinical practice and suggestions for future clinical trials on shoulder disorders.

Comprehensive Dutch and English summaries follow and the thesis ends with some acknowledgements, a curriculum vitae and a list of publications.

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Chapter 2

Physiotherapy for soft-tissue shoulder disorders

A systematic review of randomized clinical trials

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Abstract

Purpose The study was designed to assess the efficacy of physiotherapy for soft-tissue shoulder disorders.

Data sources A systematic computerized literature search in Medline and Embase was conducted, supplemented with citation tracking of all relevant publications.

Study selection Trials on physiotherapy for soft-tissue shoulder disorders published before 1996 were selected if treatment was randomly allocated and if success rates, pain, mobility or functional status were used as outcome measures.

Data extraction The validity of trial methods was systematically assessed by independent reviewers. Trials were ranked according to the extent to which bias was considered to be unlikely. Next, differences between groups in outcome and 95% confidence intervals were calculated.

Results The methods assessment was frequently hampered by insufficient information on various criteria. Furthermore, trials were often flawed by lack of blinding and a high incidence of treatment withdrawals and missing values. Trial sizes were small: only 4 trials included intervention groups of at least 25 patients. Ultrasoundtherapy, evaluated in 6 trials, was not shown to be efficacious. Only 4 other trials favoured the efficacy of physiotherapy (lasertherapy or manipulation), but the validity of their methods was unsatisfactory.

Conclusions Ultrasoundtherapy does not appear to be efficacious in the treatment of soft-tissue shoulder disorders. Due to small trial sizes and unsatisfactory methods, evidence for the efficacy of other physiotherapeutical interventions is inconclusive. Future trial should study whether these interventions are superior to treatment with analgesics, non-steroidals, steroid injections or a wait-and-see policy.

Introduction

Pain is the primary complaint of most patients with soft-tissue shoulder disorders. In many patients pain restricts the range of shoulder movement, causing limitations of daily activities. Estimates of the cumulative annual incidence of shoulder disorders range from 7 to 25 per 1000 general practice consultations¹⁻³. Five per cent of all general practice consultations is reported to be related to shoulder disorders^{4,5}. Fifty per cent of all presented episodes resolve within 6 months, but some may last over a year or more. The majority of patients with soft-tissue shoulder disorders is treated in primary care. Their management includes advice, analgesics, non-steroidals, steroid injections and physiotherapy. Randomized clinical trials on shoulder disorders show small effects in favour of the efficacy of non-steroidals⁶ and steroid injections⁷. A wide array of physiotherapy modalities is used for the treatment of shoulder disorders^{8,9}. Patients are frequently referred for physiotherapy^{10,11}, in Dutch primary care as many as 20% to 33% of all patients with shoulder disorders^{2,3,12}. So far, little effort has been invested in establishing the efficacy of common physiotherapy management before implementation in practice. The purpose of this systematic review, based on the reports of 20 randomized clinical trials, is to assess whether physiotherapy is efficacious for patients with soft-tissue shoulder disorders.

Methods

Study selection

Relevant trial reports were harvested from Medline (Index Medicus 1/1966-12/1995) and Embase (Excerpta Medica 1/1984-12/1995) according to the computerized search strategy of Dickersin et al¹³. This strategy was supplemented with citation tracking of relevant publications. GJMGH identified trial reports that met the following conditions: [1] patients had shoulder pain at inclusion; [2] treatments were allocated by a random procedure; [3] at least one of the treatments included physiotherapy; [4] success rate, pain, mobility or functional status were included as outcome measures; [5] results were published as a full report before January 1996. From this selection DAWMW and AFW independently selected the trials that included patients with soft-tissue shoulder disorders.

Methods assessment

Eight validity criteria were used for the assessment of trial methods (Table 1-A). These criteria are based on generally accepted methodological requirements for intervention research¹⁴⁻¹⁷. In addition, five data extraction criteria were used (Table 1-B) that provide information on the external validity and possibilities for statistical pooling¹⁸. DAWMW, AFW and GJMGH independently analyzed the selected trial reports for completeness of information. For each criterion they logged whether incomplete information had hampered the methods assessment. If sufficient information was reported they judged and logged whether bias was likely or not. For criteria for which consensus could not be reached, the presented results are based on agreement of 2 reviewers. The trials were subsequently ranked according to the number of validity criteria for which bias was considered to be unlikely.

Table 1a. Validity criteria for the methods assessment of randomized clinical trials of physiotherapy for shoulder disorders.

V1	Enrolment: Restriction to a population homogeneous for prognosis and susceptibility to the allocated interventions by means of explicit selection criteria. Prognostic markers used: age, duration of complaints, painful arc, pain at night, number of prior episodes, radiating pain, prior treatment.
V2	Randomization: Adequate procedure for generation of a random numbers list and concealed allocation of interventions.
V3	Baseline similarity: Similarity of intervention groups at baseline with respect to prognosis and susceptibility to allocated interventions. Prognostic markers used: baseline scores for outcome measures, age, duration of complaints, painful arc, pain at night, number of prior episodes, radiating pain, prior treatment.
V4	Treatment withdrawals: No patients withdrew from allocated treatment, or the number of patients was < 10% in each intervention group, with comparable reasons for withdrawal.
V5	Missing data (e.g. due to loss-to-follow-up): The number of randomized patients minus the number of reported patients at the main moment of effect measurement for the main outcome measure (if not stated according to the reviewers) divided by all randomized patients, times 100%: < 10% in each group.
V6	Co-interventions: Either standardized or excluded in trial design.
V7	Blinded application of interventions: Therapists: blinding by a credible placebo. Patients: blinding by a credible placebo or by enrolment of patients who were unaware of the identity of the allocated interventions.
V8	Blinded outcome assessment: Assessor of effect parameters (e.g. patient, therapist, physician or research staff) blinded for allocated interventions.

Table 1b. Data extraction criteria for the methods assessment of randomized clinical trials of physiotherapy for shoulder disorders.

D1	Sample size of groups at baseline
D2	Standardization of allocated interventions: Adequate description of intervention type, modality, application technique, intensity, and of duration, number and frequency of sessions for all allocated interventions.
D3	Reported outcome parameters: Success rate (e.g. proportion of patients cured or improved); pain; functional status (activities of daily living); mobility (range of motion); non-trial co-interventions (e.g. medication, surgery)
D4	Outcome assessments: Identical timing of assessment for all intervention groups; immediately after the last treatment or > 3 months.
D5	Actual data for outcome parameters: An adequate point estimate is presented for each intervention group - with corresponding distribution measure - for success rate or improvement for pain or most important outcome measure on the most important moment of effect measurement.

Success rates were determined for each intervention group by dividing the number of documented successes at the end of the intervention period, by the number of patients randomly allocated to the intervention (i.e. intention-to-treat analysis). When success rates could not be calculated, change scores for pain and mobility ratings were determined. Missing values for outcome measures were assumed to represent failures

(i.e. worst-case assumption). Next, the differences between groups for outcome measures were calculated, along with the 95% confidence intervals. Finally, the efficacy of physiotherapy was judged by relating these confidence intervals to the number of validity criteria satisfied.

Results

Study selection

GJMGH identified 47 trial reports that met the 5 conditions for further selection. DAWMW and AFW excluded 23 trials: 7 because the results of patients who received physiotherapy for shoulder disorders were not presented separately; 1 because similar physiotherapy was given as a co-intervention to all patients; 4 on exercise therapy after mastectomy; 4 on physiotherapy for post-fracture shoulder pain; 7 on physiotherapy for shoulder pain in hemiplegics; and 1 trial on rheumatoid arthritis. The methods of the remaining 23 trial reports were assessed¹⁹⁻⁴¹. Information was combined for 3 trials that were reported twice^{23+24,33+34,40+41}. Hence, 20 trials on the efficacy of physiotherapy for patients with soft-tissue shoulder disorders were included in this systematic review.

Methods assessment

In Table 2 the validity criteria for which bias was considered likely are listed for each trial. This table also presents the validity and data extraction criteria for which incomplete information hampered the methods assessment. The trials are ranked according to the number of validity criteria satisfied. Equally ranked trials are ordered alphabetically.

Table 2. Methods assessment. Validity criteria for which bias must be considered likely, and validity and data extraction criteria for which incomplete information hampered assessment.

First author ^{ref}	Bias considered likely	Incomplete information for validity assessment	Incomplete information for data extraction
Downing ¹⁹	-	-	-
Binder ²⁰	-	V 2,3	D 5
Leclaire ²¹	-	V 2,3	-
Saunders ²²	-	V 2,3	D 3
Berry ^{23,24}	-	V 1,2,3	D 2
Brox ²⁵	V 7,8	V 2	D 5
Chard ²⁶	V 5	V 2,3,6	-
Dacre ²⁷	V 7	V 2,3,6	D 2,5
Herrera-Lasso ²⁸	V 4,7	V 1,2	-
Nykanen ²⁹	-	V 1,2,3,4	-
Vecchio ³⁰	-	V 1,2,4,5	-
Bulgen ³¹	V 4,7	V 2,3,6	D 2,3,5
England ³²	-	V 1,2,3,4,6	D 5
Gudmundsen ^{33,34}	V 8	V 1,2,3,6	-
Knüsel ³⁵	-	V 1,2,3,6,7	D 3,4,5
Thomas ³⁶	V 7	V 1,2,3,6,8	-
Biwas ³⁷	V 4,5,7	V 1,2,3,8	D 2,3,5
Delacerda ³⁸	V 7	V 1,2,3,4,6,8	D 3,4,5
Knorre ³⁹	V 1,7,8	V 2,3,4,5,6	D 5
Lee ^{40,41}	V 1,7	V 2,3,4,5,6,8	D 3,5

Validity criteria

In many trials the information on several validity criteria was poorly reported. The randomisation procedure [V2] was adequately reported for 1 trial only¹⁹, and prognostic status at baseline [V3] for no more than 3 trials^{19,25,28}. In addition, information on co-interventions was often insufficient [V6].

Only 1 trial¹⁹ satisfied all 8 validity criteria, another 3 trials²⁰⁻²² satisfied 6 validity criteria. Three trials^{28,31,37} appeared to be flawed by a large proportion of treatment withdrawals [V4], 2 trials^{26,37} by a large proportion of missing values [V5], 9 trials^{25,27,28,31,34-39} by lack of blinding of intervention [V7] and 3 trials^{25,30,39} by lack of blinding of outcome assessment [V8].

Data extraction criteria

Study sizes [D1] were small: 6 trials^{25,26,29,33-35,39} compared groups of 25 patients or more, and 4 trials^{21,27,36,40} compared groups of 15 to 25 patients. All other trials included even smaller study populations. Data on outcome measures [D5] were poorly reported. Eleven^{19,24-26,30,32-36,38,39} trials provided sufficient data for the calculation of 95% confidence intervals.

Trial characteristics

Table 3 outlines the study population, intervention, follow-up and reported results of the assessed trials. Again, the trials are ordered by the number of fulfilled validity criteria.

In 9 trials^{19,20,22,23,25,26,28,30,33} participation was restricted to narrowly defined diagnostic categories (e.g. rotator cuff tendinitis), while other trials included a wide variety of soft-tissue disorders (e.g. painful shoulder, periarthritis humeroscapularis).

For 8 trials^{23,26-28,35,37,38,40} symptom duration at baseline was not specified as an entry criterion. Another 8 trials^{19,21,22,29,31-33,36} included patients with a symptom duration of less than 3 months at baseline, whereas in the remaining 4 trials symptom duration at baseline had to exceed 3 months.

Ultrasoundtherapy was studied in 6 trials^{19,23,28,29,38,39}, different modalities of thermotherapy in 4 trials^{26,37,38,40}, and low-level-lasertherapy in 4 trials^{22,30,32,33}. Three trials concerned magnetotherapy^{20,21,26} or manipulations or mobilisations^{27,31,36}, 2 trials involved electrotherapy^{28,35} or coldtherapy^{31,39}, and 1 trial evaluated an exercise program²⁵.

Six trials^{26,28,31,35,38,39} compared two or more modalities of physiotherapy, 7 trials^{19,20,22,25,29,32,33} compared physiotherapy with placebo treatment, while 9 trials^{24,25,27,31,32,37-40} compared physiotherapy with another intervention (mainly analgesics, NSAIDs and steroid injections). Furthermore, 3 trials^{21,31,36} included a control group without any treatment.

Results from long-term follow-up assessment (at least 2 months after randomization) were available from 4 trials^{21,25,36,39}. Follow-up in all other trials was restricted to outcome assessment directly after completion of treatment, usually 3 or 4 weeks after randomisation.

Treatment efficacy

Four^{19,23,28,29} out of 6 trials that studied the effect of ultrasoundtherapy satisfied 4 or more validity criteria, although none of the trials demonstrated evidence in favour of ultrasoundtherapy. Ultrasoundtherapy was not found to be superior to coldtherapy and

steroid injections³⁹, NSAIDs and acupuncture²³, TENS²⁸, analgesics and iontophoresis³⁸. Moreover, ultrasoundtherapy did not appear to be efficacious in placebo-controlled trials^{19,23,29}.

Two^{22,30} of the 4 trials that studied the efficacy of low-level-lasertherapy satisfied 4 or more validity criteria. Saunders et al²² could not demonstrate significant differences between active and placebo laser. Although Vecchio³⁰ did not report any significant differences, our calculations of the 95% CI demonstrate very small differences in favour of active low-level-lasertherapy. Two other trials with unsatisfactory methods reported effects in favour of the short-term efficacy of low-level-lasertherapy compared with placebo^{32,33} or with NSAIDs³².

Transcutaneous electrical stimulation did not appear to be more effective than ultrasoundtherapy²⁸ or than another electric modality³⁵. We could not find any placebo-controlled trial on electrotherapy.

Two placebo-controlled trials on pulsed electromagnetic fields^{20,26} satisfied 4 or more validity criteria and reported favourable results for active treatment. However, when analyzed according to the intention-to-treat principle, the results of Chard²⁶ appeared to be not statistically significant. Magnetic treatment did not appear to be efficacious when compared with no treatment²¹.

Coldtherapy did not prove to be more efficacious than ultrasoundtherapy³⁹, steroid injection^{31,39}, mobilisations or no intervention³¹. Different thermotherapy modalities did not show superior efficacy when compared with placebo^{26,37,38}, steroid injections and analgesics⁴⁰.

Exercises were equally effective as surgery in patients with a stage II impingement syndrome, but proved to be efficacious when compared with placebo lasertherapy²⁵. When compared to no intervention^{31,36}, mobilisations and manipulations did not contribute to recovery, nor did they prove to be superior to steroid injections^{27,31} or coldtherapy³¹.

Discussion

This systematic review is based on the reports of 20 randomized clinical trials. Its purpose is to assess whether physiotherapy contributes to the recovery of patients suffering from soft-tissue shoulder disorders. A standardized methods assessment is used in order to minimize bias.

Methods assessment

The methods assessment revealed that for only one trial¹⁹ all information was reported that was needed for validity assessment and data extraction. Many trials provided insufficient information for at least 2 validity criteria. Poor reporting might hide flaws, and so hinders the interpretation of trial results. Lack of information was most prominent for the randomisation procedure [V2], baseline similarity of treatment groups [V3] and co-interventions [V6].

Schulz et al⁴² provided empirical evidence of bias for trials with inadequate concealment of treatment allocation [V2] and lack of blinding [V7,V8]. There is reason to believe that lack of prognostic comparability at baseline [V3], withdrawals [V4] and missing data [V5] are also related to success of treatment and therefore represent major sources of bias^{43,44}.

Table 3. Trial characteristics: study populations, interventions and results.

Fist author ^{ref.}	Diagnosis Symptom duration	Interventions (number of randomized patients)
Downing ¹⁹	Supraspinatus tendinitis, Subacromial bursitis, Adhesive capsulitis ≥ 1 month	i Ultrasound, continuous, 1 MHz, 1.2 W per cm ² , 6 minutes, 3 times per week, 4 weeks (11) ii Placebo ultrasound, 3 times per week, 4 weeks (9)
Binder ²⁰	Rotator cuff tendinitis, ≥ 3 months	i Pulsed electromagnetic fields (PEMF; 73 Hz), 4 weeks: 1 hour, 5-9 times daily (15) ii Placebo PEMF, 4 weeks: 1 hour, 5-9 times daily (14)
Leclaire ²¹	Painful shoulder with ≥ 20% ROM limitation > 2 months	i Magnetotherapy, session 1-6: 10 Hz, 30 Gauss; session 7-17: 15 Hz, 40 Gauss; session ≥ 17: 30 Hz, 60 Gauss; 30 minutes per session (22) ii No magnetotherapy (25) - Both groups: 3 sessions per week ≤ 12 weeks; adjuvant hot packs (20 minutes) plus manual stretching (5 minutes) and daily home exercises (20 minutes)
Saunders ²²	Supraspinatus tendinitis ≥ 4 weeks	i Laser, Ga-Al-As diode, 820 nm, 40 mW, 5 kHz probe, 30 J/cm ² (12) ii Placebo laser (12) - Both groups: 9 sessions of 3 minutes, 3 per week
Berry ^{23,24}	Shoulder-cuff lesions Not specified	i Ultrasound therapy (12) ii Tolmetin sodium 1200 mg daily for 4 weeks plus prednisolone injection (12) iii Tolmetin placebo tablets plus prednisolone injection (12) iv Tolmetin placebo tablets plus placebo ultrasoundtherapy (12) v Acupuncture (12)
Brox ²⁵	Rotator cuff disease; stage II impingement syndrome ≥ 3 months (< 1 year: 10%; 1-3 years: 22%; > 3 years 47%)	i Daily home exercises with 2 supervised sessions per week; 6 weeks (50) ii Placebo soft laser 2 session per week; 6 weeks (30) iii Arthroscopic bursectomy and resection of acromion (partial) and coracoacromial ligament (45)
Chard ²⁶	Rotator cuff tendinitis > 3 months	i Pulsed electromagnetic fields (PEMF; 72 Hz), 8 weeks, 8 hours daily (25) ii PEMF (72 Hz), 8 weeks, 2 hours daily (25)
Dacre ²⁷	Painful stiff shoulder Not specified	i Physiotherapy only (mainly mobilisations) (20) ii Triamcinolone injection only 1x 20 mg (22) iii Physiotherapy plus triamcinolone injection (20)
Herrera-Lasso ²⁸	Bicipital tendinitis Supraspinatus tendinitis Subdeltoid bursitis- Periarthritis Humeroscapularis Not specified	i Ultrasound, 10 minutes, progressive dosage 0.5 to 1 W/cm ² (15) ii TENS (50 Hz), 20 minutes (15) - Both groups: 2 to 5 sessions per week, 13 sessions - Both groups: adjuvant pendular exercises plus infrared heat (240 W), 20 minutes, 60-90 cm distance
Nykänen ²⁹	Painful shoulder Not specified	i Ultrasound, 1 MHz, 1:4 on-off pulse ratio, 1 W/cm ² , 5 cm ² ERA, 10 minutes (35) ii Placebo ultrasound (37) - Both groups: 10-12 sessions, 3-4 per week - Both groups: In-patient rehabilitation exercise program

Results (intentions-to-treat)	Differences between groups (95% confidence interval)
Success rates at 4 weeks: free from pain or minimal interference of pain with daily living (n): (i) 7; (ii) 4; Changes since baseline at 4 weeks: Internal rotation ($\bar{x} \pm \text{sd}$) (i) $10^\circ \pm 4$ (ii) $1^\circ \pm 2$ No significant differences for flexion, abduction or external rotation.	Success rates: 20% (-23, 63) Internal rotation: 9 (6, 12)
Pain and ROM median improvement at 4 weeks: significant differences in favour of active PEMF.	Only graphical data presentation
No significant differences: Pain at 12 weeks (0-4 scale, $\bar{x} \pm \text{sd}$) (i) 1.6 ± 0.6 (ii) 1.4 ± 0.7 Abduction ($\bar{x} \pm \text{sd}$) 4 weeks (i) $115^\circ \pm 17$ (ii) $120^\circ \pm 13$; 8 weeks (i) $130^\circ \pm 22$ (ii) $136^\circ \pm 15$; 12 weeks (i) $135^\circ \pm 20$ (ii) $142^\circ \pm 13$ Flexion ($\bar{x} \pm \text{sd}$) 4 weeks (i) $149^\circ \pm 15$ (ii) $145^\circ \pm 10$; 8 weeks (i) $159^\circ \pm 19$ (ii) $167^\circ \pm 13$; 12 weeks (i) $163^\circ \pm 17$ (ii) $171^\circ \pm 12$ ADL: no significant differences, but no data presented.	No improvement scores, only absolute values
No significant differences between groups for pain and muscle force.	Only graphical data presentation
Success rates (n) after 4 weeks: (i) 6 (ii) 5 (iii) 6 (iv) 9 (v) 5 Significant improvement of mean pain and ROM scores; no significant differences between groups.	Success rates: i versus iv: -25% (-62, 12) i versus ii: 8% (-32, 48) i versus v: 8% (-32, 48)
Neer score (medians) 3 months (i) 74 (ii) 61 (iii) 84; 6 months (i) 86 (ii) 66 (iii) 87 Pain (medians) 3 months (i) 15 (ii) 15 (iii) 25; 6 months (i) 25 (ii) 15 (iii) 25 Function (medians) 3 months (i) 24 (ii) 20 (iii) 28; 6 months (i) 25 (ii) 15 (iii) 28 ROM (medians) 3 months (i) 22 (ii) 19 (iii) 21; 6 months (i) 23 (ii) 19 (iii) 22	Median pain score: iii versus i 3 months: 5 (0, 10); 6 months: 5 (0, 10) Median Neer score: iii versus i 3 months: 7.5 (0, 15); 6 months: 4 (-2, 11)
Success rates after 4 weeks (i) 12 (ii) 14 Success rates after 8 weeks (i) 13 (ii) 17	Success rates: 4 weeks: - 8% (-36, 20) 8 weeks: -16% (-43, 11)
Improvement of ROM in all directions. No significant differences between groups for pain and ROM.	Only graphical data presentation
No significant differences for improvement of pain, abduction and flexion.	Only graphical data presentation
No significant differences: Pain (1-5 scale, $\bar{x} \pm \text{sd}$) 4 weeks (i) 2.5 ± 0.7 (ii) 2.4 ± 0.9 Pain (4-20 scale, $\bar{x} \pm \text{sd}$) 4 months (i) 13 ± 5 (ii) 13 ± 4 ; 12 months (i) 13 ± 5 (ii) 13 ± 4 ADL (2-10 scale) 4 weeks (i) 4.2 ± 1.3 (ii) 4.4 ± 1.4 ADL (3-14 scale) 4 months (i) 6.9 ± 2.4 (ii) 7.4 ± 2.0 ; 12 months (i) 7.0 ± 2.4 (ii) 7.3 ± 2.3 Abduction ($\bar{x} \pm \text{sd}$) 4 weeks (i) $145^\circ \pm 27$ (ii) $146^\circ \pm 30$	No improvement scores, only absolute values

Table 3 (continued)

First author ^{ref.}	Diagnosis Symptom duration	Interventions (number of randomized patients)
Vecchio ³⁰	Rotator cuff tendinitis Not specified	i Laser (Ga-As-AL) 830 nM, 30 MW, 3 J/cm ² (19) ii Placebo laser (Ga-As-AL) 830 nM, 30 MW, 3 J/cm ² (16) - Both groups 8 weeks, 2 sessions of 10 minutes per week
Bulgen ³¹	Frozen shoulder > 1 month	i Intra-articular plus intrabursal methyl-prednisolone 20 mg and lignocaine; 3 in 1 week (11) ii Maitland mobilisations; 3 sessions per week, 6 weeks (11) iii Ice packs plus proprioceptive neuromuscular facilitation; 3 sessions per week, 6 weeks (12) iv No intervention (8) - All groups: analgesics, diazepam and pendular exercises, daily: 3 minutes per hour
England ³²	Supraspinatus or bicipital tendonitis Not specified	i Laser, infrared 904 nM, 3 mW, 5 minutes, 3 times per week, 2 weeks (10) ii Placebo laser, 5 minutes, 3 times per week, 2 weeks (10) iii Naproxen sodium, 550 mg tablets, twice daily, 2 weeks (10)
Gudmundsen ^{33,34}	Rotator cuff tendinitis ≤ 6 months	i Laser (Ga-As), pulsed 904 nM, 7.2 J/cm ² (47) ii Placebo laser (He-Ne), continuous 632 nM, 2.4 J/cm ² (44) - Both groups: 8 sessions of 8 minutes
Knüsel ³⁵	Levator scapulae syndrome Not specified	i Electrotherapy, constant current TENS, 60 Hz (30) ii Electrotherapy, constant voltage Dynatronic, 100 Hz (30) - Both groups: 12 sessions, 3 weeks
Thomas ³⁶	Frozen shoulder ≥ 2 months	i Manipulation: forced abduction to 90° with full internal and external rotation (15) ii No manipulation (15) - Both groups: started with subacromial injection 50 mg hydrocortisone acetate and 20 mg intravenous valium
Biswas ³⁷	Periarthritis Humeroscapularis Not specified	i Hydrocortisone injections (18 + 7) ii Short-wave diathermia (17 + 7) iii Aspirine 700 mg 3 times daily (12 + 7) - All groups: non painful active exercises and passive mobilisation in all directions - 120 Patients randomized
Delacerda ³⁸	Shoulder girdle myofascial syndrome Not specified	i Analgesics and muscle relaxants, 10 days (7) ii Ultrasound 4 minutes, 1.25-1.5 Watt/cm ² and 20 minutes thermotherapy, hydrocollator packs, 1 time daily, 10 days (8) iii Iontophoresis: 4% dexamethasone sodium phosphate and 4% lidocaine, 5 mA, 15 minutes daily, 10 days (8)
Knorre ³⁹	Rheumatoid conditions > 6 months	i 1x 40 mg Intra-articular triamcinolone (30) ii Ultrasound therapy (30) iii Cryotherapy: icepacks (30)
Lee ^{40,41}	Periarthritis Humeroscapularis Not specified	i Hydrocortisone intra-articular 1x 25 mg plus exercise therapy (15) ii Hydrocortisone 1x 25 mg in biceps tendon sheath plus exercise therapy (18) iii Infra-red thermotherapy plus exercise therapy (17) iv Analgesics only (15)

ADL = Activities of daily life

Results (intentions to treat)	Differences between groups (95% confidence interval)
Improvement for pain on movement: 4 weeks (i) 2.7 ± 0.8 (ii) 1.2 ± 0.9 ; 8 weeks (i) 3.6 ± 1.0 (ii) 1.8 ± 1.2 Improvement for functional status: 4 weeks (i) 2.9 ± 0.6 (ii) 2.0 ± 0.8 ; 4 weeks (i) 3.6 ± 0.9 (ii) 2.9 ± 0.7	Pain on movement (mean), at 8 weeks: 1.8 (1.1, 2.5) Functional status (mean) at 8 weeks: 0.7 (0.0, 1.4)
Improvement of ROM in all directions. Pain and ROM improvement: no significant differences.	Only graphical data presentation
Improvement scores (0-10 cm scale) at 2 weeks: i vs ii: movement 2; pain 2.5; stiffness 1; function 1.5. i vs iii: pain 2; differences for movement, stiffness and function not significant (no data) iii vs ii: movement 1.3, function 1; differences for stiffness and pain not significant (no data)	Pain improvement (median): i versus ii: 2.5 (2, 3) i versus iii: 2 (1.0, 3.5)
Success rates (number of patients much better or free of symptoms): (i) 42 (ii) 18.	Success rates: 48% (31, 65)
Success rates 3 weeks (number of patients with good/very good result): (i) 19 (ii) 21 Pain improvement (0-100 scale, $\bar{x}$) 3 weeks: 40 (i) 44 (ii)	Success rates: 7% (-15, 29)
Success rates 3 months (% patients substantially improved): (i) 80% (ii) 47% Number of patients $\geq 90^\circ$ abduction improvement: 1 month (i) 2 (ii) 0; 3 months (i) 6 (ii) 2 Number of patients without night pain: 1 month (i) 1 (ii) 0; 3 months (i) 4 (ii) 2 Number of patients without disability: 1 month (i) 2 (ii) 0; 3 months (i) 7 (ii) 2	Success rates: 33% (1, 65) $\geq 90^\circ$ abduction: 27% (-3, 57)
Success rates: symptom duration < 3 months after baseline (based on 47 out of 120 included patients) (i) 50% (ii) 47% (iii) 58%	Number of patients after randomization unclear
Success rates (number of patients with painless full ROM abduction): (i) 4 (ii) 6 (iii) 8	Success rates: ii versus i: 18% (-29, 65) iii versus i: 43% (6, 80) iii versus ii: 25% (-5, 55)
Success rates: perceived benefit 'very good' at 2 weeks (i) 47% (ii) 50% (iii) 40%; at 12 weeks (i) 40% (ii) 50% (iii) 37% Only graphical data presentation of pain: group i significantly better after 12 weeks	Success rates at 2 weeks: ii versus i: 3% (-22, 28) ii versus iii: 10% (-15, 35)
ROM improvement significantly less in group iv No significant differences for pain and ADL	Only graphical data presentation

Efficacy research on physiotherapy for shoulder disorders appears to be very heterogeneous with respect to the compared treatments, the selection of study populations and the assessment of outcome. For instance, trials on the same modality (e.g. ultrasoundtherapy or low-level-lasertherapy) differ markedly with respect to [1] the way in which these therapies were administered, e.g. intensity, duration and frequency of administration, [2] type of control group, e.g. placebo, no or alternative treatment, [3] exclusion criteria, e.g. regarding specific soft-tissue disorders or symptom duration at baseline, and [4] follow-up measurements, e.g. timing of outcome assessment and choice of outcome measures. In addition, although sufficient duration of follow-up is important in the evaluation of the efficacy of physiotherapy for shoulder disorders, only 4 trials reported follow-up assessments at 2 months after randomization or later.

Treatment efficacy

Deficiencies in the data presentation frequently hampered calculation of 95% confidence intervals. Where confidence intervals could be calculated they proved to be wide and included zero. This also holds for trials with generally more acceptable methods^{19,23,26}. The type of control treatment was not related to the study results. Few of the assessed trials favoured the efficacy of physiotherapy. Considering the large number of small negative trials, statistical pooling of the results of trials with acceptable methods would have been useful. However, pooling was impeded by the heterogeneity of trials on the interventions, the poor quality of methods and data presentation.

Conclusion

Given the generally higher validity of placebo-controlled trials on ultrasoundtherapy and their outcomes it does not appear that this modality is efficacious for shoulder disorders. One placebo-controlled trial with generally more valid methods showed that PEMF was efficacious. All the other trials that report significant results are small and have unsatisfactory trial methods. Therefore, there is insufficient evidence to draw conclusions on the efficacy of low-level-lasertherapy, thermotherapy, coldtherapy, electrotherapy, exercise therapy and mobilisations. Future trials should study whether these physiotherapy modalities for shoulder disorders are superior to a wait-and-see policy, steroid injections, analgesics or anti-inflammatory drugs. This should be particularly interesting for exercise therapy and mobilisations, which despite their frequent use for shoulder disorders rarely have been subjected to scientific scrutiny in randomized clinical trials.

Prevalent flaws, such as many withdrawals, many missing data and a lack of blinding during treatment and outcome assessment, should be avoided in future trials. Furthermore, standards of reporting trials should prevent confusion about the validity of trial methods and ensure adequate data analysis and presentation of pertinent data.

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Chapter 3

Steroid injections for shoulder disorders

A Systematic review of randomized clinical trials

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Abstract

Background Patients with shoulder disorders are believed to benefit considerably from steroid injections. However, the controversy on their efficacy persists.

Purpose The study was designed to assess the efficacy of steroid injections for shoulder disorders.

Method A systematic computerized literature search in MEDLINE (Index Medicus 1/1966-11/1995) and EMBASE (Excerpta Medica 1/1984-11/1995) was conducted, supplemented with citation tracking of all relevant publications. Studies published before November 1995 were selected if steroid injections were randomly allocated to patients with shoulder disorders and when clinically relevant outcome measures were reported. Because the validity of study outcomes depends heavily on the strength of methodological quality, the methods were assessed systematically by two 'blinded' independent reviewers. This resulted in a method score (maximum 100 points) that was based on four categories: study population, interventions, measurement of effect and data presentation and analysis. Confidence intervals for the differences between groups in success rates were calculated in order to summarize the efficacy of steroid injections.

Results Only three out of the 16 studies scored more than 50 points, indicating a generally poor quality of methods. Most studies reported small sample sizes. The flaws most often found were incomparability of co-interventions and poor blinding of therapist. The methods assessment was frequently hampered by incomplete information about randomisation, prognostic comparability, compliance, outcome measures included, blinding of patients and blinding of outcome measurement.

Conclusions The evidence in favour of the efficacy of steroid injections for shoulder disorders is scarce. The methods of most studies appear to be of poor quality. The few studies that appear to be credible do not provide conclusive evidence about which patients at what time in the course of shoulder disorders benefit most from steroid injections.

Introduction

Shoulder disorders

About 10% of the population suffer from one or more episodes of shoulder disorders in the course of their life¹. Pain and stiffness in the deltoid region, which cause limitations of daily activities, are the commonest complaints of these patients. Pain is elicited or aggravated by movement and usually restricts the range of movement. Pain when lying on the impaired shoulder results in problems with sleeping^{1,3}. Most often these shoulder complaints are caused by periarticular soft tissue impairment^{3,4}. A minority of all complaints originate from neurological or generalized musculoskeletal conditions, neoplasms or referred pain from the neck or from internal organs⁴. Five per cent of all consultations in general practice relate to shoulder disorders^{1,5,6}. Out of all newly presented episodes, 23% resolve within one month, 51% within six months, and 59% within a year [Van der Windt et al, submitted for publication].

Injection

Twelve per cent of all patient-physician contacts for shoulder disorders involve local steroid injections⁷. Steroid injections are commonly used in combination with analgesics, NSAIDs, rest, physical therapy or exercises. In the Netherlands, injection therapy is given in approximately 20% of all episodes of shoulder disorders⁸. Patients with shoulder disorders are believed to benefit considerably from steroid injections⁹. However, controversy over their efficacy persists. Anti-inflammatory effects of steroid injections are to relieve pain, improve or maintain joint function and diminish disability^{7,10}.

The postulated mechanisms for the effects of steroid injections have not been supported by sufficient clinical empirical evidence. Steroid injections should inhibit the synthesis of inflammation-mediating substances (e.g. prostaglandins), stabilize mast cells and inhibit cellular activity; pain-reducing effects have been reported¹². In addition, a decrease of tissue calcification and iron deposition has been reported, together with increased vascularization, permeability of the synovial membrane and viscosity of synovial fluid^{7,10-12}. Regenerating effects on damaged articular cartilage¹³ or slowing of the progression of cartilage attrition^{7,12} have not been demonstrated.

Adverse clinical effects of steroid injections have not been systematically investigated. Dermal atrophy, bacterial arthritis, hemarthrosis and thrombophlebitis are attributed to technical artefacts^{7,12,14}, while urticaria and facial flushing are ascribed to suspension preservatives⁷. Charcot arthropathy is reported in about 1% of all injections and systemic post-injection flare (i.e. acute steroid synovitis with fever), paresis and vertigo in about 2% of all injections. Ligamentous laxity, joint instability and calcification or rupture of tendons and joint capsules, caused by collagen necrosis and increased soft tissue degeneration, are associated with depot injections of long-acting steroids and repeated injections of the same joint^{12,13}. Therefore, repeated injections in the same joint within a short period of time should be avoided. Zuckerman recommended injecting the same joint only once in every six weeks, with a maximum of three times a year¹³.

In this systematic review we summarize the results of randomized clinical trials (RCTs) on the efficacy of steroid injections for shoulder disorders. While RCTs offer the best

possibility for a valid evaluation of treatment efficacy¹⁵⁻¹⁷, many aspects of design, conduct and analysis require careful handling for conclusions to be valid. In order to minimize bias we assessed the methods of available trials according to generally accepted methodological requirements for intervention research¹⁵⁻²⁰.

Methods

We identified relevant publications by means of computerized searches and citation tracking. The search strategy included MEDLINE (Index Medicus 1/1966-11/1995) and EMBASE (Excerpta Medica 1/1984-11/1995). Potentially relevant papers were harvested from a total of 105 records in Index Medicus and a total of 101 records in Excerpta Medica. In addition, relevant citations of available papers were traced.

For this systematic review, we included studies that met the following conditions:

- Patients had shoulder pain at the moment of inclusion;
- At least one of the treatment regimens included steroid injections;
- Treatment regimens were allocated by a random procedure;
- Clinically relevant outcome measures were included (e.g. treatment success, pain, mobility or functional status);
- Results were published as a full report before November 1995.

GJMGH selected the study reports. In order to minimize potential reviewer bias, he blinded papers for author(s), journal identification, results and conclusions. BWK and JK independently assessed the blinded reports with respect to the quality of study methods. Then, still blinded, they resolved disagreement in a consensus discussion. Our assessment of methods was based on four categories (Table 1): (1) study population, (2) interventions, (3) measurement of effect and (4) data presentation. We divided these four categories into 15 different criteria (A-O).

Table 1. Criteria list for a methods assessment of randomized clinical trials of steroid injections for shoulder disorders.

Criteria	Weight
Study population	
A Selection	4
B Adequate randomisation procedure	5
C Study size	15
D Comparability of relevant prognosis at baseline	10
E Drop-outs described for each treatment group separately	6
F Loss-to-follow-up described for each treatment group separately	5
Interventions	
G Description of treatment(s)	12
H Co-interventions avoided (or comparable)	4
Measurement of effect	
I Patients blinded	4
J Therapist blinded	4
K Observer blinded	4
L Relevant outcome measures	10
M Blinded outcome measurement	5
N Duration of follow-up	4
Analysis and results	
O Adequate analysis and presentation	8

- A Two points if target population is defined by means of explicit selection criteria; 2 points if selection is restricted to a population homogenous for relevant prognostic markers (e.g. duration of complaints, painful arc, pain at night, radiating pain, prior treatment).
- B Five points if number generation and concealed allocation is used for treatment allocation
- C Five points if smallest group is bigger than 25 patients immediately after randomisation; 10 points if more than 50 patients; 15 points if more than 75 patients.
- D Two points each if study groups are comparable at baseline for (1) duration of the complaint; (2) baseline scores for outcome measures; (3) age; (4) number of relapses; (5) radiating pain.
- E Six points if no patients withdrew after randomisation (drop-outs). 2 points if the number of drop-outs is presented for each study group separately; 4 additional points if reasons for withdrawal are specified for each study group separately.
- F Loss-to-follow-up: {1 minus [the number of patients at the main moment of effect measurement for the main outcome measure (if not stated according to the reviewers), divided by all randomized patients]}, times 100%.
One point if loss-to-follow-up is less than 20% in each group; 4 points if it is less than 10% in each group.
- G One point for every adequately described feature of injection and reference treatment: treatment type; steroid type or modality; needle placement or application technique; intensity or solution; treatment number and frequency; compliance. 2 additional points if both placebo and pragmatic control group are included.
- H One point if co-interventions are comparable between the groups; 3 points if co-interventions are standardized or avoided in study design.
- I Two points if blinding of patients was attempted or only naive patients were enrolled, 2 additional points if blinding for treatment contrast proved successful.
- J Two points if blinding of therapists was attempted, 2 additional points if blinding for treatment contrast proved successful.
- K Two points if blinding of observer was attempted, 2 additional points if blinding for treatment contrast proved successful.
- L Two points for every assessed outcome measure: (1) pain; (2) success rate or proportion for global measure of improvement or recovery; (3) functional status (activities of daily living); (4) mobility (range of motion); (5) medical consumption (e.g. medication, surgery).
- M One point for every blindly assessed outcome measure (see L)
- N Two points if outcomes were assessed immediately after the last treatment; 2 additional points if this was done 3 months or longer after randomisation.
- O Five points if data for most important outcome measure on the most important moment of effect measurement are adequately presented (frequencies or mean & standard deviation or centiles). 3 additional points for an adequate analysis, with adjustment for drop-outs, loss-to-follow-up, missing values, non-compliance and co-interventions if appropriate.

Similar criteria are used in peer review systems of journals²¹⁻²⁴ and have been used in other systematic reviews²⁵⁻³³. For this review, we adjusted the criteria for application to steroid injections and shoulder disorders.

For each of the 15 criteria (A-O), we assigned a weight relative to its putative importance for validity, precision or clinical relevance. The information from the papers about each criterion was analysed. If sufficient information was reported the likelihood of potential bias was evaluated. If bias was unlikely, the criterion was rated as satisfied. For each study, we calculated a method score by summing the weights for all criteria satisfied. The studies were subsequently ranked according to this sumscore. The theoretical maximum sumscore of 100 points could be obtained when the design, conduct and results of a study were adequately reported and bias was considered to be unlikely in all criteria.

Incomplete information about study methods may hamper the assessment of the quality of methods. The sumscore of the weights for insufficiently reported criteria indicates the amount and magnitude of this incomplete information.

Success-rates were determined for each intervention group, by dividing the number of documented successes at the end of the intervention period by the number of patients randomly allocated to the intervention. These calculations were made according to the intention-to-treat principle; drop-outs and loss-to-follow-up were assumed to represent failures. The differences between the success rates, and the corresponding 95% confidence intervals (95% CIs) were calculated for all relevant comparisons.

Results

Methodological quality

We identified 23 papers reporting studies that met our five conditions for inclusion in the blinded method assessment. We excluded five studies: one³⁴ because it was only published as an abstract; one³⁵ because the results of patients who received injection could not be identified separately; and three studies³⁶⁻³⁸ without a contrast for injection between intervention groups. The quality of methods of studies that are reported in the remaining 16 papers and 2 theses³⁹⁻⁵⁶ was assessed.

Initial disagreement between the two independent reviewers was found mostly to result from reading errors. All discrepancies were easily resolved during a consensus discussion, the methods scores are based on the reviewers full agreement. For two studies that have been reported more than once^{48,49,55,56}, we calculated the method scores from the combined information. Hence, the results of 16 RCTs are presented. Table 2 presents, for each study, the points assigned to each criterion and the method score.

Table 2. Results of the methods assessment of the randomized clinical trials of steroid injections for shoulder disorders

First author ^{ref}	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	Method score	Information incomplete
	4	5	15	10	6	5	12	4	4	4	4	10	5	4	8		
Petri ³⁹	2	5	5	2	-	5	12	-	2	2	2	8	4	2	8	59	26
Adebajo ⁴⁰	4	-	-	6	6	5	12	-	2	-	2	6	3	2	8	56	16
Vecchio ⁴¹	4	-	5	6	6	5	10	3	2	-	-	6	-	2	5	54	36
De Jong ⁴²	2	5	-	6	6	1	8	3	2	2	2	6	2	2	-	47	31
Richardson ⁴³	2	-	5	6	2	1	8	3	2	-	2	4	2	2	5	44	37
White ⁴⁴	4	-	-	8	2	-	8	-	2	-	2	6	2	2	5	41	45
Withrington ⁴⁵	-	-	-	4	6	5	8	3	2	-	2	4	2	2	3	41	34
Jonquière ⁴⁶	4	5	10	4	2	-	8	-	-	-	2	6	-	4	5	40	44
Jacobs ⁴⁷	2	-	-	4	6	1	8	-	-	-	2	6	-	4	5	38	35
Berry ⁴⁸	2	-	-	2	6	5	6	-	-	-	2	6	1	2	5	37	29
Rizk ⁵⁰	4	-	-	6	2	1	8	3	-	-	2	4	1	4	-	35	40
Hollingsworth ⁵¹	2	-	5	2	-	-	8	-	2	-	2	2	1	2	5	31	53
Knorre ⁵²	-	-	5	4	-	-	8	-	-	-	-	4	-	2	5	28	47
Dacre ⁵³	4	-	-	4	-	1	2	-	-	-	2	4	1	4	-	22	49
Bulgen ⁵⁴	4	-	-	-	-	-	6	-	-	-	2	4	-	4	-	20	57
Lee ⁵⁵	2	-	-	-	-	-	4	-	-	-	-	2	-	2	-	10	51

The main features of the design of the sixteen RCTs and their results are given in Table 3. All studies scored less than 60 points. Only three studies³⁹⁻⁴¹ attained a method score of more than 50 points, indicating the overall poor methodological quality of most studies.

In general, studies proved to be methodologically sound with respect to (A) patient selection, (E) reported drop-outs, (G) intervention descriptions, and (O) analysis and presentation of data. Nevertheless, the range of the method score is wide (average 37 points, range 10-59). The most prevalent flaws were in (H) incomparability of co-interventions and (J) poor blinding of therapist. In addition, most study sizes (C) were small.

The sumscore for insufficiently reported criteria varied widely (average 39 points, range 16-57). Methods assessment was often hampered by incomplete information about (B) the randomisation procedure, (D) prognostic comparability of study groups at baseline, (G) compliance with interventions, (L) outcome measures, and blinding (I) of patients, (K) of observer and (M) during effect measurement. In addition, reporting of long-term adverse effects was deficient.

Efficacy of steroid injections

Whereas reporting of data for treatment success and pain relief generally was informative enough to support the conclusions, several authors drew conclusions about additional outcome measures for which no data were presented. We used differences in proportions of treatment success in order to evaluate efficacy of steroid injections. Poor presentation of data impeded these calculations for five studies^{42,47,53-55}. In only one study⁵⁰ did our intention-to-treat analysis result in slightly different success rates compared with the results reported in the original publication.

In Table 4, the 95% confidence intervals are presented for comparisons between steroid injections and placebo interventions. The studies are ranked according to quality of methods. The two studies^{39,40} with the highest method scores reported a significantly higher success rate for steroid injection (95% CIs exclude zero), but in only one study⁴⁰ did the lower limit of the 95% CI exceed a difference in success rate of 20%.

Table 5 shows the 95% CIs for comparisons between steroid injections and competing treatment modalities (mainly physiotherapy or medication). In two of the three studies with method scores above 50 points^{39,40}, the lower limit of the 95% CI exceeded a 10% difference in success rate in favour of steroid injection. Other studies reporting results in favour of steroid injection^{42,47,51} did not reach a method score of 50 points.

Discussion

Our search strategy in the medical literature identified 16 studies that met our inclusion criteria. It is not very likely that we have missed large RCTs by our rather extensive searches. Nevertheless, additional relevant studies might have remained unpublished or have been published in journals that are difficult to retrieve.

Although the checklist used is not exhaustive, it represents a high standard for quality of methods. Therefore, the maximum score of 100 points is probably not easily reached. However, it is disappointing to find that the quality of methods of the published RCTs is so low. This indicates that serious bias was present in most of the available studies. In addition, incomplete information about important features of design and conduct frequently hampered the assessment of the quality of methods. Incomplete information can indicate only poor reporting, but can also disguise additional flaws. Guidelines have been proposed to improve the reporting of RCTs^{57,58}. It is hoped that better reporting of trials will also improve the informativeness of systematic reviews.

Table 3. Details of randomized clinical trials of steroid injections for shoulder disorders

First author ^{ref.}	Method score	Diagnostic group symptom duration	Steroid injections (number of patients)
Petri ³⁹	59	Painful shoulder ≤ 6 months	i 1x 40 mg Intrabursal triamcinolone and lidocaine plus placebo naproxen (25) ii 1x 40 mg Intrabursal triamcinolone and lidocaine plus naproxen 1000 mg daily (25)
Adebajo ⁴⁰	56	Rotator cuff tendinitis ≤ 6 months	i 1x 80 mg Subacromial triamcinolone hexacetonide and lignocaine plus placebo diclofenac (20)
Vecchio ⁴¹	54	Rotator cuff tendinitis ≤ 3 months	i 1x 40 mg Subacromial methylprednisolone plus lignocaine (28)
De Jong ⁴²	47	Capsulitis No restriction	i 3x 40 mg Intra-articular triamcinolone (25) ii 3x 10 mg Intra-articular triamcinolone (32)
Richardson ⁴³	44	Painful shoulder > 6 months	i 2x Intra-articular and intrabursal 25 mg prednisolone acetate plus distalgalic (54)
White ⁴⁴	41	Rotator cuff tendinitis No restriction	i 1x 40 mg Intrabursal triamcinolone acetone plus placebo indomethacin (20)
Withrington ⁴⁵	41	Supraspinatus tendinitis ≤ 3 months	i 1x Supraspinatus tendon 80 mg methylprednisolone and lignocaine (12)
Jonquière ⁴⁶	40	Painful shoulder > 6 months	i Cyriax treatment: local triamcinolone, local anaesthesia, physiotherapy (22)
Jacobs ⁴⁷	38	Capsulitis No restriction	i 3x 40 mg Intra-articular triamcinolone (15) ii 3x 40 mg Intra-articular triamcinolone plus distension (18)
Berry ⁴⁸	37	Shoulder cuff lesion No restriction	i 1x 40 mg Intra-articular methyl-prednisolone and lignocaine plus placebo tolmetin sodium (12) ii 1x 40 mg Intra-articular methyl-prednisolone and lignocaine plus tolmetin sodium 1200 mg daily (12)

Reference treatment(s) (number of patients)	Reported results ¹	Authors' conclusions ²
iii 1x Intrabursal lidocaine plus placebo naproxen tablets (25) iv 1x Intrabursal lidocaine plus naproxen 1000 mg daily (25)	Success rates after 2 weeks: (i) 8% (ii) 20% (iii) 4% (iv) 12% Success rates after 4 weeks: (i) 28% (ii) 28% (iii) 20% (iv) 8% Improved pain scores ($\bar{x} \pm s$) after 4 weeks: (i) 2.04 ± 0.31 (ii) 1.95 ± 0.35 (iii) 1.76 ± 0.31 (iv) 1.00 ± 0.32	Significant differences for success rate, pain, ROM, and functional status in favour of triamcinolone (i and ii)
ii 1x Subacromial lignocaine plus diclofenac 150 mg daily (20) iii 1x Subacromial lignocaine plus placebo diclofenac (20)	Success rates after 4 weeks: (i) 70% (ii) 30% (iii) 0% Improvement pain scores ($\bar{x} \pm s$) after 4 weeks: (i) 4.95 ± 0.74 (ii) 3.60 ± 0.67 (iii) 1.35 ± 0.74	Significant difference for success rate in favour of triamcinolone (i). Significant difference for pain ROM, functional status in favour of i and ii.
ii 1x Subacromial lignocaine (27)	Success rates after 12 weeks: (i) 32% (ii) 26% Improvement pain scores (median): after 2 weeks (i) 10 (ii) 7.5 after 4 weeks (i) 10 (ii) 8 after 12 weeks (i) 8 (ii) 8 Improvement pain scores: (x%) after 1 week: (i) 22% (ii) 7% after 3 weeks: (i) 40% (ii) 19% after 6 weeks: (i) 54% (ii) 31%	No significant differences for success rate, pain and ROM Significant differences for ROM, pain, functional status, sleep disturbance in favour of high dose triamcinolone (i)
ii 2x Intra-articular and intrabursal saline plus distalgalic (47)	Success rates: after 2 weeks (i) 33% (ii) 20% after 6 weeks (i) 53% (ii) 46%	No significant differences for success rate, ROM, and pain.
ii 1x Intrabursal saline plus indomethacin 100 mg daily (20)	Success rates after 6 weeks: (i) 45% (ii) 50% Improvement pain scores ($\bar{x} \pm s$): (i) 4.3 ± 5.2 (ii) 5.5 ± 8.3	No significant differences for success rate, pain and ROM.
ii 1x Supraspinatus tendon saline (13)	Success rates after 2 weeks (i) 58% (ii) 31% after 8 weeks (i) 42% (ii) 23% Improvement pain scores ($\bar{x}$): after 2 weeks (i) 3.7 (ii) 1.8 after 8 weeks (i) 2.7 (ii) 1.2	No significant differences for success rate, pain and ROM
ii Local anaesthesia, physiotherapy (36)	Success rates after 16 weeks: (i) 64% (ii) 72%	No significant differences for success rate and number of sick leave days
ii Distension only (14)	Improvement of abduction ($\bar{x} \pm s$): (i) 3.4 ± 2.2 (ii) 4.3 ± 2.2 (iii) 1.0 ± 3.8	Significant differences for ROM in favour of i and ii; no significant cant differences between i and ii.
iii Acupuncture (12) iv Ultrasound therapy (12) v Placebo ultrasound therapy (12)	Success rates after 4 weeks: (i) 50% (ii) 42% (iii) 42% (iv) 50% (v) 75% Improvement pain scores ($\bar{x}$): (i) 12 (ii) 10 (iii) 7 (iv) 7 (v) 30	No significant differences for success rates, pain and ROM.

Table 3. Continued

First author ^{ref}	Method score	Diagnostic group symptom duration	Steroid injections (number of patients)
Rizk ⁵⁰	35	Adhesive capsulitis ≤ 3 months	i 3x 40 mg Intra-articular methyl-prednisolone and lidocaine (16) ii 3x 40 mg Intra-bursal methyl-prednisolone and lidocaine (16)
Hollingworth ⁵¹	31	Painful shoulder No restriction	i 40 mg Methylprednisolone functional (39) ii 40 mg Methylprednisolone + lignocaine tender or trigger point injection (38)
Knorre ⁵²	28	Rheumatoid conditions > 6 months	i 1x 40 mg Intra-articular triamcinolone (30) ii ultrasound therapy (30)
Dacre ⁵³	22	Painful stiff shoulder No restriction	i 1x 20 mg Triamcinolone (22) ii 1x 20 mg Triamcinolone plus physiotherapy (mainly mobilisations) (20)
Bulgen ⁵⁴	20	Frozen shoulder > 1 month	i 3x 20 mg Intra-articular plus intra-bursal methyl-prednisolone and lignocaine (11)
Lee ⁵⁵	10	Periarthritis No restriction	i 1x 25 mg Intra-articular hydrocortisone acetate plus exercise therapy (15) ii 1x 25 mg Biceps tendon sheath hydrocortisone plus exercise therapy (18)

R ± s = mean ± standard deviation.

Table 4. Point estimates and 95% confidence intervals for the difference in success rates in studies comparing steroid injections with placebo treatment for shoulder disorders. The studies are ranked according to methodological quality.

First Author ^{ref}	Method score	Comparison	Difference in success rates	95% Confidence limits
Petri ¹⁹	59	i + ii versus iii + iv	14%	1, 27
Adebajo ⁴⁰	56	i versus iii	70%	50, 90
Vecchio ⁴¹	54		6%	-18, 30
Richardson ⁴³	44		7%	-13, 27
Withrington ⁴⁵	41		27%	-11, 65
Berry ⁴⁸	37	i versus v	-25%	-62, 12
Rizk ⁵⁰	35	i + ii versus iii + iv	-9%	-25, 9

Reference treatment(s) (number of patients)	Reported results ¹	Authors' conclusions ²
iii 3x Intra-articular lidocaine (8) iv 3x Intrabursal lidocaine (8)	Success rates after 4 weeks: (i + ii) 3% (iii + iv) 12% Improvement pain scores (R): at 4 wks (i) 0.1 (ii) 0.4 (iii + iv) 0.7 at 11 wks (i) 0.1 (ii) 0.3 (iii + iv) 0.7 at 24 wks (i) 0.1 (ii) 0.9 (iii + iv) 1.1	No significant differences for success rate, pain and ROM.
ii Ultrasound therapy iii Cryotherapy: icepacks (30)	Success rates: after 1 week (i) 60% (ii) 20% after 2 weeks (i) 59% (ii) 19%	Significant difference in favour of group i.
iii Physiotherapy only (20)	Perceived benefit "very good" according to patients: at 2 wks (i) 47% (ii) 50% (iii) 40% at 12 wks (i) 40% (ii) 50% (iii) 37%	Pain scores in group i after 12 weeks significantly better than in other groups.
ii Maitland mobilisations (11) iii Ice packs plus proprioceptive neuromuscular facilitation (12) iv Pendular exercises, analgesics, diazepam (8)	Only graphical data presentation.	No significant differences for pain or ROM.
iii Infra-red irradiation plus exercise therapy (17) iv Analgesics only (15)	Only graphical data presentation.	No significant differences, except for less improvement for ROM in group iv.

1 Reported data for improvement of pain or success rate (ratio of recovered/improved patients to those allocated to respective groups)

2 P-values < 5% were considered to be statistically significant, ROM = Range of motion.

Table 5. Point estimates and 95% confidence intervals for the difference in success rates in studies comparing steroid injections with currently applied treatment modalities for shoulder disorders. The studies are ranked according to methodological quality. Five studies^{42,47,53-55} provided insufficient data for the calculation of confidence intervals.

First Author ^{ref}	Method score	Comparison	Difference in success rates	95% Confidence limits
Petri ³⁹	59	i versus iv	20%	13, 27
Adebajo ⁴⁰	56	i versus ii	40%	13, 68
White ⁴⁴	41		- 5%	-35, 25
Jonquière ⁴⁵	40		- 8%	-33, 17
Berry ⁴⁸	37	i versus iii	8%	-32, 48
		i versus iv	0%	-40, 40
		ii versus iii	0%	-40, 40
		ii versus iv	8%	-48, 32
Hollingsworth ⁵¹	31		40%	20, 60
Knorre ⁵²	28	i versus ii	- 3%	-28, 22
		i versus iii	7%	-18, 32

Our scoring system provides a quantitative index of the likelihood that the reported results of RCTs are free of bias. However, combining information from different study features in a sumscore for quality of methods may conceal variation between studies, thereby reducing informativeness. Hence, method scores must be interpreted as relative scores, and one must be cautious in comparing the scores between reviews with different research questions.

When the studies are ranked according to their method scores, however, the order of studies included in both our review on NSAIDs²⁶ and the present one does not differ substantially^{39,40,44,48}, despite slightly different criteria and different reviewers. The same holds for studies that were included in both our review about physiotherapy²⁵ and the present one^{46,48,53-55}. Only one study⁴⁸ was ranked higher in both the other reviews.

The studies included in this review were aimed at a wide variety of conditions and disorders. Unfortunately, there is much confusion and lack of consensus regarding the classification of shoulder disorders. For disorders labelled seemingly straightforwardly as tendinitis or capsulitis, diagnostic criteria even differed between studies. In addition, the majority of the studies included heterogeneous populations with respect to the duration of the shoulder disorders. In order to identify any difference in efficacy of steroid injections between indications, we included diagnostic categories in Table 3; there was no strong evidence for such differences.

A valid randomization procedure, with adequate generation of random number sequence and concealed assignment, can prevent selection bias⁵⁹. In addition, randomization in blocks can balance sample sizes between treatment groups. Although we excluded studies without random treatment allocation, biased results cannot be ruled out completely, since method assessment revealed that only a few papers gave a clear description of the randomization procedure. Reporting and interpretation of prognostic comparability of groups at baseline was deficient in many studies. An adequate randomisation procedure does not always guarantee equal distribution of confounding variables among the study groups, particularly when the study size is small⁶⁰. Documentation of confounding variables and baseline rates of outcome measures gives some indication whether the randomization procedure has been successful for these (known and measured) variables. Only occasionally relevant prognostic variables were accounted for, such as recurrence status, prior treatment (e.g. steroid injections), involvement of both shoulders and antecedent trauma.

Blinding can prevent information bias during outcome measurement⁶¹. In a placebo-controlled study, blinding of both patient and therapist can be ensured when the milky colour of steroid injection fluid is masked, by covering the ampule. However, only a few studies reported on blinding of patients and therapists or blinded effect measurement, or attempts to do so. Clinical evidence on the importance of needling techniques is scarce. Although standardisation of injections seemed to be adequate, problems with placement of injections due to anatomical variations⁶² or inaccurate intra-articular needling techniques⁶³, might contribute to poor clinical outcome. Hollingworth *et al.*⁵¹ reported higher success rates for injections aimed at the impaired soft tissue structure that was identified during physical assessment compared to tender or trigger point injection.

Little information was provided about the scales and procedures employed during outcome measurement. Pain and recovery or general improvement were the most frequently reported outcome variables. Few studies provided data about other relevant outcome measures, such as range of motion, functional status and medical consumption. Moreover, although the statistical significance of results was always reported, the statistical tests on which the conclusions were based were reported only occasionally. Little attention was given to the clinical relevance of the results⁶⁴. Different authors claim positive short-term effects of triamcinolone injection. However, no long-term effects have been reported. In addition, because the generally very short follow-up impeded detection of more serious long-term adverse effects, a valid benefit-risk estimation is not possible. Hence, its effect on long term prognosis remains unclear.

Although reporting of confidence intervals⁶⁵ was deficient in most studies, only a few studies failed to provide sufficient data about pain and recovery essential for our calculations of 95% CIs. A sufficiently large study size is necessary in order to detect clinically relevant differences in outcome between interventions. Most 95% CIs proved to be wide owing to small study sizes. Statistical pooling can increase power, but we decided not to pool the data because of the widely varying quality of study methods and inadequate reporting. Pooling was further impeded by the heterogeneity of the studies included with respect to populations, interventions, outcome measures and duration of follow-up. For these reasons, and because of our fear that statistical pooling would yield a biased effect estimate, we preferred systematic methods assessment to study the evidence and to identify and present sources of disparity and conflict among clinical trials.

The evidence in favour of the efficacy of steroid injections for shoulder disorders is scant. Only a few of the available RCTs seem to be credible, but they do not provide conclusive evidence about the efficacy and safety of steroid injections for shoulder disorders, especially regarding long-term outcome. Because of the poor quality of methods of most available studies, it is not possible to formulate a strong and valid judgement for or against the use of steroid injections for shoulder disorders. There is more evidence for the short-term efficacy of periarticular triamcinolone injection^{39,40} than for prednisolone injection. Future studies into the efficacy of steroid injection should focus on the comparison of periarticular triamcinolone injection with no intervention or a placebo injection. In addition, studies comparing steroid injections with competing treatment modalities should focus on long-term (cost-)effectiveness and benefit-risk ratios. Methodological flaws presented in this review should be avoided. During the design and conduct of studies, more attention should be given to recruitment of a sufficient sample size, a valid randomization procedure, determination of prognostic comparability at baseline, compliance with interventions, restriction or standardisation of co-interventions, blinding of therapists, patients and effect measurement, sufficient duration of follow-up, and documentation of adverse effects. In addition, more attention should be given to adequate reporting of design, conduct and results of such studies.

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Chapter 4

Non-steroidal anti-inflammatory drugs (NSAIDs) for shoulder complaints

A systematic review

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Abstract

The medical literature was evaluated with respect to the efficacy of NSAIDs for shoulder complaints. Nineteen randomized clinical trials (RCTs) met the selection criteria and were included in this review. Each publication was independently scored by two blinded reviewers, according to a standardized set of 17 methodological criteria. The RCTs were ranked according to their total methods score (maximum 100 points). The methodological quality of the majority of the RCTs was rather disappointing; only 5 RCTs received a methods score exceeding 50 points. Furthermore, methodological criteria were often inadequately described, particularly those regarding the randomization procedure, co-interventions and control of compliance. The three RCTs with the highest methods scores demonstrated superior short-term efficacy of NSAIDs in comparison with placebo intervention. Fourteen RCTs comparing two types of NSAIDs showed no conclusive evidence in favour of a particular NSAID with respect to efficacy or tolerability.

Future RCTs should compare the benefit-risk ratios of NSAIDs and analgesics for shoulder complaints in order to establish whether the use of NSAIDs is more favourable than analgesics, despite the higher risk of adverse reactions from NSAIDs.

Introduction

A painful or stiff shoulder may be the result of a variety of diseases and conditions. Shoulder complaints occur frequently: epidemiological studies have reported point-prevalences ranging from 7% to 25% in western general populations^{1,2,3}. The annual incidence is estimated at 10 per 1000, peaking at 25 per 1000 in the age-category of 42-46 years¹. Approximately 50% of these patients consult a physician for their shoulder complaints. The incidence of shoulder complaints in Dutch general practice is estimated at 13 per 1000 registered patients per year⁴.

Shoulder complaints are usually a self-limiting condition of relatively short duration. In 48% of the patients, pain or stiffness will disappear or substantially improve within 1 month after consulting their general practitioner (GP) [unpublished observations]. Unfortunately, the long-term outcome is not always this favourable. Persisting pain or restriction of movement, due to more chronic conditions, may last for several years^{5,6,7}. A painful shoulder may be caused by articular or peri-articular rheumatic conditions, or may be the result of neurological or vascular disorders, neoplasms, or referred pain from internal organs. Because of the complex functional anatomy of the shoulder girdle, even intrinsic complaints which emanate from the shoulder joint may constitute a diagnostic challenge. To date, there is no conclusive evidence on either the pathogenesis of shoulder disorders or the accuracy of diagnostic procedures such as X-ray, magnetic resonance imaging, computed tomography or ultrasonography^{8,9}. A wide variety of treatment modalities has been introduced, including medication, physical therapy modalities, exercise therapy, corticosteroid injections and surgery. In primary health care, therapy is frequently initiated with the prescription of a non-steroidal anti-inflammatory drug (NSAID)⁴. A variety of NSAIDs is available to the GP, and new drugs are being introduced on a regular basis. NSAIDs are assumed to act by inhibiting prostaglandin synthesis, resulting in relief of pain and suppression of inflammatory processes in articular or peri-articular structures¹⁰. Adverse reactions include mild gastrointestinal symptoms which occur frequently, as well as more serious complications, such as gastrointestinal bleeding, renal insufficiency, hepatitis and bronchospasm. The efficacy of NSAIDs should be studied in terms of benefit-risk ratios, in order to determine whether the advantages of NSAIDs outweigh the risk of adverse reactions.

The efficacy of NSAIDs has been studied extensively, but most randomized clinical trials (RCTs) have included rheumatic conditions affecting various joints. The purpose of this paper was to evaluate the medical literature with respect to the efficacy of NSAIDs for patients with shoulder complaints only. There is still much confusion and corresponding lack of consensus regarding the classification of shoulder disorders. Periarthritis humeroscapularis or a painful stiff shoulder do not constitute clearly defined clinical entities. Diagnostic criteria may even differ between studies for disorders seemingly straightforward labelled as tendinitis or bursitis. We therefore prefer to present one overview of the use of NSAIDs for all indications. In this systematic review, conclusions with respect to the efficacy of NSAIDs were made after blinded assessment of the methodological quality of the RCTs according to standardized methodological criteria.

Methods

Study selection

A Medline literature search of the period (1966-1993) was conducted, using the keywords shoulder, analgesics, anti-inflammatory drugs, bursitis, tendinitis, periarthritis, capsulitis, comparative study and evaluation study. All Medline citations referring to review articles or RCTs were retrieved and examined. The references of all retrieved articles were screened for additional relevant publications.

Studies had to meet the following criteria to be included in this review: (1) The study population included patients with intrinsic shoulder complaints; (2) At least one of the interventions under study included NSAIDs; (3) Patients were randomly allocated to the interventions under study; (4) The publication was a full report. Letters and abstracts were excluded; (5) In publications concerning various rheumatic disorders, the results of patients with shoulder complaints were presented separately, or at least 90% of the study population had to be composed of patients with shoulder complaints; (6) The publication was written in English, German, French or Dutch.

Methods assessment

The selected publications were blinded for author(s), source and results by removing sections of the text, tables and figures. GJMGH and RJPMS independently scored each publication according to a standardized set of 17 methodological criteria (A-Q), referring to the selection of the study population, description of interventions, outcome measurements, analysis and presentation of data (Table 1).

Table 1. Criteria list for a methodological assessment of RCTs for shoulder complaints.

Methodological aspect	Weighting
Study population	35
A selection and restriction: homogenous study population	4
B adequate randomization procedure	3
C prognostic comparability at baseline	7
D drop-outs	3
E loss to follow-up < 20% or loss to follow-up < 10%	1 3
F smallest study group ≥ 25 subjects or smallest study group ≥ 50 subjects or smallest study group ≥ 75 subjects	6 9 15
Interventions	25
G informative description of each intervention	10
H placebo-controlled study	5
I pragmatic study	5
J co-interventions avoided	5
Measurement of outcome	25
K blinding of patient and physician	7
L relevant outcome measures	8
M blinded assessment of outcome measures	5
N adequate follow-up period	5
Analysis and presentation of data	15
O analysis according to intention-to-treat principle	5
P adequate presentation of data	5
Q adjustment for confounding variables and/or differences of prognostic indicators at baseline.	5

- A Clearly described criteria for selection (1 pt). Restriction to a homogenous population with respect to diagnosis, duration of complaint, previous treatments, contra-indications for treatment with NSAIDs (3 pts).
- B Randomization procedure is described and is a procedure which excludes bias (e.g. sealed envelopes, allocation by telephone, pre-coded packaged medication (3 pts)).
- C Comparability for duration of complaints (2 pts), baseline scores for outcome measures (2 pts), age (1 pt), recurrence status (1 pt), previous treatment of complaint (1 pt).
- D No drop-outs (3 pts). If there are drop-outs: the number of drop-outs (1 pt) and the reason for withdrawal (1 pt) is presented for each study group.
- E Loss to follow-up: $\{1 - (\text{number of patients at main moment of effect measurement} / \text{number of patients at randomization})\} \times 100\%$.
- F Smallest study group immediately after randomization.
- G Description of type of intervention (4 pts), dosage schedule or intensity of treatment (2 pts), duration of treatment or number of injections (2 pts), control of compliance (2 pts).
- H A comparison is made with a study group receiving a placebo treatment only.
- I A comparison is made between two or more existing interventions, medication or otherwise. (No addition of any placebo to the other study group.)
- J All other interventions are avoided (5 pts) or comparable co-interventions between study groups (3 pts).
- K Double-dummy system (5 pts) or some other attempt at blinding of the patient (2 pts) and the physician (1 pt). Blinding of patient (1 pt) or physician (1 pt) is evaluated and successful.
- L Results are presented of: pain (2 pts), global measure of improvement (2 pts), functional status (1 pt), range of movement (1 pt), adverse reactions (2 pts).
- M Blinded assessment of the outcome measures mentioned under L (1 pt each).
- N Timing of effect measurement is identical for all study groups (3 pts). Final effect measurement at least three months after randomization (2 pts).
- O When loss to follow-up $\leq 10\%$: analysis according to intention-to-treat principle: results on all randomized patients are presented for most outcome measures, and on the most important moments of effect measurement, irrespective of drop-outs or missing values.
When loss to follow-up $> 10\%$: intention-to-treat-analysis plus alternative analysis that accounts for drop-outs and missing values.
- P Presentation of frequencies or means and SD of the most important outcome measures for each study group at most important moments of effect measurement.
- Q Adjustment of the results for confounding variables (e.g. differences of prognostic indicators at baseline, compliance, additional medication) by using multivariate analysis.

The reviewers rated each methodological criterion according to the following rules:

- + : Informative description of the criterion at issue; adequate design and conduct (prevention of bias).
- : Informative description, but inadequate design or conduct.
- ? : Lacking or insufficient information, assigning either '+' or '-' was not possible.

Disagreements between the reviewers were identified and subsequently discussed during a consensus meeting. If disagreements were not resolved during this meeting BWK was consulted for a final judgement. Next, all methodological criteria rated 'plus' were scored using the weighting factors listed in Table 1. Each RCT was assigned a total methods score by summing up all weighted criteria. This evaluation finally resulted in a hierarchical order, ranking the RCTs according to methodological quality. The methodological criteria and matching weights are based on the criteria used by Koes *et al.*^{11,12}, but were adjusted to fit the disorders and interventions included in this review.

Data abstraction

The success rate in each intervention group was determined by using information from text and tables of the original publications. Whenever possible, success was defined as recovery or substantial improvement from baseline, according to the patient. The exact definition of success may somewhat differ between RCTS, and will be presented in tables summarizing the details and results of the RCTS. Success rates were calculated according to the intention-to-treat principle, dividing the number of documented successes at the end of the intervention period by the number of patients allocated to the intervention by randomization (irrespective of drop-outs and loss to follow-up during the study). There will probably be a number of successfully recovered patients among the drop-outs, but the reasons for drop-out are not always clearly described. Consequently, for some RCTS our calculations will be an underestimation of the real success rate and produce somewhat lower success rates than the results reported in the original publications. The differences between the success rates in groups treated with NSAIDs and reference groups were calculated, along with the corresponding 95% confidence intervals (95% CIs)¹³.

In order to estimate the ability to detect a clinically relevant difference, the power of each study was determined¹³. For these calculations a difference in success rate of 25% between intervention groups was considered to be clinically relevant.

The conclusions of the RCTS regarding the efficacy of NSAIDs were marked as being "positive" or "negative". A RCT was marked "positive" if NSAIDs proved to be significantly ($p < 0.05$) more effective than a reference treatment with respect to at least two relevant outcome measures (e.g. severity of pain or functional limitation) or with respect to our calculations of differences in success rates (95% confidence interval excludes a difference of '0'). Conclusions were marked "negative" if treatment with NSAIDs was less effective than a reference treatment, or if there were no statistically significant differences.

Results

The literature search resulted in the identification of 63 publications on the efficacy of NSAIDs for shoulder complaints. Forty four publications were excluded, being either non-randomized trials, abstracts, or RCTS concerning several joints or disorders without a separate presentation of the outcome for intrinsic shoulder complaints. Eighteen publications met the selection criteria and were included in this review¹⁴⁻³¹, one of which reported on two different RCTS which have been reviewed separately²³. GJMGH and RJPMS initially agreed on 840 of the 931 items scored (90%). Nearly all disagreements were due to reading errors or a difference in interpretation of the methodological criteria. Since all disagreements were resolved during the consensus meeting, BWK did not have to be consulted.

Methodological quality

In Table 2, scores assigned to each methodological criterion, together with the final methods score, are presented for each RCT. Only 5 RCTS¹⁴⁻¹⁸ received a methods score exceeding 50 points, indicating a rather poor methodological quality of most of the evaluated publications. Design or conduct was often inadequate (rated '-') with respect to loss to follow-up (E), sample size (F) and analysis according to the intention-to-treat principle (O).

A considerable amount of relevant information on methodological criteria was lacking or inadequate, representing a total of 12²⁶ to 43 points²⁹ (Table 2). Description of the following criteria was often considered to be inadequate: selection criteria and restriction to a homogeneous study population (A), randomization procedure (B), co-interventions (J), prognostic comparability at baseline (C), control of compliance (G4) and adjustment for confounding variables (Q).

Table 2. Methodological quality of RCTs on the efficacy of NSAIDs for shoulder complaints.

First author ^a	Methodological criteria*																Methods score 100	Inadequate info [†]	Indication	Conclusion [‡]
	A	B	C	D	E	F	G	H	I	J	K	L	M	N	O	P				
Petri ¹⁴	4	3	2	-	3	6	8	5	-	-	5	8	5	3	-	5	57	24	painful shoulder	2 w: pos.
Adebajo ¹⁵	4	3	5	3	3	-	8	5	-	-	5	4	3	3	5	5	56	20	tendinitis < 3m	4 w: neg.
Mena ¹⁶	4	-	3	2	3	6	10	5	-	-	3	7	3	3	-	5	54	23	tendinitis/bursitis < 4d	pos.
Zuinen ¹⁷	4	-	6	-	1	15	8	-	5	-	3	7	2	3	-	-	54	23	tendinitis/bursitis < 3d	neg.
Berry ¹⁸	1	-	5	3	3	-	6	5	5	-	2	5	4	3	5	5	52	24	rotator cuff lesions	neg.
Menkes ¹⁹	1	-	3	1	-	9	8	-	-	-	5	6	3	3	5	5	49	28	periarthritis	neg.
Friis ²⁰	-	-	3	2	3	9	10	-	-	3	5	4	2	3	-	5	49	19	tendinitis	neg.
Duke ²¹	1	-	3	2	-	6	8	-	-	-	5	8	4	3	-	5	45	18	various conditions	neg.
Thumb ²²	-	-	5	2	1	-	8	-	5	-	3	7	4	3	-	5	43	21	periarthritis	neg.
Ginsberg ²³	-	-	3	1	1	-	8	-	-	5	5	7	4	3	-	5	42	23	tendinitis/bursitis	neg.
Ginsberg ²³	-	-	3	1	1	-	8	-	-	5	5	7	4	3	-	5	42	23	tendinitis/bursitis	neg.
Famaey ²⁴	-	-	3	2	3	6	8	-	5	-	3	7	1	3	-	-	41	23	various conditions	neg.
White ²⁵	4	-	6	1	-	-	8	-	-	-	5	7	4	-	-	5	40	17	tendinitis < 3m	neg.
Huskisson ²⁶	1	-	3	2	3	-	8	-	-	5	5	7	3	3	-	-	40	12	painful stiff shoulder	neg.
Wielandts ²⁷	-	-	3	1	-	-	8	5	-	3	7	3	3	-	5	-	38	22	tendinitis	neg.
Smith ²⁸	1	-	3	2	1	-	10	-	-	-	5	5	1	3	-	5	36	24	chronic pain shoulder	neg.
Yamamoto ²⁹	1	-	-	-	-	9	8	-	-	-	5	2	-	3	-	5	33	43	periarthritis	neg.
Rhind ³⁰	-	-	1	2	-	-	6	-	-	-	5	7	3	3	-	5	32	23	periarthritis	neg.
Valtonen ³¹	-	-	-	1	3	-	8	-	-	-	5	4	2	3	-	5	31	36	various conditions	1 w: pos. 2 w: neg.

* Points are assigned to criteria rated '+' (no points for '-' or '-').

† Amount of points assigned to criteria rated '-'.
Pos.: 'Positive' if treatment with NSAIDs (treatment i) in Table 4 or 5 is significantly ($p < 0.05$) more effective than a reference treatment with respect to success rate or at least two other relevant outcome measures.

Neg.: 'Negative' if treatment with NSAIDs is less effective than a reference treatment or if there are no significant differences.

Table 3 presents the ranking of the RCTs according to their methods score, as well as the ranking under the assumption that the RCT was in fact adequately performed with respect to insufficiently described methodological criteria. The maximum attainable scores would range from 52²⁶ to 81 points¹⁴, provided that more informative description of design and conduct did not reveal any bias. This assumption did not result in dramatic changes in the ranking of the RCTs according to methodological quality. Exceptions are the RCT by Valtonen³¹ and, in particular, the RCT by Yamamoto *et al.*²⁹, which would be ranked among the first 6 RCTs. Both publications report on rheumatic conditions affecting several joints, including only a limited amount of information on shoulder complaints.

Table 3 also presents the ranking of RCTs under the assumption that all methodological criteria are equally important. Calculation of unweighted methods scores resulted in some minor changes in the hierarchical order. However, the hierarchical order of the 5 RCTs with the highest methods scores remains the same when using a scoring system without weighting factors.

Table 3. Methods scores and ranking * of the RCTS according to their methodological quality under three different assumptions.

First author ^{ref}	Weighted scores ¹ (ranking I)	Maximal attainable scores ² (ranking II)	Unweighted scores ³ (ranking III)
Petri ¹⁴	57 (1)	81 (1)	24 (1)
Adebajo ¹⁵	56 (2)	76 (5)	23 (2)
Mena ¹⁶	54 (3)	77 (2)	23 (2)
Zuinen ¹⁷	54 (3)	77 (2)	22 (4)
Berry ¹⁸	52 (5)	76 (5)	22 (4)
Menkes ¹⁹	49 (6)	77 (2)	20 (6)
Friis ²⁰	49 (6)	68 (8)	19 (10)
Duke ²¹	45 (8)	63 (13)	20 (6)
Thumb ²²	43 (9)	64 (11)	20 (6)
Ginsberg ²³	42 (10)	65 (10)	19 (10)
Famaey ²⁴	41 (11)	64 (11)	17 (13)
White ²⁵	40 (12)	57 (16)	20 (6)
Huskiison ²⁶	40 (12)	52 (18)	19 (10)
Wielandts ²⁷	38 (14)	60 (14)	17 (13)
Smith ²⁸	36 (15)	60 (14)	16 (15)
Yamamoto ²⁹	33 (16)	76 (5)	10 (18)
Rhind ³⁰	32 (17)	55 (17)	13 (16)
Valtonen ³¹	31 (18)	67 (9)	13 (16)

* RCTS with equal scores are given the same ranking in the hierarchy.

1 Weighted methods scores as presented in (Table 2).

2 Methods scores under the assumption that all criteria assigned a question-mark would have received points if relevant information had been available. Points reflecting "insufficient information" (Table 2) have been added to the weighted methods score.

3 Methods scores under the assumption that all methodological criteria are equally important: methods scores are calculated without the use of weighting factors.

Comparison of NSAIDs with placebo intervention or other treatment modalities

Table 4 summarizes the design and results of 5 RCTS which have included a placebo treatment and/or other treatment modalities for shoulder complaints. The RCTS varied considerably with respect to the type of NSAID used, dosage schedule, diagnosis or indication, duration of complaints and the exact definition of success. These differences may account for some of the variation in success rates between RCTS, which ranged from 20%¹⁴ to 86%¹⁶ in groups taking NSAIDs.

Four of these 5 RCTS scored more than 50 points^{14-16,18}. The RCT described by Petri et al.¹⁴ was assigned the highest methods score (57 points). In this RCT, naproxen was compared with triamcinolone injections in 100 patients with a painful shoulder, using a double-dummy technique to ensure blinding of both patient and physician. All 4 intervention groups received an injection (triamcinolone or lidocaine) as well as tablets (naproxen or placebo). After 2 weeks, improvement in functional status and range of movement was significantly larger when using naproxen than placebo tablets (group i versus iv in Table 4). This difference was not statistically significant after conclusion of the intervention period at 4 weeks.

Mena *et al.*¹⁶ conducted the only RCT in this review which compared a NSAID (flurbiprofen) with placebo tablets in patients with acute tendinitis or bursitis of the shoulder. The results show a significant difference in favour of flurbiprofen. This publication received a relatively high methods score (54 points). In all, only 4 RCTs compared the efficacy of NSAIDs with a placebo intervention, using placebo tablets alone¹⁶ or in combination with local infiltration of an anaesthetic or corticosteroid^{14,15,18}. Three of these RCTs, all of relatively high methodological quality, demonstrated superior short-term efficacy of NSAIDs¹⁴⁻¹⁶.

In 2 out of 4 RCTs comparing NSAIDs with other treatment modalities, corticosteroid injections appeared to be significantly more effective than NSAIDs^{14,15}.

Comparison between two types of NSAIDs

The majority of the RCTs included in this review were designed to study the differences between NSAIDs, with respect to efficacy or tolerability, and have not included a placebo intervention. Details of the design and results of 14 comparative RCTs are presented in Table 5.

Success rates in the intervention groups varied between 10%²⁶ and 79%^{22,29}. As mentioned earlier, this variation may partly be the result of differences with respect to intervention protocol, characteristics of the study population and the exact definition of success. Due to the intention-to-treat analysis, in some RCTs our calculations produced lower success rates than the results reported in the original publications^{19,23,27,31}. Menkes¹⁹ presented success rates of 62% (etodolac) and 43% (piroxicam) for patients who did not deviate from the protocol, whereas we calculated success rates of 46% and 33%, respectively (Table 5).

The RCTs revealed few differences between the various types of NSAIDs. With the exception of the study by Valtonen³¹, the conclusions of all RCTs were rated 'negative'. Valtonen demonstrated a significantly larger improvement of a combined symptom score in patients receiving diclofenac than in patients receiving naproxen. This difference was only statistically significant after 1 week, halfway through the intervention period. According to Yamamoto *et al.*²⁹, indomethacin was more effective than piroxicam with respect to relief of pain, but these differences were not reflected by differences in success rates. Smith *et al.*²⁸ reported a significantly larger reduction of pain at night for piroxicam, compared with naproxen. However, it must be noted that the intervention groups were not comparable with respect to severity of nocturnal pain at baseline. There was no adjustment for this difference in the analysis of the results. Methods scores of these 3 RCTs^{28,29,31} were low (31, 33 and 36 points, respectively). Only one of the RCTs listed in Table 5 was assigned more than 50 points¹⁷. In this RCT the efficacy and tolerability of diclofenac (187 patients) was compared with a combination of diclofenac and misoprostol (185 patients). The two formulations proved to be of equal efficacy, showing similar success rates and improvement in tenderness, pain and range of movement.

In Table 6 the results of power calculations are presented for each RCT. Only 3 RCTs were designed with sufficient power ($1-\beta > 0.80$) to demonstrate a difference in success rate of 25%^{17,20,29}.

Table 4. Details of RCTS studying the efficacy of NSAIDs for shoulder complaints: comparison with placebo treatment or other treatment modalities.

First author ^{ref.}	Treatment with NSAID* (no. of patients)	Reference treatment (s) (no. of patients)
Petri ¹⁴	i Naproxen 1000 mg daily for 4 weeks plus 1x intrabursal injection of lidocaine (25) ii Naproxen 1000 mg daily for 4 weeks plus 1x intrabursal injection of lidocaine and triamcinolone (25) <i>double-dummy</i>	iii Naproxen matched placebo tablets plus 1x intrabursal injection of triamcinolone and lidocaine (25) iv Naproxen matched placebo tablets plus 1x intrabursal injection of lidocaine (25)
Adebajo ¹⁵	i Diclofenac 150 mg daily for 4 weeks plus 1x subacromial injection of lignocaine (20) <i>double-dummy</i>	ii Diclofenac matched placebo tablets plus 1x subacromial injection of lignocaine and triamcinolone (20) iii Diclofenac placebo tablets plus 1x subacromial injection of lignocaine (20)
Mena ¹⁶	i Flurbiprofen, dosage decreasing from 300 mg to 200 mg daily for a maximum period of 14 days (35)	ii Flurbiprofen matched placebo tablets (34)
Berry ¹⁸	i Tolmetin sodium 1200 mg daily for 4 weeks plus 1x intra-articular injection of prednisolone and lignocaine (12)	ii Tolmetin matched placebo tablets plus 1x injection of prednisolone + lignocaine (12) iii Ultrasound therapy (12) iv Tolmetin matched placebo tablets plus placebo ultrasound therapy (12) v Acupuncture
White ²⁵	i Indomethacin 100 mg daily for 25 days plus 1x intrabursal injection of saline (20) <i>double-dummy</i>	ii Indomethacin placebo matched tablets plus 1x intrabursal injection of triamcinolone (20)

SR = Success Rate

ROM = Range Of Movement

95% CI = 95% Confidence Interval

* Some RCTS have used a double-dummy system in order to maintain the double-blind nature of the trial. Additional placebo tablets or injections are provided for each intervention group, matched to the reference medication.

Adverse reactions

Adverse reactions were reported by 8%¹⁴ to 76%³⁰ of the patients receiving NSAIDs (Tables 4 and 5). Side-effects were mainly of gastrointestinal nature or included skin rash, headache or dizziness. Adverse reactions were usually considered to be of a moderate or mild nature, and were the reason for withdrawal in less than 10% of all participants in most RCTS. However, Rhind *et al.*³⁰, Friis *et al.*²⁰ and Famaey and Ginsberg²⁴ reported higher drop-out rates due to side-effects: 20, 19 and 12%, respectively. In RCTS comparing 2 different types of NSAIDs, the incidence of adverse reactions was approximately similar, except for the RCTS conducted by Friis *et al.*²⁰, Huskisson *et al.*²⁶ and Zuinen¹⁷ (Table 5).

Methods score	Results * (p-values < 0.05 were considered significant)	% Patients with adverse reactions
57	Improvements of ROM and limitation of function were significantly larger when using naproxen than placebo at 2 weeks. At 4 weeks naproxen was not significantly better than placebo. Triamcinolone was superior to naproxen in relief of pain and global clinical index. SRs (perfect score of global index) after 4 weeks: 20% (i), 28% (ii), 28% (iii), 8% (iv). Difference i vs iv: 12%, 95% CI (-6, 31).	8% (i) 16% (ii) 12% (iii) 12% (iv)
56	Groups i and ii showed significant benefit over those taking placebo in improvement of pain, ROM and functional limitation. SRs (improvement in all three outcome measures) was significantly higher in group ii than in i and iii (SRs: 70%, 30%, 0%, respectively). Difference i vs iii: 30%, 95% CI (10, 50).	?
54	The pattern of dose reduction during treatment was evident in group i, not in ii. Group i showed a larger proportion of patients with improvements in pain, tenderness, swelling, and ROM. SRs (better according to investigator) were: 86% (i) and 56% (ii). Difference: 30%, 95% CI (10, 50).	23% (i) 9% (ii)
52	There were no significant differences in pain score, ROM and SR between the five groups. SRs (success according to the investigator) were 50% (i), 50% (ii), 50% (iii), 75% (iv), 42% (v). Difference i vs ii: -8%, 95% CI (-48, 32).	active tolmetin: 33% (i) placebo: 25% (ii + iv)
40	In each group pain and ROM improved significantly, but there were no significant differences between the groups. SRs (global assessment score ≤ 4) were: 50% (i) and 45% (ii). Difference: 5%, 95% CI (-26, 36).	?

* Success rates (SR) were calculated according to the intention-to-treat principle, using data presented in the original publications. Unless stated otherwise, results are presented for success rates according to the patient. For each RCT the definition of success rate is given in the last column. Differences between success rates were calculated together with the 95% confidence intervals, using the following equation:

$$(p_i - p_c) \pm z_{\alpha} \sqrt{p_i(1-p_i)/n_i + p_c(1-p_c)/n_c}$$

p_i = success rate in group i (NSAIDS)

n_i = sample size in group i (NSAIDS)

p_c = success rate in the reference group

n_c = sample size in the reference group

z_{α} = 1.96

Notwithstanding a higher incidence of gastrointestinal side-effects in his RCT, Zuinen recommends use of the combined formulation diclofenac/misoprostol, referring to previous studies in rheumatoid arthritis and osteoarthritis in which misoprostol was ascribed a gastroprotective benefit.

The issue of benefit-risk ratio was only addressed by Menkes¹⁹, who calculated the ratio of opinions on efficacy and safety of both patient and investigator, with very similar results for the two NSAIDs under study, etodolac and piroxicam.

Table 5. Details of RCTs studying the efficacy of NSAID shoulder complaints: comparison between two NSAIDs.

First author ^{ref}	Treatment with NSAID* (no. of patients)	Alternative treatment with NSAIDs (no. of patients)
Zuinen ¹⁷	i Diclofenac/misoprostol for 2 weeks (185) 100-150 mg/400-600 µg daily	ii Diclofenac 100-150 mg daily for 2 weeks (187)
Menkes ¹⁹	i Etodolac 400 mg daily for 2 weeks (52) <i>double-dummy</i>	ii Piroxicam 40 mg daily for 2 days, followed by 20 mg daily for 12 days (52)
Friis ²⁰	i Sustained release ibuprofen 2400 mg daily: 2x daily 2 tablet for 3 weeks (73) <i>double-dummy</i>	ii Conventional ibuprofen 2400 mg daily: 2x daily 1 tablet for 3 weeks (74)
Duke ²¹	i Naproxen 825 mg daily for 4 weeks (30) <i>double-dummy</i>	ii Indomethacin 100 mg daily for 4 weeks (29)
Thumb ²²	i Fentiazac 400 mg daily for 3 weeks (19)	ii Diclofenac 50 mg daily for 3 weeks (19)
Ginsberg ²³	i Slow release fentiazac 300 mg daily; 1x daily 1 tablet for 2 weeks (17) <i>double-dummy</i>	ii Conventional fentiazac 400 mg daily: 4x daily 1 tablet for 2 weeks (15)
Ginsberg ²³	i Slow release fentiazac 300 mg daily; 1x daily 1 tablet for 2 weeks (17) <i>double-dummy</i>	ii Conventional fentiazac 200 mg daily: 2x daily 1 tablet for 2 weeks (16)
Famaey ²⁴	i Ibuprofen 1600 mg daily for 2 weeks (25)	ii Diclofenac 100 mg daily for 2 weeks (25)
Huskisson ²⁶	i Diclofenac 150 mg daily for 2 weeks (20) <i>double-dummy</i>	ii Ibuprofen 1200 mg daily for 2 weeks (20)
Wielandts ²⁷	i Fentiazac 400 mg daily for 1 week (14) (one patient with tendinitis of the elbow was included in the RCT)	ii Phenylbutazone 400 mg daily (12)
Smith ²⁸	i Piroxicam 20 mg daily for 21 days (20) <i>double-dummy</i>	ii Naproxen 250 mg daily for 21 days (20)
Yamamoto ²⁹	i Indomethacin 25 mg daily for 2 weeks (148, 67 with PHS) <i>double-dummy</i>	ii Piroxicam 20 mg daily for 2 weeks (147, 79 with PHS)
Rhind ³⁰	i Naproxen 750 mg daily for 4 weeks (20) <i>double-dummy</i>	ii Indomethacin 50 mg daily for 4 weeks (21)
Valtonen ³¹	i Diclofenac sodium 25 mg daily for two weeks (60, 16 with shoulder complaints) <i>double-dummy</i>	ii Naproxen 250 mg daily for 2 weeks (60, 15 with shoulder complaints)

Consult table 4 for legend

Methods score	Results* (p-values < 0.05 were considered significant)	% Patients with adverse reactions
54	Both groups showed steady improvements in pain, limitation of movement and tenderness, but there were no significant differences between the groups. SRs (maximal or moderate improvement from baseline) are 48% (i) and 47% (ii). Difference: 1%, 95% CI (-4, 6).	38% (i) 25% (ii)
49	Both groups improved significantly within 1 week, but there were no significant differences with regard to spontaneous pain, pain on movement, functional score, and use of acetaminophen. SRs (better compared to initial state): 46% (i) and 33% (ii). Difference: 13%, 95% CI (-6, 32).	27% (i) 23% (ii)
49	A significantly larger proportion showed complete relief of pain in group i: 21% versus 7%. SR (better or complete relief) was not significantly different between the groups: 66% (i) and 76% (ii). Difference: -10%, 95% CI (-25, 5).	51% (i) 38% (ii)
45	There were no significant differences with regard to pain, ROM, stiffness, restriction or limitation of activity between the groups. SRs (cured or better): 50% (i) and 52% (ii). Difference: -2%, 95% CI (-28, 24).	33% (i) 28% (ii)
43	There were no differences between the groups with respect to pain, ROM, global benefit or side-effects. SRs (well or very well) were 79% (i) and 68% (ii) for global benefit. Difference: 11%, 95% CI (-17, 39).	26% (i) 21% (ii)
42	There was significant improvement in tenderness, pain and ROM, but there were no significant differences between the groups. SRs (complete relief according to the investigator) were 59% (i) and 53% (ii). Difference: 6%, 95% CI (-28, 40).	13% (i) 20% (ii)
42	There were no significant differences between the two formulations. Improvements in pain, ROM, and tenderness were significant in both groups. SRs were 47% (i) and 44% (ii). Difference: 3%, 95% CI (-31, 37).	20% (i) 27% (ii)
41	There were no significant differences in perceived benefit and improvements of pain and ROM between the groups. SRs (efficacy good or very good) were 52% (i) and 48% (ii). Difference: 4%, 95% CI (-24, 32).	20% (i) 24% (ii)
40	There were no significant differences with regard to pain score or ROM. Diclofenac showed a faster improvement of pain scores (results presented in graphs). SRs (efficacy excellent or good) were: 15% (i) and 10% (ii). Difference: 5%, 95% CI (-15, 25).	35% (i) 20% (ii)
38	There were no significant differences with respect to tenderness, pain, function loss or ROM. SRs (improved compared to initial state) were 50% (i) and 42% (ii). Difference: 8%, 95% CI (-30, 46).	?
36	Piroxicam was significantly more successful in relieving pain at night. No drug was superior for treatment of pain on movement or ROM. No data have been given on any measure of global benefit.	40% (i) 50% (ii)
33	Patients' perceptions of improvement slightly favoured indomethacin. SRs (improvement according to the physician) were 79% (i) and 73% (ii). Difference: 6%, 95% CI (-8, 19).	18% (i) 14% (ii) (all patients)
32	There were significant improvements of stiffness, ROM, and pain in both groups. 40% of patients in group i and 48% in ii reported being cured or better. Difference: -8%, 95% CI (-38, 22).	70% (i) 76% (ii)
31	Results of total symptom score (pain, swelling, tenderness, functional impairment, ROM, disturbed sleep) were significantly better in group i than in group ii after the first week. SRs (improvement according to the physician) in the total study population after two weeks were 72% (i) and 57% (ii). Difference: 15%, 95% CI (-2, 32). (No separate presentation of these data for shoulder patients.)	26% (i) 25% (ii) (all patients)

Table 6. Power calculations for each RCT: the ability of the RCTs to detect a clinically relevant difference* between intervention groups.

First author [ref.]	Mean number of patients per group	Success rate in least successful group	Power (1-β)	Conclusion
Petri ¹⁴	25	8%	0.59	positive at 2 weeks negative at 4 weeks
Adebajo ¹⁵	20	0%	0.68	positive
Mena ¹⁶	35	59%	0.64	positive
Zuinen ¹⁷	186	47%	0.99	negative
Berry ¹⁸	12	42%	0.23	negative
Menkes ¹⁹	52	43%	0.74	negative
Friis ²⁰	74	67%	0.97	negative
Duke ²¹	30	50%	0.52	negative
Thumb ²²	19	68%	0.49	negative
Ginsberg ²³	16	53%	0.31	negative
Ginsberg ²³	17	47%	0.31	negative
Famaey ²⁴	25	48%	0.44	negative
White ²⁵	20	45%	0.36	negative
Huskisson ²⁶	20	11%	0.46	negative
Wielandts ²⁷	13	50%	0.25	negative
Smith ^{28†}	20	-	-	negative
Yamamoto ²⁹	73	73%	0.99	negative
Rhind ³⁰	21	40%	0.36	negative
Valtonen ³¹	16	63%	0.37	positive at 1 week negative at 2 weeks

* A difference in success rate of 25% between intervention groups was considered to be clinically relevant. Power (1-β) was calculated according to the formula described by Friedman *et al.* [13]:

$$z_{\beta} = \frac{-z_{\alpha} \sqrt{2p(1-p)} + \sqrt{N}(p_c - p_i)}{\sqrt{p_c(1-p_c) + p_i(1-p_i)}}$$

p_i = success rate in group i ($p_c + 25\%$)

p_c = success rate in the reference group

p = mean success rate

N = mean sample size

Values of z_{α} were converted to β using statistical tables of standard normal distributions.

† Smith *et al.* have not presented data on success rate or any other measure of perceived benefit. Therefore, it was not possible to make a power calculation for this RCT.

Discussion

Studies of low methodological quality may introduce bias and may consequently result in different effect sizes. Therefore, we assessed the efficacy of NSAIDs for shoulder complaints after evaluation of the methodological quality of the RCTs, in order to avoid conclusions based on RCTs of inferior methodological quality. Blinding of the publications enabled us to evaluate the methods of the RCTs objectively. Each methodological criterion was assigned a weighting factor which reflected our assessment of the relative importance of the criteria. These weighted criteria were summated into a final score, reflecting the methodological quality of a RCT. The resulting hierarchical order of RCTs, according to methodological quality, was not severely affected when the methods scores were recalculated under different assumptions. The 6 RCTs with the highest methods scores remained in the first 6

positions when points were assigned for inadequately described methodological criteria or when weighting factors were totally discarded (Table 3). This means that our scoring system could discriminate between studies of higher and lower methodological quality, regardless of weighting factors. Conclusions on the efficacy of NSAIDs for shoulder complaints were therefore based on RCTs which are listed in the top of our ranking. When weighting factors are used, the quality of the RCTs is measured on a numerical scale, rather than a ranking scale. This may have consequences for concluding statements if final conclusions are based on RCTs with, for example, at least 50 points or a minimum of 60 points for methodological quality.

The methodological quality of the majority of RCTs was disappointingly low; only 5 RCTs received a methods score exceeding 50 points. Furthermore, a considerable amount of information, relevant for the evaluation of the methodological quality, seemed to be missing. An adequate description of the randomization procedure is very important, as valid randomization is the only way to prevent selection bias. A brief description of the randomization procedure was only provided by two RCTs^{14,15}. Even when an adequate randomization procedure has been carried out, it does not guarantee equal distribution of prognostic factors and confounding variables among the study groups, particularly when a study size is small. Documentation of relevant prognostic indicators and baseline rates of outcome measures gives some indication whether the randomization procedure has been successful for these variables. However, in a considerable number of RCTs, baseline characteristics were not presented, or only partly presented (Table 2). In addition, only 4 RCTs received points for description of co-interventions^{20,23,26,27} or control of compliance^{16,20,28}. Interpretation of the efficacy of NSAIDs is difficult when information on the use of co-interventions is limited and no information is presented with respect to the adherence of the participants to the treatment regimen. A complete and more informative report may have revealed additional flaws in the design or conduct of the RCTs included in this review.

In our scoring system no category for the quality of outcome measure is included, although this is a very relevant aspect of a clinical trial. Apart from the frequently applied visual analog scales for pain, a wide variety of outcome measures was used for the assessment of global improvement, functional limitation, swelling and tenderness. Most of these measures have probably been designed on the basis of face validity, and may have proved useful in clinical practice. A thorough assessment of the quality of outcome measures for shoulder complaints requires a detailed study of their applicability, reliability, validity and responsiveness. Unfortunately, this was not feasible within the scope of this review.

The efficacy of NSAIDs was compared with a placebo intervention in 4 RCTs^{14,15,16,18}. Three of these RCTs, all highly positioned in our methodological hierarchy, demonstrated the superior short-term efficacy of NSAIDs. Corticosteroid injections showed even better results in 2 of these RCTs^{14,15}, but NSAIDs may be considered useful in the short-term management of shoulder complaints. We hoped to find out whether NSAIDs are useful for shoulder disorders in general and, if possible, for which type of patient. In order to detect these differences, RCTs should have a relatively homogeneous study population with respect to prognosis and susceptibility to treatment. However, selection criteria varied over the RCTs and were often inadequately described, or a wide

variety of patients were included within one RCT. Consequently, there was no strong evidence for any differences in efficacy of NSAIDs between the various indications and diagnoses in this review.

The intention-to-treat analysis for the calculation of success rates may have underestimated true effect rates, but it might also be possible that the review has overestimated effect rates. Publication bias, for example, may have resulted in an overrepresentation in the literature of RCTs with positive results. Definite answers on the efficacy of NSAIDs can only be provided after conducting RCTs of adequate methodological quality and power.

If studies do not recruit a sufficiently large study population, they are a priori only able to detect very large, improbable differences between groups. An adequate sample size enhances the precision of an estimated effect size and enables the detection of more subtle though clinically relevant differences. However, the results of power calculations vary depending on a number of factors, including the goal of the RCT, the choice of outcome measure, the variability of the results of the outcome measure, the size of a clinically relevant difference and the level of significance. We considered a 25% difference between groups in success rate (on a dichotomous scale) to be clinically relevant. Power calculations showed that only 3 RCTs had sufficient power to detect this rather large difference. These 3 RCTs^{17,20,29} compared different types of NSAIDs and detected only minor differences between intervention groups. The methodological quality of 2 of these powerful RCTs^{20,29} was disappointing. Nevertheless, other RCTs studying the efficacy of NSAIDs in rheumatoid arthritis, osteoarthritis, soft tissue rheumatism and sports injuries have also demonstrated that not many differences should be expected between the various types of NSAIDs^{10,32,33,34}. Any preference for a particular NSAID will probably be influenced by differences in tolerability, cost or convenience of dosage schedule. The less frequent administration of slow-release formulations may offer advantages in terms of patient compliance, although this issue could not be studied by Friis *et al.*²⁰ or Ginsberg and Famaey²³. The use of a double-dummy system in these RCTs hindered the assessment of differences in compliance, as all participants received the same number of tablets.

Despite the lack of power of most RCTs, the results of the RCTs were not pooled in order to avoid pooling data from RCTs of widely varying methodological quality. As mentioned earlier, the outcome of studies of low quality may be biased. Furthermore, pooling was impeded by the fact that most RCTs differed considerably with respect to the intervention under study (type of NSAID and dosage schedule), the selection criteria for the study population and the choice of outcome measures. The possibilities of pooling were further restricted by incomplete reporting in some publications with respect to selection criteria and outcome measures.

The tolerability of NSAIDs varies considerably between patients, but the use of NSAIDs is quite frequently accompanied by adverse reactions, mostly of gastrointestinal nature. More serious adverse reactions, such as bronchospasm, renal insufficiency, gastrointestinal bleeding, hepatitis and allergic reactions are less often reported and may be prevented by careful prescription³⁵. The RCTs in this review reported few differences between NSAIDs with respect to the incidence of adverse reactions. Fries *et al.*³⁶ studied the comparative toxicity of NSAIDs by constructing a summary index of

symptoms, laboratory abnormalities and hospitalization in a large number of patients with rheumatoid arthritis. The most toxic drugs appeared to be indomethacin, tolmetin and meclofenamate, whereas coated aspirin, salsalate and ibuprofen were the least toxic drugs.

Although side-effects were often considered to be moderate or mild in the evaluated RCTS, a substantial number of participants discontinued medication because of adverse reactions. Moreover, it is uncertain whether the NSAIDs were merely effective as an analgesic or also because of their anti-inflammatory properties. It would be interesting to know whether simple analgesics, such as paracetamol, are as effective as NSAIDs without producing the accompanying adverse reactions. Bradley et al.³⁷ demonstrated a similar short-term efficacy of acetaminophen and ibuprofen in patients with osteoarthritis, whether ibuprofen was administered in an analgesic or in a higher, anti-inflammatory dose. Unfortunately, we could not find any reports of RCTS comparing the efficacy of NSAIDs with simple analgesics for soft-tissue rheumatic conditions of the shoulder. Studies comparing the benefit-risk ratios of NSAIDs and analgesics should indicate whether the benefit of NSAIDs outweighs the risk of adverse reactions, which may be avoided by prescribing more simple analgesics. This is particularly relevant for the treatment of musculoskeletal disorders in elderly people, who are at an increased risk of NSAID-induced toxicity³⁸.

In conclusion, the RCTS with the highest methods scores seemed to demonstrate a superior short-term efficacy of NSAIDs, compared with a placebo intervention. However, the methodological quality of the majority of RCTS studying the efficacy of NSAIDs for shoulder complaints was rather disappointing. When designing and conducting RCTS studying the efficacy of NSAIDs for shoulder complaints, more attention should be given to recruiting a sufficient sample size, limitation of the number of drop-outs, adequate data analysis and the writing of a more informative report of the RCT. There was no conclusive evidence in favour of any particular type of NSAID for the treatment of shoulder complaints. Future RCTS should compare the benefit-risk ratios of NSAIDs and analgesics for shoulder complaints, in order to establish whether the use of NSAIDs is more favourable than analgesics, despite the higher risk of adverse reactions from NSAIDs.

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Chapter 5

The efficacy of ultrasoundtherapy and electrotherapy for shoulder disorders

Results of a randomized placebo-controlled clinical trial

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Abstract

Purpose The study was designed to assess the efficacy of electrotherapy (ET) and ultrasoundtherapy (US) as adjuvants to exercise therapy for shoulder disorders.

Design Randomized placebo-controlled trial with a 2 by 2 factorial design plus an additional control group without adjuvants.

Setting Seventeen primary care physiotherapy practices in the south of the Netherlands.

Patients Patients with shoulder pain and/or restricted shoulder mobility without underlying generalized disorder were enrolled if they had not recovered with 6 sessions of exercise therapy in 2 weeks.

Interventions Patients received a maximum of 12 sessions of exercise therapy in 6 weeks. Additionally, they were randomized to receive (1) active ET plus active US; (2) active ET plus dummy US; (3) dummy ET plus active US; (4) dummy ET plus dummy US; or (5) no adjuvants.

Follow-up Outcome measures: recovery, functional status, main complaint, pain, symptoms and restriction of mobility. Measurement at baseline, 6 weeks and 3, 6, 9 and 12 months later was blinded for treatment.

Results After written informed consent 180 patients were randomized. Both active and dummy treatments were given to 73 and 72 patients respectively; 35 patients received no adjuvants. The prognosis of groups appeared similar at baseline. Blinding was successfully maintained. At 6 weeks 20% of the patients without adjuvants reported complete recovery or substantial improvement, 23% and 22% with active and dummy ET, and 26% and 19% with active and dummy US. These proportions increased up to 3 months, but remained virtually stable thereafter. Up to 12 months follow-up the 95% CI for differences between groups for all outcomes include zero.

Conclusion ET and US, either active or dummy, are inefficacious as adjuvants to exercise therapy for shoulder disorders.

Introduction

About 10% of the population suffer from one or more episodes of shoulder disorders in the course of their life¹. Pain and stiffness in the deltoid region are prevalent symptoms. When pain is elicited or aggravated by movement, it usually limits daily activities and restricts the range of motion. Pain when lying on the impaired shoulder commonly causes problems with sleeping^{1,3}. Soft-tissue impairment is reported to be the most common source of these symptoms^{3,4}. A minority of all cases originate from generalized conditions, such as a stroke, polyneuropathy, multiple sclerosis, rheumatoid arthritis, polymyalgia, ankylosing spondylitis, or from malignancies or referred pain from the neck or internal organs⁴.

Of all newly presented episodes of shoulder disorders, in general practice about 50% resolve within 6 months, but some last over a year⁵. Shoulder disorders make up 10% of all referrals to physiotherapists^{6,9}. Exercise therapy is considered to be the cornerstone of physiotherapy for shoulder disorders¹⁰. However, frequent use of electrotherapy (ET) and ultrasoundtherapy (US), mainly as adjuvants to exercise therapy, has been reported for several countries¹¹⁻¹³. ET and US are supposed to be effective for soft-tissue shoulder impairment such as bursitis, tendinitis or capsulitis, regardless of its anatomical site. They are both believed to promote recovery from shoulder disorders by elevation of the pain threshold and promotion of muscle relaxation¹⁶⁻¹⁸. Furthermore, ET is supposed to support recovery by inhibition of activity of the sympathetic nerve system¹⁶, and US by enhancement of soft-tissue flexibility, acceleration of tissue repair, promotion of cellular metabolic rate and reduction of inflammatory reactions of soft-tissue^{17,18}.

To date, 7 randomized clinical trials studying the efficacy of US for shoulder disorders¹⁹⁻²⁶, and 6 randomized clinical trials studying the efficacy of ET for shoulder disorders²⁷⁻³¹ have been published. None of these studies showed a statistically significant effect in favour of either ET or US. The studies were remarkably different with respect to the type of patients included, the way outcomes were measured and the way ET and US were administered. The validity of their results is jeopardized by insufficient blinding of treatment and outcome assessment, dissimilarities of prognosis of groups at baseline, too short follow-up, withdrawal from treatment and loss to follow-up and missing data³². In addition, the studies lack statistical power due to small sample sizes³². Therefore, doubt persists about the efficacy of ET and US for shoulder disorders, applied either separately or as an adjuvant to exercise therapy^{32,33}. In the present randomized placebo-controlled trial we studied the efficacy of ET and US as adjuvants to exercise therapy for patients with shoulder disorders.

Methods

Enrolment

Potential participants were patients of 18 years and older, who had been referred to cooperating private physiotherapy practices in primary care ($n = 17$; 2 therapists per practice) by general practitioners or hospital physicians. Patients with either or both [1] pain in the deltoid region that could be elicited or aggravated by active or passive

glenohumeral movement and [2] a restricted passive range of glenohumeral motion were selected if the therapist considered [3] US and ET to be indicated.

Patients with a stroke; polyneuropathy; multiple sclerosis; rheumatoid arthritis; polymyalgia; ankylosing spondylitis; referred pain from the neck or from internal organs; prior fractures or prior surgery of the shoulder, upper limb, neck or thorax were excluded. Also excluded were patients with contra-indications for the study treatments, i.e. malignancy; haemophilia; motor and sensory deficits in the shoulder, upper limb, neck or thorax.

Patients willing to take part entered a 2-week qualification period³⁴ with a maximum of 6 sessions of at least 20 minutes of exercise therapy. In addition, they received a booklet containing advice on continuation and adaptation of shoulder activities, and protection of the shoulder from overuse. At the end of the qualification period the research physiotherapist (JJDV) excluded patients who were completely or nearly completely free of symptoms; who indicated reluctance to adhere to the allocated treatment or to complete follow-up and who had already received ET or US during the current episode. Next, she excluded patients on the basis of information obtained from referring physicians about exclusion criteria and contraindications or after identifying shoulder hypermobility; complete rotator cuff tears; referred pain in the shoulder; glenohumeral joint inflammation; wounds and defects of the skin in the shoulder, upper limb, neck or thorax during a standardized clinical assessment (consult legend of Table 1 for elements included in the clinical assessment).

Subsequently, the research physiotherapist excluded patients with substantial improvement, who fulfilled 3 or 4 of the following putative indicators of a favourable prognosis: [1] only dominant side impaired, [2] first episode ever, [3] no pain radiating below the elbow, [4] no co-existent cervical or elbow disorder. She also excluded patients without any improvement, who fulfilled 3 or 4 of the following putative indicators of a poor prognosis: [1] non-dominant side or bilaterally impaired, [2] prior episodes, [3] pain radiating below the elbow, [4] co-existent cervical or elbow disorder. Written consent was provided by patients who qualified for participation. Finally, the research physiotherapist documented putative prognostic indicators and baseline values of outcome measures.

Treatment assignment

After stratification for physiotherapy practice and involvement of the dominant side, treatment was assigned. In order to balance treatment groups within the strata, randomized permuted blocks were generated per stratum. With equal weights within the blocks patients were randomized to receive [1] active ET plus active US; [2] active ET plus dummy US; [3] dummy ET plus active US; [4] dummy ET plus dummy US; or [5] no adjuvants. Sealed opaque envelopes were prepared and numbered accordingly. These contained specific instructions for the therapist concerning the use of the treatment device. The research physiotherapist labelled the appropriate envelope with the patient's name and identification number in accordance with the order in which patients enrolled. The envelope was sent to the appropriate therapist, who opened it at the first treatment session.

Interventions

After randomization, 12 treatment sessions were given over 6 weeks. Treatment could be stopped before the 12th session if a patient was free of symptoms. We asked the patients and therapists to refrain from non-study treatments (e.g. stroking and kneading massage, deep friction, orthopaedic manipulation and steroid injections) until 3 months after randomization. Analgesics and NSAIDs taken during the qualification period could be continued after randomization.

The 17 physiotherapy practices were provided with identical devices, with a 5% range for output calibration. In each session the same, fixed sequence of treatments was applied: [1] ET, [2] US and [3] exercise therapy.

Electrotherapy

A 4 KHz sinusoidal bi-phasic electric current with a modulated amplitude was administered. The frequency of the amplitude modulation varied between 60 and 100 Hz with constant phases of 2 seconds and a fade in and fade out of 1 second each. This electric current had no resulting galvanic charge. With a non-painful intensity it has been reported to selectively excite large diameter nerve fibres³⁶. According to the gate control principle, this excitation is considered to temporarily inhibit transmission of nociceptive signals in the spinal dorsal horn from pain mediating small diameter nerve fibres³⁶. An intensity sufficient to evoke electric paraesthesia would be a precondition for this effect³⁷. Postponement of stimulus habituation by frequency modulation and an increase of the intensity of the current should lengthen the episodes of electroanalgesia³⁷.

For each patient 2 reusable hypoallergic self-adhering electrodes (5 × 9 cm) were used; one was placed in the deltoid region, the other over the homolateral erector trunci, parallel to the spine between the processus spinosus of the 4th and 9th thoracic vertebrae. Stimulation with the deltoid electrode should produce electroanalgesia in the shoulder by inhibition of signal transmission in the dorsal horn of the 4th and 5th cervical spinal segments. It has been postulated that sympathetic outflow from the lateral horn of the 4th to the 9th thoracic spinal segments, through the stellate ganglion, sensitizes for shoulder pain as a result of which can cause, amplify and maintain pain³⁸. Stimulation of large diameter cutaneous nerve fibres of the ramus dorsalis of the 4th to the 9th thoracic spinal segments with the thoracic electrode should diminish this sympathetic outflow to the shoulder and thus contribute to alleviation of shoulder pain. This electrotherapeutical concept is commonly recommended and used^{16,35}. The position of both electrodes was kept fixed during all treatment sessions.

The therapist administered either active or dummy ET according to the instructions from the randomization envelope. Active ET: the therapist quantified the intensity for the perception-threshold of electric paraesthesia at the start of each session. Subsequently, the therapist raised the intensity so that the patient felt intense non-painful electric paraesthesia under both electrodes, without continuous muscle contractions. When after a while stimulus habituation occurred, i.e. the electric paraesthesia diminished, the therapist raised the intensity until paraesthesia was felt again. Active ET treatment took 15 minutes at the most, or was stopped earlier after the third habituation. Dummy ET: the therapist quantified the intensity for the perception-threshold of electric

paraesthesia at the start of each session and repeated this 5, 10 and 15 minutes later. After each threshold determination, the therapist immediately set the intensity to zero. Hence, there was no electric output between subsequent determinations of the threshold. The duration of dummy ET treatment was fixed at 15 minutes.

Ultrasoundtherapy

The frequency of the US beam was 0.8 MHz, and the effective radiating transducer area was 4 cm². In order to reduce the risk of hot spots and subsequent tissue damage due to reflection and interferential phenomena over superficial bone structures, intermittent US with a duty cycle of 20% (i.e. on-off ratio of 2:8) and slow circular transducer movements was applied. The transmission of US was enhanced by the use of inert aquasonic hypo-allergic coupling-gel. The therapist set the treatment device to a code included in the instructions from the randomization envelope. Only the manufacturer knew the identity of the 10 codes for active US and the 10 codes for dummy US.

The US beam was directed at the impaired soft-tissue structure identified by the therapist during a clinical assessment at the start of the first session. Sonation time was fixed at 2 min/cm² of the tender area over this structure. The spatial average temporal average (SATA) transducer output to which the device was to be set was calculated by adding the estimated energy absorption between the transducer and the identified lesion to a fixed minimum penetration of 0.25 Watt/cm².

With the fixed sonation time and a beam non-uniformity ratio ranging from 4 to 6, sonation resulted in an exposure far above 50 Joules/cm² that is reported to be the threshold for biostimulation in mammalian tissue³⁵. At the first session, the therapist calculated the SATA transducer intensity and the total sonation time. These values were kept constant during all subsequent sessions.

Exercise therapy

Exercise therapy during the qualification period and after randomization was adjusted to individual symptoms. Each session the treatment goals had to include pain reduction and mobility improvement. Muscle relaxation and strengthening were additional treatment goals. Exercise methods comprised active and passive abduction, flexion, internal and external rotation, extension, and adduction, as well as stretching, functional training and proprioceptive neuromuscular facilitation techniques.

Blinding

US and ET without output were used as dummy treatments. The display of the treatment device was identical for active and dummy treatments. During all treatments the device beeped every 15 seconds and its cooling fan was constantly running. In order to keep the patient and the therapists blinded for the identity of US, the transducer automatically heated to 30° Celsius before the codes from the randomization envelope could be set. The therapist knew which patient received active or dummy ET. In order to keep patients masked, therapists were asked not to talk about the identity of ET with patients. Blinding of therapists or patients for adjuvant treatment is obviously impossible due to the very nature of adjuvant treatment. Blinding of patients for active and dummy treatments was verified 6 weeks after randomization. In order to keep the research physiotherapist blinded during outcome assessment, patients were asked not to talk about treatments with her.

Outcome assessment

Patients were asked not to take analgesics or NSAIDs 24 hours before each outcome assessment. At baseline and at 6 weeks, 3, 6, 9 and 12 months patients were asked to rate recovery and functional status by completing a questionnaire. During outcome assessments up to 3 months, patients rated the severity of restriction of daily activities, various dimensions of shoulder pain and their main complaint, after reviewing their previous scores. Based on a standardized clinical assessment at baseline and 6 weeks and 3 months thereafter, the research physiotherapist then rated restriction of functional shoulder mobility and symptom severity (consult legend of Table 1 for elements included in the clinical assessment). She also checked for side effects.

Data analysis

Data analysis was performed with SPSS³⁹ and Minitab⁴⁰, according to the intention-to-treat principle. Blinding was broken after completion of the data analysis. We calculated proportions of patients indicating complete recovery or substantial improvement. The calculated 95% confidence intervals (CI) of differences between groups for these proportions are based on a Chi-square test. For all other outcome measures we calculated changes in severity scores for each patient by subtracting the baseline values from the respective follow-up values. For all groups these change scores had a non-Gaussian distribution. Therefore, the calculated 95% CI for median differences between groups were based on the rank-sumtest⁴¹. Interaction between US and ET and the influence of prognostic indicators and baseline values of outcome measures on recovery was examined by means of a linear multivariable regression analysis.

Results

Enrolment and baseline similarity

Figure 1 summarizes the routing of patients through the study. In total 855 patients were screened in participating practices. Of the 343 patients who entered the qualification period 180 were finally randomized. Table 1 shows that the groups were similar with respect to the prognostic indicators and baseline values of outcome measures.

The mean number of patients recruited per practice was 11 (range: 4-27). In 8 practices less than 10 patients were recruited, 7 practices recruited between 10 and 20 patients, while 1 practice recruited 22 and another one 27 patients. Ten practices together filled up 20 blocks (twice 4 blocks, and each four times 1 block and 2 blocks), while 7 practices recruited insufficient numbers of patients to fill up at least one block.

Interventions

Electrotherapy

For dummy ET the median intensity for the perception-threshold of electric paraesthesia was 15 milli-Amperes (interquartile range [IQR]: 9, 28). The median intensity of this threshold for active ET, determined at the start of each session, was 14 milli-Amperes (IQR: 10, 26). There was virtually no within-subject change during subsequent treatment sessions for this threshold. The 3 subsequent stimulus habituations during active ET occurred after 3 minutes (median, range 1-5), with a median intensity of 29, 34 and 39 milli-Amperes, respectively.

* Between 1 May 1992 and 1 November 1994

Figure 1. Routing of patients.

Ultrasoundtherapy

For active US, the median SATA transducer was 0.6 Watt/cm² and the exposure through the identified impaired soft-tissue structure was 107 Joules/cm² (median; IQR: 85, 124). Although there was no output for dummy US, according to the device setting the transducer output would have been 0.6 Watt/cm², while the exposure would have been 104 Joules/cm² (median; IQR: 87, 124). The median session duration for active US was 5 minutes (IQR: 4, 6) and 4.5 minutes (IQR: 3, 6) for dummy US.

Table 1. Prognostic similarity of groups at baseline.

	Active ET n=73	Dummy ET n=72	No ET/no US n=35	Active US n=73	Dummy US n=72
Age ($\bar{x} \pm sd$)	51 $\pm$ 14	50 $\pm$ 13	54 $\pm$ 13	50 $\pm$ 13	51 $\pm$ 14
Females (%)	46	56	51	52	50
Previous episodes (%)					
0	56	50	60	49	57
1-5	33	40	26	36	37
> 5	11	10	14	14	7
Co-existent disorders					
cervical	88	78	77	88	78
homolateral elbow	25	32	31	25	32
Impaired shoulder					
dominant	51	47	54	45	53
left	44	42	34	49	35
Duration (%)					
0 $\leq$ 3m	41	37	37	38	39
3 $\leq$ 6m	21	33	26	22	22
6 $\leq$ 12m	22	15	20	18	19
> 12m	17	15	17	22	10
Pain radiating below elbow (%)	75	76	60	67	85
Caused by trauma (%)	8	12	17	8	13
Gradual onset (%)	68	71	63	66	74
Symptoms (%)					
increased	67	73	71	68	72
stable	8	10	14	7	11
decreased	25	17	15	25	17
Prognostic grading ^{1*}	51 (27, 68)	48 (30, 70)	39 (25, 72)	50 (25, 70)	50 (24, 68)
Main complaint ^{1*}	73 (53, 84)	73 (59, 86)	70 (52, 79)	73 (55, 84)	75 (59, 90)
Functional status ^{1*}	75 (63, 81)	69 (56, 87)	75 (63, 87)	69 (56, 81)	75 (63, 87)
Shoulder pain					
after assessment ^{1*}	39 (11, 59)	45 (15, 64)	33 (13, 61)	34 (8, 52)	48 (22, 65)
yesterday ^{1*}	46 (28, 59)	50 (30, 63)	46 (32, 61)	46 (25, 55)	51 (31, 67)
last night ^{1*}	43 (20, 67)	50 (20, 76)	49 (24, 65)	44 (20, 71)	48 (20, 72)
Physical impairment ^{1*}	43 (17, 75)	50 (24, 69)	43 (26, 65)	49 (19, 67)	49 (20, 77)
Symptom score ^{1*}	48 (28, 61)	47 (30, 63)	50 (31, 67)	49 (27, 60)	47 (32, 65)
Mobility ^{1*}	48 (16, 67)	37 (22, 68)	44 (27, 75)	44 (17, 68)	39 (19, 64)

Due to the factorial trial design the ET groups and the US groups represent the same patients.

$\bar{x}$ mean sd standard deviation

n number of patients w weeks

* Median (interquartile range)

† Severity rating of research physiotherapist on a 100-millimeter visual analogue scale (0/100: best/worst), based on a standardized clinical assessment. This assessment involved a standardized history; inspection of contour, muscle wasting and swelling; active and passive evaluation of range of motion and pain on abduction, flexion, internal and external rotation, extension and adduction; evaluation of the functional mobility and active glenohumeral-scapulo-thoracic rhythm; evaluation of joint play and pain on accessory movements; evaluation of muscle weakness and pain on isometric muscle testing; and palpatory assessment of pain and tissue condition.

† Patient rating for severity during the previous week on a 100-millimeter visual analogue scale (0/100: best/worst). The main complaint was logged at baseline, and was defined as an unavoidable painful and/or limited functional activity in which the shoulder is involved. Physical impairment was defined as restriction of daily activities.

§ Patient rating for severity of functional status limitation during the last 24 hours on the 16-item Shoulder Disability Questionnaire (0/100: best/worst).

Rating of research physiotherapist on a 100-millimeter visual analogue scale (0/100: best/worst), based on a standardized assessment of active functional mobility: [1] glenohumeral-scapulo-thoracic rhythm; reaching with the index finger to [2] the heterolateral scapular angulus inferior and [3] the second thoracic processus spinosus; [4] flexion and [5] abduction.

Exercise therapy

No differences were found between the groups with respect to employed methods and goals of exercise therapy. During the qualification period, exercise therapy was aimed at pain reduction and mobility improvement in 5 (median; IQR 3, 6) of the 6 sessions. During the 12 sessions after randomization, it was aimed at pain reduction in 10 sessions (median; IQR 6, 12) and at improvement of mobility in 11 sessions (median; IQR 6, 12). Muscle relaxation was a treatment goal in half of all sessions.

Protocol violations and missing data

In all, 171 patients completed all 12 sessions with the assigned treatment. One patient with active US plus dummy ET withdrew from treatment due to complete recovery, and 8 patients did so due to symptom deterioration: 2 without adjuvant treatment, 2 with both active treatments, 1 with both placebo treatments, 2 with dummy ET plus active US, and 1 with active ET plus dummy US. Up to 3 months, 7 patients received non-study treatments; all steroid injections: 1 without adjuvant treatment, 1 with both active treatments, 2 with dummy ET plus active US, 3 with active ET plus dummy US. Patients did not report any side-effects. All randomized patients were present at the 6 weeks follow-up visit. Ratings from the research physiotherapist were missing for 3 patients who were unable to attend the 3 months follow-up visit. Two of these patients completed and returned questionnaires by post. By telephone, the third patient reported being completely recovered. After 3 months, 1 patient was lost-to-follow-up. Sporadically, details of other outcome measures were missing.

Verification of blinding

At 6 weeks after randomization 67 patients (92%) with active ET and 51 (71%) with dummy ET believed that they were being treated with active ET. The difference in recovery rates between patients who believed to be treated with active and dummy US was 5% [95% CI: -14%, 23%]. Furthermore, 42 patients (58%) with active US and 43 (60%) with dummy US believed that they were being treated with active US. The difference in recovery rates between patients who believed to be treated with active and dummy US was -1% [95% CI: -15%, 13%].

Outcome measures

Much or very much deterioration of symptoms was reported by 6 patients at 6 weeks: 1 with both active treatments, 1 with both dummy treatments, and 4 with active ET and dummy US; and by 4 patients at 3 months: 1 without and 1 with both active treatments and 2 with dummy ET and active US. Up to 12 months there were virtually no differences between groups for the proportions of patients reporting complete recovery or substantial improvement, while the 95% CIs (Table 2) generally rule out large effects. At 6 weeks and 3 months there were virtually no differences between groups for median changes in severity scores since baseline of all other outcome measures, and the 95% CIs (Table 3 and 4) rule out large effects.

When restricted to the filled blocks only, the analysis revealed similar outcomes. The linear regression analysis revealed that at 6 weeks the effect of the combination of ET and US on the recovery rate was 10% higher [95% CI: -18%, 37%] than for ET or US alone. The interaction effect became even weaker with wider CIs during later follow-up.

Table 2. Recovery rates and differences between groups.

	n = 73 (%)	n = 72 (%)	n = 35 (%)	Δ (95%CI)	Δ (95%CI)
<i>Electrotherapy</i>	<i>Active</i>	<i>Dummy</i>	<i>None</i>	<i>Active-dummy</i>	<i>No-dummy</i>
6 weeks	23	22	20	1 (-13, 15)	- 2 (-19, 15)
Adjusted				- 1 (-15, 13)	- 0 (-18, 18)
3 months	41	39	40	2 (-14, 18)	1 (-19, 21)
Adjusted				- 3 (-19, 13)	- 4 (-24, 17)
6 months	32	46	34	-14 (-30, 2)	-12 (-32, 9)
Adjusted				-20 (-35, -4)	- 8 (-28, 12)
9 months	40	49	31	- 9 (-25, 7)	-18 (-37, 3)
Adjusted				-11 (-28, 7)	-19 (-41, 3)
12 months	37	53	37	-16 (-32, 0)	-16 (-36, 5)
Adjusted				-13 (-30, 4)	-19 (-41, 3)
<i>Ultrasoundtherapy</i>	<i>Active</i>	<i>Dummy</i>	<i>None</i>	<i>Active-dummy</i>	<i>No-dummy</i>
6 weeks	26	19	20	7 (- 7, 20)	1 (-16, 17)
Adjusted				8 (- 6, 23)	1 (-16, 19)
3 months	42	38	40	5 (-11, 21)	3 (-18, 23)
Adjusted				4 (-13, 20)	- 1 (-23, 21)
6 months	40	38	34	2 (-14, 18)	- 4 (-23, 17)
Adjusted				1 (-15, 17)	3 (-16, 21)
9 months	41	47	31	- 6 (-23, 10)	-16 (-36, 4)
Adjusted				- 7 (-25, 10)	-16 (-38, 6)
12 months	42	47	37	- 5 (-21, 12)	-10 (-30, 10)
Adjusted				- 9 (-26, 8)	-14 (-35, 7)

Recovery was rated by patient on an 8-point Likert scale. Presented is the proportion of patients indicating complete recovery or substantial improvement. The complementary proportion reported being much improved, little improved, unchanged, little worse, much worse, very much worse.

US Ultrasoundtherapy

ET Electrotherapy

Adjusted Recovery adjusted for prognostic indicators (dominant status of the impaired shoulder, duration of current episode, number or previous episodes, pain radiating below the elbow and prognostic grading).

Δ Differences between groups; negative values denote a difference in favour of the dummy treatment.

CI Confidence interval.

In a multivariable linear regression analysis, putative prognostic indicators (dominant status of the impaired shoulder, duration of current episode, number or previous episodes, pain radiating below the elbow and prognostic grading) did not show any influence on differences in recovery between active and dummy treatment or between dummy treatment and no adjuvants (Table 2). Neither did these prognostic indicators alter the results for any other outcome measure.

Table 3. Electrotherapy (ET): Medians and interquartile ranges for changes in scores since baseline and median differences between groups with 95% confidence intervals

	Active ET n = 73	Dummy ET n = 72	No ET n = 35	Active-dummy ET Δ (95%CI)	No-dummy ET Δ (95%CI)
Main complaint					
6 weeks	24 (3, 48)	20 (0, 45)	27 (2, 42)	- 3 (-13, 6)	4 (- 7, 16)
3 months	36 (9, 61)	39 (18, 64)	35 (20, 57)	4 (- 6, 15)	- 3 (-15, 8)
Functional status					
6 weeks	8 (0, 25)	8 (- 3, 31)	9 (- 6, 38)	0 (- 6, 8)	0 (-10, 10)
3 months	13 (0, 38)	21 (9, 55)	18 (7, 45)	11 (0, 19)	- 2 (-13, 8)
6 months	21 (-13, 56)	31 (8, 49)	10 (- 8, 60)	7 (- 6, 21)	-10 (-26, 8)
9 months	34 (- 2, 58)	36 (9, 57)	24 (- 3, 56)	0 (-11, 13)	- 7 (-22, 9)
12 months	44 (13, 63)	44 (18, 66)	30 (-11, 44)	3 (- 9, 14)	-19 (-37, 5)
Pain after assessment					
6 weeks	12 (0, 34)	7 (0, 29)	7 (- 1, 28)	- 3 (-10, 2)	- 1 (- 9, 6)
3 months	7 (- 1, 36)	14 (4, 36)	11 (0, 28)	5 (- 2, 12)	- 6 (-16, 2)
Pain yesterday					
6 weeks	21 (3, 39)	9 (- 1, 30)	13 (2, 21)	- 5 (-13, 2)	2 (- 6, 9)
3 months	15 (1, 45)	23 (11, 45)	19 (5, 33)	6 (- 2, 15)	- 3 (-13, 6)
Pain last night					
6 weeks	19 (2, 42)	10 (0, 30)	15 (1, 29)	- 7 (-16, 1)	3 (- 6, 13)
3 months	19 (0, 46)	24 (6, 46)	18 (9, 53)	4 (- 6, 14)	0 (-10, 11)
Physical impairment					
6 weeks	15 (1, 29)	13 (0, 29)	11 (0, 23)	- 1 (- 8, 4)	- 1 (- 8, 8)
3 months	18 (2, 39)	23 (8, 39)	19 (4, 34)	5 (- 2, 13)	- 4 (-15, 5)
Symptom score					
6 weeks	20 (4, 45)	16 (4, 31)	21 (10, 29)	- 4 (-13, 4)	3 (- 5, 12)
3 months	21 (6, 45)	25 (10, 36)	27 (14, 32)	1 (- 8, 9)	1 (- 8, 7)
Mobility					
6 weeks	10 (1, 39)	10 (- 3, 27)	14 (2, 30)	- 3 (-11, 49)	3 (- 6, 13)
3 months	10 (0, 44)	13 (2, 31)	15 (3, 32)	- 1 (- 9, 7)	1 (- 8, 9)

Consult legend for Table 1 for outcome measures.

Negative values for medians or interquartile ranges denote deterioration.

Negative values for differences between groups (Δ) and 95% confidence interval (CI) denote a difference in favour of the dummy group.

Discussion

The primary goal of our study was to assess whether US and ET add to the effect of exercise therapy for shoulder disorders. A secondary goal was to examine the magnitude of a potential placebo effect of US and ET. We used a factorial study design because of its statistical efficiency. Interaction between US and ET was considered unlikely and could, indeed, not be shown by our data. Most patients improved over time, irrespective of the treatment allocated. The recovery rate for the whole population was 22% at 6 weeks and increased to 40% at 3 months. The absence of differences in improvement between groups is consistent for all outcome measures. At 6 weeks, the statistical power (1- β , 2-sided: $\alpha = 5\%$) to detect a difference in recovery rates of at least 25% between active and dummy ET is 90% and 92% for such differences between active and dummy US. After 3 months this power was 88% for both treatments. Therefore, it is unlikely that we have missed a large effect of ET and US.

Table 4 Ultrasoundtherapy (US): Medians and interquartile ranges for changes in scores since baseline and median differences between groups with 95% confidence intervals

	Active US n = 73	Dummy US n = 72	No US n = 35	Active-dummy US Δ (95%CI)	No-dummy US Δ (95%CI)
Main complaint					
6 weeks	22 (2, 55)	22 (1, 44)	27 (2, 42)	-3 (-12, 6)	- 4 (-15, 7)
3 months	31 (14, 61)	41 (16, 62)	35 (20, 57)	3 (- 6, 15)	3 (- 2, 16)
Functional status					
6 weeks	11 (0, 31)	7 (- 3, 20)	9 (- 6, 38)	-6 (-13, 2)	- 2 (-13, 7)
3 months	23 (0, 47)	15 (0, 51)	18 (7, 45)	-3 (-13, 7)	- 4 (-16, 7)
6 months	36 (6, 52)	25 (- 3, 50)	10 (- 8, 60)	-3 (-16, 9)	3 (-13, 21)
9 months	33 (1, 56)	38 (9, 60)	24 (- 3, 56)	2 (-10, 14)	7 (- 9, 23)
12 months	38 (8, 63)	49 (25, 65)	30 (-11, 44)	9 (- 2, 20)	23 (7, 39)
Pain after assessment					
6 weeks	9 (0, 32)	7 (0, 31)	7 (- 1, 28)	-1 (- 6, 5)	3 (- 4, 12)
3 months	11 (0, 35)	14 (2, 39)	11 (0, 28)	2 (- 5, 9)	4 (- 4, 15)
Pain yesterday					
6 weeks	12 (0, 32)	13 (1, 34)	13 (2, 21)	1 (- 7, 8)	1 (- 7, 10)
3 months	19 (0, 34)	22 (8, 47)	19 (5, 33)	4 (- 5, 13)	2 (- 8, 13)
Pain last night					
6 weeks	12 (0, 49)	15 (0, 30)	15 (1, 29)	-4 (-14, 4)	- 1 (-10, 8)
3 months	25 (1, 51)	19 (1, 45)	18 (9, 53)	-2 (-12, 8)	- 3 (-14, 7)
Physical impairment					
6 weeks	15 (0, 29)	13 (1, 30)	11 (0, 23)	0 (- 6, 6)	1 (- 7, 9)
3 months	20 (2, 39)	22 (4, 39)	19 (4, 34)	1 (- 7, 9)	2 (- 7, 13)
Symptom score					
6 weeks	18 (4, 34)	13 (4, 37)	21 (10, 29)	-2 (-10, 7)	- 2 (-12, 8)
3 months	23 (8, 40)	23 (8, 42)	27 (14, 32)	0 (- 7, 9)	0 (- 8, 10)
Mobility					
6 weeks	9 (1, 30)	10 (- 4, 32)	14 (2, 30)	-1 (- 7, 8)	- 1 (-12, 10)
3 months	13 (1, 37)	12 (1, 38)	15 (3, 32)	1 (- 8, 7)	0 (-10, 10)

Legend see Table 3.

Similarity of groups

After randomization baseline values of outcome measures appeared to be balanced between groups. In a multivariable regression analysis, the few differences regarding prognostic status at baseline did not alter the results for US and ET. Furthermore, it does not seem likely that the few protocol violations (i.e. treatment withdrawal, loss-to-follow-up and non-study treatment) have resulted in bias of any importance. Their negligible number can be explained by the restriction of enrolment to patients willing to adhere to the allocated treatment and to complete follow-up.

Treatment contrasts and blinding

ET and US without output were used in order to control for potential placebo effects. Therapists could be blinded for the identity of US, but not for the identity of ET. The patients and the research physiotherapist were kept blinded for the identity of active and dummy treatments. Blinding of patients for treatment identity was considered to be successful, since active and dummy treatments appeared equally convincing to patients. Identification of the true nature of treatments at 6 weeks did not appear to be related to their effect. Therefore, it is not likely that unmasking resulted in bias of any importance.

ET was administered according to the concept of non-painful transcutaneous stimulus induced analgesia. This concept is based on assumptions about generation and maintenance of pain and related sympathetic involvement. Although according to this concept ET was expected to support recovery, we could not demonstrate a beneficial effect in favour of active ET. To date, there is no evidence from randomized clinical trials to substantiate the efficacy of any other form of ET³³.

While intermittent US and slow circular transducer movements reduce the risk of tissue damage, a 0.8 MHz US beam possesses sufficient penetration for the glenohumeral region. The administered exposure was higher than the 50 Joules/cm² threshold for biostimulation and was therefore expected to promote recovery. Nevertheless, we have not been able to demonstrate beneficial effects in favour of active US. It is not likely that the benefit of an increased dose of ultrasound exposure, if any, would outweigh the potential risk of tissue damage. To date, there is no evidence from randomized clinical trials to substantiate the efficacy of US³³.

An effect of exercise therapy could have masked a possible difference between the active and dummy treatments, but it is not likely that such a difference, if it exists at all, will be large enough to be clinically relevant. Hence, it must be concluded that US and ET, adjuvant to exercise therapy, have no treatment-specific beneficial effect for shoulder disorders.

In order to study the magnitude of a potential placebo effect we included a control group without adjuvant treatment. This treatment comparison could not be blinded for therapists and patients, but the groups were similar as far as exercise therapy was concerned. Although outcome assessment by the research physiotherapist was blinded, we could not demonstrate a difference in favour of dummy-ET and dummy-US. Therefore, a placebo effect of US and ET is also considered to be unlikely.

Study population

US and ET are supposed to be effective for soft-tissue disorders of the shoulder, regardless of the anatomical site of the soft-tissue involved. Hence, enrolment was not limited to a specific type of soft-tissue shoulder disorder, such as bursitis, tendinitis or capsulitis. For reasons of efficiency enrolment was restricted to a study population that was as homogeneous as possible with respect to putative prognostic indicators. In addition, participation was confined to patients who were considered most likely to respond favourably to US and ET and who were highly motivated to adhere to treatment and to complete follow-up. Since no benefit could be demonstrated, less susceptible and less motivated patients with soft-tissue shoulder disorders are even less likely to benefit from US and ET.

Outcome measures

Patient-tailored outcome measures are clinically relevant and have been reported to be sensitive to change⁴². We therefore used ratings of patients for recovery and the change in severity of the main complaint, pain, functional status impairment as outcome measures. All severity scores were rated on visual analogue scales, while recovery was evaluated on a Likert scale. These scales are reported to be valid and reproducible for measurement of pain and functional capacity⁴³⁻⁴⁶, especially for serial measurements when previous scores are made available^{47,48}. The Shoulder Disability Questionnaire is

considered to be sensitive to change in the evaluation of functional status limitation of patients with shoulder disorders⁴⁹.

Conclusion

During the design and conduct of our study, we have been able to overcome the most important potential threats to validity. Consequently, the results allow a clear conclusion: neither US nor ET prove to be effective as adjuvants to exercise therapy for shoulder disorders.

So far, few studies on the efficacy of exercise therapy shoulder disorders have been reported³². There are indications that NSAIDs and steroid injections may be effective as primary care treatment for shoulder disorders^{50,51}. Therefore, future studies on the efficacy and cost effectiveness of physiotherapy for shoulder disorders should compare exercise therapy with NSAIDs and steroid injections, but also with analgesics, advice and no treatment (e.g. rest, waiting list). In addition, creative effort could be invested in the development of a credible dummy for exercise therapy that controls for the effects of hands-on therapy and therapeutic attention (e.g. reassurance, support, transfer of knowledge).

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Chapter 6

Shoulder disability questionnaire

Design and responsiveness of a functional status measure

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Abstract

The Shoulder Disability Questionnaire (SDQ) is a functional status measure covering 16 items that was designed to evaluate disability in patients with shoulder disorders. According to 273 experienced physiotherapists and 47 researchers specialized in the field of shoulder disorders the 16 items are the problems most frequently mentioned by patients with shoulder disorders, having the largest impact for their functional status. In addition, these items are considered as most crucial in the evaluation of treatment outcome.

The responsiveness of the SDQ was evaluated for 180 patients with shoulder pain and/or restricted shoulder mobility, without underlying systemic disorders. They participated in a randomized placebo-controlled trial, in which ultrasoundtherapy and electrotherapy appeared to be ineffective as adjuvants to standardized exercise therapy.

At baseline and at 6 weeks follow-up, patients completed the SDQ and rated severity of shoulder pain and their main complaint, while a research physiotherapist rated severity of symptoms and restriction of functional mobility. At 6 weeks follow-up patients also rated overall change since baseline: complete recovery, substantially improved and much improved was referred to as *clinical improvement*, little improved, unchanged and little worse as *clinical stability*, while much worse and substantially worse was referred to as *clinical deterioration*.

The SDQ appears to be a responsive measure in evaluating disability. According to the calibrated responsiveness ratio (CRR) and the area under the receiver operator characteristic curve (AUC) it discriminates accurately between clinically stable and improved subjects. The CRRs for the SDQ, shoulder pain, the main complaint and symptoms and functional mobility are 1.14, 1.96, 1.59, 0.56 and 0.40 respectively. Their AUCs are 0.72, 0.80, 0.79, 0.76 and 0.67 respectively. It would be worthwhile to evaluate the responsiveness of the SDQ in other populations and relative to that of other disability measures.

Introduction

Shoulder disorders may limit functional status, i.e. the ability of patients to perform daily activities. Apart from alleviation of pain and improvement of functional mobility, improvement of functional status is an important goal in the treatment of patients with shoulder disorders. Therefore, functional status measures are essential in the evaluation of treatment outcome. Yet, in clinical trials on shoulder disorders little attention is given to functional status measurement¹⁻³.

It is fundamental that the components of functional status measures focus on the actual execution of activities that are important in daily life, and that the components together cover all crucial elements of functional status. Furthermore, functional status measures must be brief, take a short time to complete, and ideally should allow self-assessment and completion by patients. In addition, they must be responsive. This means they must be able to detect clinically relevant changes over time, i.e. changes which are not due to measurement error and biological variability. A summary score should facilitate statistical processing and simple, direct interpretation⁴.

Several outcome measures in the evaluation of surgical intervention for specific shoulder disorders⁵⁻¹² include an evaluation of functional status. However, they predominantly focus on assessment of symptoms, such as pain, restricted mobility, and decreased muscle power, that are correlates of disability. Their evaluation of functional status typically addresses the physician's perspective on the ability to perform daily activities, instead of the patient's report of their actual execution. Little is known about the responsiveness and the applicability of such outcome measures for evaluation of non-surgical interventions.

Almost simultaneously with the SDQ, the Croft Disability Questionnaire¹³ and the Shoulder Pain and Disability Index¹⁴ have been developed for evaluation of disability due to shoulder disorders. Both appear to focus on the perspective of disability of patients in primary care.

This paper describes the design of the Shoulder Disability Questionnaire (SDQ), a functional status measure for disability evaluation in patients with shoulder disorders. It also presents information on its responsiveness on the basis of secondary analysis of data from a randomized placebo-controlled clinical trial in which ultrasoundtherapy and electrotherapy turned out to be ineffective as adjuvants to standardized exercise therapy for soft-tissue shoulder disorders¹⁵.

Questionnaire design

Item selection

A pool of 60 candidate items was selected from routine history of patients with shoulder disorders in physiotherapy and by reviewing various functional status measures. Suitable items had to refer to activities in daily life involving the upper extremities. In order to focus items on the shoulder we attached a subclause to each item that explicitly referred to the shoulder. Items were phrased so that they addressed the actual execution of a particular activity, rather than focusing on the perceived ability to perform it. Items which included positive, negative or ambiguous expressions were

rephrased neutrally. Likewise, items with limited applicability were rephrased in more general wording. For example, *My shoulder hurts when I put a wallet in my backpocket* was rephrased as *My shoulder hurts when I reach towards my buttocks*, while *My shoulder hurts when I fasten my bra* was changed into *My shoulder hurts when I reach towards the back of my chest*.

Item reduction

Item reduction was aimed at maximizing the validity of the SDQ according to the judgemental approach as described by Guyatt and co-workers^{4,16}. We mailed the list of 60 candidate items to 273 experienced physiotherapists working in private primary care practices in the south of the Netherlands and to 47 researchers who had published of papers on shoulder disorders in Dutch medical journals (1990-1991). The addressees were asked to select 15 items concerning functional limitations mentioned most frequently by patients with shoulder disorders. They were asked to focus on symptoms and complaints, rather than on attribution of symptoms to an underlying disorder.

Next, they had to estimate the impact of every selected item on functional status (Likert scale: 1 to 5: not at all limiting to extremely limiting). The respondents were encouraged to comment the list of items and to add any items they felt had been left out. The response to this mailing was 56% for physiotherapists and 60% for researchers. Items were ranked according to the weight-frequency product that was calculated from the returned questionnaires by multiplying the endorsement frequency by the mean impact. Guided by comments, unclear or confusing items were rephrased. Ranking of items revealed only minor differences between the 2 groups of respondents.

The 30 items with the highest overall weight-frequency product were selected for a second mailing, in which the 273 physiotherapists and 47 researchers were asked to select the 15 items they considered most crucial in the evaluation of treatment outcome. They had to estimate the sensitivity to change of every selected item of functional status (Likert scale: 1 to 5: not at all sensitive to change to extremely sensitive to change). Again, the respondents were encouraged to comment the list of items and to add any items they felt had been left out. The response rate for this mailing was 55% for physiotherapists and 72% for researchers. Items were ranked according to the weight-frequency product calculated from the returned questionnaires by multiplying the endorsement frequency by the mean sensitivity to change. The draft SDQ consisted of the 20 items with the highest overall weight-frequency-product. The 2 groups of respondents showed virtually no differences in ranking of these items. The majority of the 20 items involved pushing, pulling, reaching, leaning or carrying.

Finalization for clinical use

Yes-no answer options were used, where "yes" means that the patient is limited with respect to the particular activity. To improve accuracy, the recall period in the patient instructions was limited to the past 24 hours, and the answer option "not applicable" was added, indicating that the activity of the particular item, e.g. carrying something, was not performed during the past 24 hours. The ratio of the number of items with an affirmative answer over the number of applicable items is multiplied by 100. This ratio is used as summary score and ranges from maximum (100, i.e. affirmative answer to all applicable items) to no (0) functional status limitation.

In order to evaluate the applicability of the items and the appropriateness of the answer pattern, 12 patients treated by physiotherapists for shoulder disorders completed the draft SDQ. They were asked to comment on the format and item wording, and to add any items they felt were missing. Their comments resulted in refinements in the wording of 5 items. Eight items addressing similar upper extremity activities were combined: writing and typing; opening and closing a door; holding the steering wheel of the car or the handlebars of the bike; putting on a coat or a sweater. An English translation of the final version of the SDQ can be found in the appendix.

Methods

Patients and data collection

The responsiveness of the SDQ was evaluated in 180 patients, who participated in a randomized placebo-controlled trial about physiotherapy for patients with shoulder disorders. Between 1 May 1992 and 1 November 1994 they had been referred for physiotherapy with either or both [1] pain in the deltoid region that could be elicited or aggravated by shoulder movement and [2] a restricted range of shoulder movement. All patients received exercise therapy, while according to a 2 by 2 factorial randomization table 34 patients received both active treatments, 33 patients both dummy treatments, two groups of 39 patients received one active and one dummy treatment, while an additional control group of 35 patients received no adjuvant treatment. Before randomisation patients with rheumatoid arthritis; polymyalgia; ankylosing spondylitis; malignancy; haemophilia; polyneuropathy; multiple sclerosis; stroke; motor and sensory deficits in the shoulder, upper limb, neck or thorax; referred pain from the cervico-thoracic spine or from internal organs; prior fractures or prior surgery of the shoulder, upper limb, cervico-thoracic spine or thorax were excluded. Furthermore, at the end of 2-week a qualification period with standardized exercise therapy, prior to randomisation, patients were excluded when they were free of symptoms, when they had a favourable or a poor prognosis or when they indicated reluctance to complete follow-up or to adhere to the allocated treatment¹⁵.

In addition to completion of the SDQ at the end of the qualification period and 6 weeks later, patients gave visual analogue scale (VAS) severity ratings for [1] the main complaint in the preceding week; [2] shoulder pain in the preceding week.

Simultaneously, based on a standardized clinical assessment, the research physiotherapist gave VAS severity ratings for [3] symptoms and [4] functional mobility restriction. The legend of Table 1 provides a more detailed description of these measures. All ratings ranged from 0 (minimum) to 100 (maximum).

At 6 weeks, patients rated overall change since baseline on an 8 point Likert transitional scale. This rating was used as an external criterion for the analysis of responsiveness.

Complete recovery, substantially improved and much improved was referred to as *clinical improvement*, little improved, unchanged and little worse as *clinical stability*, while much worse and substantially worse was referred to as *clinical deterioration*.

Data were analysed with SPSS for Windows (Version 6.1.2).

Ability to detect change

We evaluated which individual SDQ items were capable of detecting change. For this purpose we plotted for each item the distribution of change in answer options since baseline, either improvement or deterioration, for all 180 patients.

We also explored potential floor and ceiling effects, i.e. the inability of an outcome measure to detect change towards the end of its scale¹⁷. The presence of a floor effect was studied in subjects with the lower quartile or the best SDQ baseline summary scores, by calculating the proportion of clinically improved subjects with SDQ score improvement since baseline. The presence of a ceiling effect was studied in subjects with the upper quartile or the worst SDQ baseline summary scores, by calculating the proportion of clinically deteriorated subjects with SDQ score deterioration since baseline.

Responsiveness

Responsiveness is the ability of an instrument to detect clinically important change over time¹⁸. It implies the availability of an external criterion for clinically relevant change. We defined responsiveness as the ability of an instrument to discriminate between clinically stable and improved subjects. In the absence of a gold standard for clinical change, we consider the average change since baseline in clinically stable subjects to be the best estimate of the true value for stability.

We explored the responsiveness of the SDQ and other outcome measures by their distribution of change in score since baseline of clinically stable and improved subjects. The smaller the range of these distributions and the smaller their overlap, the larger the responsiveness of an outcome measure is. Because all outcome measures are used simultaneously in the same study population, we evaluate and compare their responsiveness by 2 parameters: the calibrated responsiveness ratio and the area under the receiver operator characteristic curve.

1 The calibrated responsiveness ratio (CRR) is the ratio of the difference between the median change in score since baseline for clinically improved and stable subjects, over the interquartile range (IQR) of this change in clinically stable subjects. Because the change in score since baseline of clinically stable and improved subjects of the compared outcome measures had non-Gaussian distributions we calculated non-parametric CRRs with medians and IQRs.

Responsiveness, above all, is a function of the variability in clinically stable subjects^{19,20}. Comparison of responsiveness of different outcome measures may, however, be complicated by systematic changes in score since baseline in clinically stable subjects. To avoid this, we calibrate the outcome measures for these changes. There is no uniform threshold for the CRR above which an outcome measure can be called responsive. The larger the CRR, the larger the responsiveness of the outcome measure. If an outcome measure has a CRR smaller than 1, the change in scores since baseline of improved subjects does not exceed all possible variance in stable subjects, and we consider it not responsive.

2 The area under the ROC curve. The area under the curve (AUC) for changes since baseline represents the probability of correct discrimination between pairs of clinically stable and improved subjects^{20,21}. In this context, the ROC curve plots the true-positive proportion (Y-axis) against the false-positive proportion (X-axis)^{20,21} of clinically

improved subjects with a change in score since baseline equal to or larger than a cutoff point in the score range. There is no uniform threshold for the AUC above which an outcome measure is responsive. However, if the AUC is equal to 0.5, i.e. the true and false positive proportions describe a 45° line of identity throughout the score range, it means that the outcome measure does not discriminate between clinically stable and improved subjects. This indicates that the outcome measure is not responsive. The AUC approaches 1.0 if the ROC curve reaches higher and towards the left in the diagram, indicating that the outcome measure approaches perfect accuracy in discriminating between pairs of clinically stable and improved subjects^{20,21}. Under the assumption of equal utility of true and false positive, the point most upper left in the diagram represents the best cut off point, i.e. the optimal trade off between true and false positive proportion. The use of such a cut off point may facilitate decisions concerning treatment of patients with shoulder disorders.

Results

Subjects and ability to detect change

Table 1 presents the clinical characteristics of the 180 included subjects, 92 (51%) of whom were clinically improved and 82 (46%) were clinically stable. All subjects could easily complete the SDQ; completion took between 5 and 10 minutes.

Very few subjects gave an affirmative answer at baseline for items 7 and 16. For all 180 subjects, a change in answer from 'yes' at baseline to 'no' 6 weeks later or vice versa, was most frequently reported for items 1, 2, 4, 6 and 12 to 14, while the least change was reported for items 7, 10 and 16 (Figure 1).

Of the 59 subjects with the best (or lower quartile) SDQ baseline scores (0-63), the change in SDQ scores since baseline exceeded zero in 25 (71%) of the 35 clinically improved subjects and in 8 (33%) of the 24 non-improved subjects. This suggests that the SDQ is also able to distinguish between improved and non-improved subjects when there is relatively little functional status limitation at baseline. Therefore, an important floor effect for the SDQ summary score appears to be unlikely in the study population. Of the 40 subjects with the worst (or upper quartile) SDQ baseline scores (87-100), the SDQ scores since baseline deteriorated in none of the 6 clinically deteriorated subjects (0%) and in 2 of the 34 non-deteriorated subjects (6%). This suggests that the SDQ is not able to distinguish between deteriorated and non-deteriorated subjects with relatively severe baseline functional status limitation. Therefore, a ceiling effect for the SDQ summary score appears to be very likely in the study population.

Responsiveness

Figure 2 displays the distributions of change in score since baseline of clinically stable and improved subjects of the compared outcome measures. The median change in SDQ score since baseline for clinically stable subjects is small, while it is large for improved subjects. There is some overlap of the IQRs around these medians. For shoulder pain and main complaint there is no overlap of the IQRs around their medians (Figure 2). The non-parametric CRRS for the SDQ, the main complaint and shoulder pain are 1.14, 1.59 and 1.96 respectively. Since the CRRS of symptoms (0.56) and functional mobility (0.40) are smaller than 1, we consider these outcome measures as being not responsive.

Table 1. Clinical characteristics of subjects included.

	All n = 180	Stable n = 82	Improved n = 92
Age (mean $\pm$ sd)	51 $\pm$ 13	51 $\pm$ 12	51 $\pm$ 14
Females (%)	51	49	52
Previous episodes (%)			
none	56	44	65
1-2	27	30	26
> 2	18	26	9
Co-existent disorders (%)			
cervical	86	85	86
homolateral elbow	68	70	66
Impaired shoulder (%)			
dominant	50	50	51
right	59	56	62
Duration prior to intake (%)			
0 weeks $\leq$ 3 months	38	35	42
3 months $\leq$ 6 months	27	30	22
6 months $\leq$ 12 months	19	16	21
> 12 months	16	18	15
Radiating pain below elbow (%)	73	67	76
Cause current episode (%)			
trauma	12	26	39
unknown	52	56	48
Onset current episode (%)			
acute	32	26	39
gradual	68	74	61
Symptoms prior to intake (%)			
stable	10	5	14
increased	71	72	68
decreased	19	23	17
Prognostic grading**	49 (25,69)	51 (30,73)	43 (25,66)
SDQ†	73 (63,87)	74 (63,85)	70 (58,87)
Shoulder pain‡	54 (40,70)	59 (40,72)	54 (42,67)
Main complaint§	73 (57,85)	74 (66,86)	71 (52,84)
Symptoms**	47 (30,63)	47 (27,69)	47 (30,62)
Functional mobility¶	44 (20,68)	42 (21,69)	39 (18,67)

Presented are medians with 25th and 75th percentiles between brackets.

* Prognostic grading by the research physiotherapist on a visual analogue scale (VAS; 0/100: best/worst), is based on symptom severity combined with presented clinical characteristics. Rating of symptom severity (VAS; 0/100: best/worst) was based on a standardized assessment, including history; inspection of contour, muscle wasting and swelling; active and passive evaluation of range of motion and shoulder pain on abduction, flexion, internal and external rotation, extension and adduction; evaluation of the functional mobility and active glenohumeral-scapulo-thoracic rhythm; evaluation of joint play and shoulder pain on accessory movements; evaluation of muscle weakness and shoulder pain on isometric muscle testing; and palpatory assessment of shoulder pain and tissue condition.

† Shoulder Disability Questionnaire (0/100: best/worst).

‡ Severity rating by the patient for the shoulder pain during the preceding week (VAS; 0/100: best/worst).

§ Severity rating by the patient for the main complaint during the preceding week (VAS; 0/100: best/worst). The main complaint was defined as the major unavoidable painful and/or limited daily activity in which the shoulder is involved.

¶ Severity rating for restriction of active functional mobility by research physiotherapist (VAS; 0/100: best/worst), based on a standardized assessment of [1] glenohumeral-scapulo-thoracic rhythm; reaching with the index finger towards [2] the heterolateral scapular angulus inferior and [3] the second thoracic processus spinosus; [4] flexion and [5] abduction.

Figure 1. Bar chart for changes in answers between baseline and follow-up for 16 SDQ items in 180 subjects.

Boxes represent ranges between 25th and 75th percentiles, horizontal lines inside boxes represent medians, tails represent ranges between 5th and 25th and between 75th and 95th percentiles.

Figure 2. Box plot for changes in score since baseline of compared outcome measures for in stable subjects ($n = 82$) and improved subjects ($n = 92$).

Figure 3 displays the ROC curves for the compared outcome measures. We consider them all responsive, since their AUCs all exceed 0.5: SDQ: 0.72; shoulder pain: 0.80; main complaint: 0.79; symptoms: 0.76; and functional mobility: 0.67. Under the assumption of equal utility of true and false positives, the optimal cutoff point for the SDQ is found between 20 and 60 points improvement. Below 20 points improvement the SDQ does not accurately discriminate between clinically stable and

improved subjects. Below this cut off point the true-positive proportion drops abruptly, while the false positive proportion decreases only marginally. Above 60 points improvement the false-positive proportion increases sharply, while the true-positive proportion increases only marginally.

Figure 3. Receiver operator characteristic (roc) curves for stable subjects ($n=82$) and improved subjects ($n=92$) at multiple cut off points for changes in score since baseline of compared outcome measures.

Discussion

We wanted to know whether patients with shoulder disorders perceived overall change, and in particular if they noticed any change in their ability to perform daily activities in relation to their condition.

For this purpose we designed the SDQ, a 16 item functional status measure for patients with shoulder disorders, by selecting a number of daily activities. The selection was based on the functional limitations most frequently mentioned and judged crucial in the evaluation of treatment outcome by relevant health care professionals. The SDQ focusses on how symptoms and complaints of patients with shoulder disorders affect their ability to perform daily activities. We believe that the SDQ is a sensible functional status instrument for clinical practice and that it is convenient for patients since it is easy to complete and takes only little time to complete. The chosen answer options are easily quantifiable and interpretable, both on item level and as a summary score.

There is no gold standard that provides a valid and reliable estimate for overall change in patients with shoulder disorders. In the absence of such a gold standard, we consider patients to be the best judges in the evaluation of overall change. We therefore included their assessment as an external criterion in the analysis of responsiveness. Although this external criterion appears to provide a clinically relevant difference it does not necessarily represent the minimal clinically relevant change. Nevertheless, the SDQ detected relatively small changes in scores since baseline for clinically stable subjects and relatively large changes for clinically improved subjects. The identification of a ceiling effect in the study population might be explained by the small number of clinically deteriorated subjects.

We consider the SDQ to be an outcome measure for the severity of functional status limitation in patients with shoulder disorders that is as responsive as any other common outcome measures for patients with shoulder disorders, such as severity of symptoms, functional mobility restriction, shoulder pain and the main complaint. The optimal cutoff point for accurate discrimination between clinically stable and improved subjects with the SDQ is found between 20 and 60 points improvement.

The relative ranking of the outcome measures according to the CRR and AUC is quite similar. Thus, our results are not the result of expressing responsiveness according to one or the other method. The most likely explanation for the differences in responsiveness between the compared outcome measures is the difference in the score change variance since baseline in clinically stable subjects. Differences in responsiveness might also be explained by the different aspects of shoulder disorders determined by the compared outcome measures. For example, the main complaint is an individually-tailored disability measure related to only one activity of daily life. In addition, these different aspects of shoulder disorders will have variable recovery patterns. For example, shoulder pain is known to subside rapidly over a short time in many patients, while functional mobility restriction resolves only slowly. Finally, variation in recall period, e.g. 24 hours for the SDQ versus 1 week for the other outcome measures, might also affect responsiveness.

Two almost simultaneously developed functional status measures are comparable with the SDQ. The Disability Questionnaire includes 22 items with a yes-no answer scale and a 24 hour recall frame. The Shoulder Pain and Disability Index (SPADI), developed by Roach et al., consists of a separate 5 item pain scale and an 8 item disability scale, with the preceding week as the recall frame. In order to make the SPADI suitable for telephone administration, the original visual analogue answer scales have been converted into 0-10 numerical scales. The SDQ, Disability Questionnaire and the SPADI all include items that refer to problems with sleeping, moving the arm and dressing. The overlap with respect to item content is largest between the SDQ and the Disability Questionnaire. Responsiveness of the SPADI was established during a survey in general practice in North Carolina (USA): AUC 0.91 at 3 months follow-up²². Van der Windt et al. reported AUCs of 0.84 and 0.90 at 3 and 6 months follow-up respectively for the SDQ during a survey in general practice in the Netherlands²³. In all studies a similar external criterion was used.

It may be possible that the SDQ is responsive in the trial population only and not in other populations. For the reason, it would be worthwhile to evaluate the

responsiveness of the SDQ in other populations, and compare the results directly with the responsiveness of other shoulder disability measures⁵⁻¹⁴. Furthermore, since it has been shown to improve responsiveness of other disease specific functional status questionnaires^{24,25}, revision of for instance the number of items included or a modification of their content should be given attention in future studies.

At the same time, item weights, such as VAS or Likert scales, might be used because they also are likely to improve responsiveness²². When such weights are multiplied by the frequency of item endorsement, they result in a frequency weight product per item. These products could be summed in a new SDQ composite score, comparable with the presented summary score that is based on summing affirmative item answers.

Although our results require confirmation by other investigators, they do suggest that the SDQ is ready for use in clinical trials in which investigators wish to determine the treatment effect on disability of patients with shoulder disorders.

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Appendix shoulder disability questionnaire

How to complete the questionnaire When your shoulder hurts, you may experience problems performing your daily activities. This list contains 16 statements shoulder disorder patients have used to describe in what kind of situations they experience pain and what some of the effects may be. When you read the statements, you may find that some stand out because they apply to your situation today (past 24 hours). As you go through the list, think of how you felt today (past 24 hours). For each entry, check for yourself whether you performed the mentioned activity.

Examples

- You did not perform the activity during the past 24 hours, e.g.: you **did not** lie on your shoulder during the past 24 hours, put a check mark in the box for NA (not applicable).
NA YES NO
☒ ☐ ☐ My shoulder is painful when I lie on it.
- You did perform the activity during the past 24 hours, e.g. you opened or closed a door during the past 24 hours. If your shoulder **was painful** while you were opening or closing a door, put a check mark in the box for YES.
NA YES NO
☐ ☒ ☐ My shoulder is painful when I open or close a door.
- You did perform the activity during the past 24 hours, e.g. you did lean on your elbow or hand during the past 24 hours. If your shoulder **was not painful** while you were leaning on your elbow or hand, put a check mark in the box for NO.
NA YES NO
☐ ☐ ☒ My shoulder is painful when I lean on my elbow or hand.

Shoulder Disability Questionnaire

- 01 I wake up at night because of shoulder pain.
- 02 My shoulder is painful when I lie on it.
- 03 Because of pain in my shoulder I have trouble putting a coat or a sweater on.
- 04 My shoulder is painful during my usual daily activities.
- 05 My shoulder is painful when I lean on my elbow or hand.
- 06 My shoulder is painful when I move my arm.
- 07 My shoulder is painful when I write or type.
- 08 My shoulder is painful when I hold the steering wheel of my car or the handlebars of my bike.
- 09 My shoulder is painful when I lift and carry something.
- 10 My shoulder is painful when I reach or grasp above shoulder level.
- 11 My shoulder is painful when I open or close a door.
- 12 My shoulder is painful when I bring my hand towards the back of my head.
- 13 My shoulder is painful when I bring my hand towards my buttocks.
- 14 My shoulder is painful when I bring my hand towards my lower back.
- 15 I rub my painful shoulder more than once during the day.
- 16 Because of my shoulder pain I am more irritable and bad tempered with people than usual.

Chapter 7

General discussion

In this final chapter we reflect on the findings of the present thesis. We present an overview and discussion of the 3 systematic reviews that we performed¹⁻³ (Chapters 2 through 4) and our study on the responsiveness of outcome measures⁴ (Chapter 6). Special attention is given to our clinical trial⁵ (Chapter 5).

Systematic reviews

In general, randomized clinical trials offer the best possibility for a valid evaluation of treatment effects⁶. Although to date many clinical trials on NSAIDs, steroid injections and physiotherapy for shoulder disorders have been published, a sound review on their efficacy is lacking so far. Therefore, we systematically reviewed clinical trials on the efficacy of physiotherapy¹, steroid injections² and NSAIDs³.

While the methods we have used for the selection of trials and for the assessment of their methods are to some extent arbitrary, they are fully explicit and in line with generally accepted requirements for the critical evaluation of efficacy studies⁶⁻¹⁰. With the methods assessment, we believe that we were able to discriminate between good and poor quality of methods. In all our three reviews we used identical criteria lists for the methods assessment. Our list is based on criteria lists of similar systematic reviews about musculoskeletal disorders¹¹. We adjusted the criteria to match the interventions and populations. Furthermore, we evaluated whether poor reporting hampered the methods assessment.

In all our 3 reviews it appeared that only few trials were adequately reported. Methods assessment was frequently hampered by insufficient reporting of the success of blinding of outcome measurement, parameters of the employed treatment and information on the operationalisation of the outcome measures. This poor reporting hindered the interpretation of the results of many trials and impeded pooled analysis of data. We believe that in future trials reporting of these aspects can easily be improved.

In the reviews about the efficacy of NSAIDs and steroid injections we used summed item weights in order to rank the trials according to the extent to which bias was considered to be likely. These weights are based on similar reviews. They are to some extent

arbitrary. In Chapter 4 we report that the rank order of the trials on NSAIDs does not alter much when equal weights are used. In an additional analysis we found that the rank order of the trials on physiotherapy and steroid injections does also not alter much when weights are used. For our systematic review about the efficacy of physiotherapy, we therefore ranked the trials according to the number of validity criteria that were satisfied. In order to simplify description and the interpretation of results of this review we only present the criteria that were not satisfied or incompletely reported.

In all our reviews it appeared that the quality of methods of most trials was rather poor. The validity of many trials is jeopardized by inadequate randomization procedures, dissimilarities of prognosis of groups at baseline, poor blinding of patients and therapists for treatment identity, poor blinding of outcome assessments, too short follow-up, withdrawal from treatment, contamination, loss-to-follow-up and missing data. In addition, most studies lack sufficient statistical power due to rather small sample sizes.

So far, the efficacy of physiotherapy for shoulder disorders, electrotherapy (ET) included, has not at all been demonstrated, while ultrasoundtherapy (US) does not appear to be efficacious¹ (Chapter 2). The placebo-controlled trials with the highest quality of methods show a small effect in favour of steroid injections² (Chapter 3) and NSAIDs³ (Chapter 4) for shoulder disorders.

At present, a few new studies on the efficacy of steroid injections and physiotherapy for shoulder disorders are being carried out. Their results might add to the outcome of the respective reviews. Although we might have missed some published trials during our searches, it is not very likely that such trials would have altered the general conclusions of our reviews.

Shoulder disability questionnaire

During the design of our trial there was no measure available for the evaluation of disability in patients with shoulder disorders in primary care physiotherapy. Therefore, we decided to design a Shoulder Disability Questionnaire (SDQ)⁴ (Chapter 6). The purpose of its development was to focus it on activities that are directly affected by shoulder disorders of patients in primary care physiotherapy. According to workers in the field of shoulder disorders the included items are most frequently mentioned by patients with shoulder disorders, having the largest impact on their functional status. In addition, they consider these items as being most crucial in the evaluation of treatment outcome.

We evaluated the responsiveness of the SDQ, i.e. the ability to detect clinically relevant change over time, in a secondary analysis of data of the 6 weeks follow-up of our clinical trial. So far, a variety of methods has been used to evaluate the responsiveness of outcome measures. There appears to be no consensus about the best method. Moreover, the comparison of the responsiveness of outcome measures may be complicated by the lack of a gold standard for clinically important change. As it is, the definition of such change depends on the subjective judgement by either the clinician or the patient.

We compared the responsiveness of the SDQ, shoulder pain, the main complaint, symptoms, functional mobility in the same population. We used the patient rating for overall change since baseline at 6 weeks follow-up as an external criterion for clinically

important change: *improvement* (complete recovery, substantially improved and much improved), *stability* (little improved, unchanged and little worse) and *deterioration* (much worse and substantially worse). We believe that this rating is a very important outcome measure and a valid estimate of recovery.

We found that the SDQ in fact is a responsive measure for evaluating disability; it accurately discriminates between clinically stable and improved subjects. The SDQ is slightly less responsive than shoulder pain and the main complaint only slightly more responsive than symptoms and functional mobility.

Almost simultaneously with the SDQ two comparable functional status measures have been developed: the Disability Questionnaire¹² and the Shoulder Pain and Disability Index¹³. They also focus on patients in primary care and have a considerable overlap in content. Rather than developing yet another measure, researchers should directly compare the performance of these 3 new measures in future studies.

Clinical trial

The primary goal of the clinical trial⁵ (Chapter 5) was to examine whether ultrasoundtherapy (US) and electrotherapy (ET) add to the effect of exercise therapy for shoulder disorders. A secondary goal was to study possible placebo effects. Our strategy in designing the trial was to increase the likelihood of finding a difference in favour of the active treatments by careful patient selection and by maximization of the potential contrast between active, dummy and no adjuvant treatments. The principle behind this strategy was that if in this group of patients no effects could be detected in favour of these treatments, other patients were even less likely to benefit from them. It turned out that many patients improved over time, irrespectively of the treatment allocated. However, we found no differences between the groups, neither when active and dummy treatments were compared, nor when dummy treatments and no adjuvant treatment were compared. This absence of effect was consistent for all outcome measures.

Trial efficiency

In order to increase its efficiency, our trial was designed as a 2 by 2 factorial design with an additional control group. For the same reason we tried to form a population of patients with a similar prognosis and who are most likely to benefit from US and ET. These patients were selected after a 2 week qualification period¹⁴, during which they received only standardized exercise therapy. For each session the therapeutic goal of exercise therapy had to include alleviation of pain and mobility improvement, while the range of techniques to be used was restricted. At the end of the qualification period we excluded patients who had an extremely favourable prognosis, patients who already were completely or nearly completely free of symptoms, as well as patients who had a very poor prognosis and patients who already had proved resistant to primary care treatment. These patients could not reasonably expect a major contribution of US and ET to the recovery of their shoulder disorders.

It turned out that the patients who were excluded because of their favourable prognosis did indeed show a more beneficial outcome: their proportion of recovery was 43% at 6 weeks follow-up. This was 11% higher than the proportion of recovery at 6 weeks for all trial participants. These exclusions, have therefore certainly increased the precision

of the trial results. With the 180 patients who were finally enrolled, the statistical power of our trial ($1-\beta$) to detect the anticipated difference in favour of the active treatments of 25% above the recovery proportions of the dummy treatments exceeded 85% at $\alpha = 5\%$ (2-sided)¹⁵. Hence, it seems unlikely that we have missed a large clinically relevant effect of US or ET.

Recruitment problems

Initially, 10 physiotherapy practices were invited to participate in the trial. Each practice was expected to recruit 30 patients within the planned recruitment period of 24 months. Before patient recruitment started, the number of referrals per practice was counted.

In accordance with Lasagna's law¹⁶, the anticipated accrual rate turned out to be too optimistic. In order to augment accrual, 7 additional practices were invited to participate. During the conduct of the trial, however, 8 practices failed to recruit enough patients. In order to increase the monthly accrual rates these 8 practices were replaced. Finally, after an extension of the recruitment period with 6 months, 180 patients were enrolled.

Patients

All patients enrolled in this study showed clinical signs of shoulder entesopathies (tendinitis, bursitis or capsulitis), and had no apparent generalized underlying disorder for their symptoms. The common pathological mechanism behind these differently labelled entesopathies appears to be an inflammatory reaction of soft-tissue, most often due to subacromial impingement of peri-articular structures¹⁷. Enrolment was not restricted to a subgroup of patients with a specific type of entesopathy, because US and ET are supposed to be effective for these soft-tissue shoulder disorders regardless of the anatomical site of the soft-tissue involved. Hence, it seems unlikely that the selection criteria are responsible for the fact that we have been unable to demonstrate any effect in favour of US and ET. Furthermore, after randomization the groups were quite similar regarding baseline values of outcome measures and prognostic indicators. Therefore, it is unlikely that the trial results have been seriously biased by these potential confounders.

Ultrasoundtherapy

In laboratory research ultrasound application results in promotion of the cellular metabolic rate and increased visco-elastic properties of collagen¹⁸. In animal studies an exposure to 1 MHz ultrasound with 50 Joules per cm² is reported to be sufficient to increase tissue temperature¹⁹. This temperature increase is reported to be the mediating mechanism for acceleration of tissue repair, enhancement of soft-tissue flexibility, promotion of muscle relaxation and alleviation of inflammatory reactions of soft-tissue¹⁸⁻²⁰. In addition, US is supposed to reduce pain¹⁸. During the application of US on the shoulder girdle the described effects are expected to promote recovery from shoulder disorders.

The reports of randomized clinical trials that have been published so far, provide little information about which type of US is the most effective¹ (Chapter 2). The ultrasound frequency of 0.8 MHz that has been applied in our trial is sufficient for penetration of the soft-tissue surrounding the glenohumeral joint. The employed exposure exceeds the

50 Joules per cm^2 threshold for thermal effects. Therefore, the employed dose should be sufficient to promote recovery from shoulder disorders. There is no consensus in the literature regarding the most effective parameters of ultrasound dosage, such as duty cycle, transducer size, session duration and frequency and number of sessions. The employed type of US, however, is the one most frequently used in current physiotherapy. Any beneficial effect in favour of active US could not be demonstrated. It is not likely that the benefit of an increased ultrasound exposure, if any, will outweigh the potential risk of tissue damage.

Electrotherapy

Transcutaneous stimulation using an electric current is reported to selectively excite large diameter cutaneous nerve fibres, evoke electric paraesthesia and is supposed to result in pain threshold elevation and muscle relaxation²¹. The principle of inhibition of transmission of nociceptive signals from small diameter nerves in the spinal dorsal horn, according to the gate control theory²¹ and the theory of sympathetically maintained pain^{22,23} provides the most plausible explanation for the mechanism behind these effects.

The recommendations regarding the most effective form of ET in the treatment of shoulder disorders vary widely with respect to intensity, duration and frequency of stimulation, the electrode position and the frequency and number of sessions. The reports of randomized clinical trials provide little information about what is supposed to be the most effective form of ET¹(Chapter 2). The type of ET that was used in our trial, however, is generally applied in current primary care physiotherapy. Any beneficial effect in favour of active ET could not be demonstrated. Theoretically, types of ET other than the one we studied may be effective. Especially painful stimulation according to the concept of diffuse noxious inhibitory controls (DNIC)²⁴ might offer an alternative, because it is based on a totally different mechanism. There is, however, no evidence from randomized clinical trials to substantiate the efficacy of such stimulation or of any other form of ET.

Blinding

Therapists were blinded for the identity of US. Because they received different instructions for active and dummy ET, therapists could not be blinded for the identity of ET. During all outcome assessments the research physiotherapist was blinded for the identity of all treatments.

Patients who know that they received dummy treatment are generally expected to rate their outcome less favourably than patients with active treatment. Therefore, at 6 weeks follow-up patients were asked if they believed in the true nature of their treatment. According to these opinions, active and dummy US appeared equally convincing, while dummy ET appeared less convincing than active ET. Identification of the true nature of treatments appeared not to be related to their effect. Therefore, the potential unmasking of ET will not have resulted in bias of any importance. In addition, the results of this evaluation of the success of patient blinding support the credibility of both dummy treatments.

Since patients in the group without adjuvant treatments know that treatments are withheld from them, they are generally expected to rate their outcome relatively less

favourably than the patients with dummy treatments. As no difference between any of the treatment groups was found for any outcome measure, we think that neither US nor ET has a substantial placebo effect. This lack of placebo effect might be explained by the decreased room for improvement for active and dummy treatments, due to the standardized exercise therapy. In addition, comparison of active and dummy treatments without exercise therapy might reveal an effect in favour of active treatments. But, given the absence of effects in the clinical trial, it is unlikely that they will contribute significantly to the recovery of shoulder disorders.

The lack of blinding of patients and therapists for adjuvant treatments on the one hand and no adjuvant treatments on the other, is generally expected to result in contamination by non-study treatments. For our study this also is expected to result in departures from the standardized exercise therapy employed in the group without adjuvant treatment. We found that virtually no contamination occurred in any of the groups. Hence, it is unlikely that contamination resulted in bias of any importance.

Outcome assessment

So far, it is unclear what the optimal timing of outcome assessment is in relation to the effects of US and ET. The first outcome assessment in our trial coincided with the end of the usual 6 weeks treatment period. Subsequently, 6 weeks and 3 months follow-up visits and 6, 9 and 12 months follow-up postal questionnaires were planned. Nearly full participation was obtained for all outcome assessments and the loss-to-follow-up was only marginal.

Since there is no gold standard that provides a valid and reliable estimate for overall change in patients with shoulder disorders, we consider patients the best judges for the evaluation of overall change. Therefore, patient rating of overall recovery was used as the principal outcome measure. According to this principal outcome measure, but also according to all other outcome measures, many patients improved over time. Nevertheless, no difference between treatment groups could be found for any of the outcome measures. Therefore, it is quite unlikely that we have missed a clinically relevant effect in favour of US or ET.

Assessment of our clinical trial

Our three systematic reviews on the available clinical trials on common primary treatments for shoulder disorders¹⁻³ (Chapters 2 through 4) clearly show that very few trials are adequately reported and provide valid results. The assessors of the trials on physiotherapy for shoulder disorders¹ (Chapter 2) applied the criteria for validity and data abstraction to our clinical trial⁵ (Chapter 5). They found that our trial could be improved with respect to blinding of therapists for ET, and evaluation of success of blinding of therapists for US and of the research physiotherapist for identity of treatments. In addition, insufficient data about compliance with protocol for treatments were presented, no data on medical consumption as outcome measure were presented, while the group without US and ET was relatively small. Furthermore, it is obvious that it was not feasible to blind patients who did not receive additional US and ET. From this critical evaluation of methods it appeared that we have indeed managed to overcome the most important potential threats to validity. Hence, in our systematic

review on the efficacy of physiotherapy for soft-tissue shoulder disorders our trial would have been ranked among the trials with the highest quality of methods.

Conclusion

During the design and conduct of the clinical trial we have been able to increase the statistical efficiency and at the same time overcome the most important potential threats to validity. Consequently, the results allow a clear conclusion: neither US nor ET prove to be effective as adjuvants to exercise therapy for shoulder disorders. Neither have these treatments been shown to have a placebo effect.

Recommendations for clinical practice and future research

The purpose of treatment of patients with shoulder disorders is to increase the extent and speed of recovery. Neither US nor ET as adjuvants to exercise therapy for shoulder disorders turned out to be effective. Consequently, any further application of these adjuvant treatments in patients with shoulder disorders should be strongly discouraged. This can be done by updating treatment guidelines or by withholding reimbursement for US and ET.

Although exercise therapy appears to be the cornerstone of physiotherapy for shoulder disorders, there is only one hospital-based trial on its effectiveness. This trial revealed that exercise therapy was equally effective as surgery²⁵.

Future clinical trials on the efficacy and cost-effectiveness of physiotherapy for shoulder disorders should focus exclusively on the effectiveness of exercise therapy. Since there are some indications for the efficacy of steroid injections and NSAIDs, priority should be given to a comparison with these treatments. Steroid injections and NSAIDs, however, have a relatively high risk of adverse effects. Therefore, frequently applied primary care treatment strategies that are less likely to be harmful, such as analgesics, advice and no treatment (e.g. rest, waiting list) would also be relevant options for comparison in future trials.

During the design and conduct of future trials specific attention should be given to the principles of improvement of validity and statistical efficiency. In addition, creative effort could be invested in the development of a credible dummy for exercise therapy that controls for hands-on therapy and therapeutic attention, including reassurance, support and transfer of knowledge.

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Summary

This thesis deals with shoulder disorders, the central subject being a randomized placebo-controlled clinical trial on the efficacy of ultrasoundtherapy and electrotherapy as adjuvants to exercise therapy for patients with soft-tissue shoulder disorders in primary care physiotherapy.

Pain and stiffness in the deltoid region are the leading symptoms of patients with shoulder disorders. From the background information (Chapter 1) it appears that about 10% of the primary care population suffer from one or more episodes of shoulder disorders in the course of their life. The majority of all shoulder disorders is reported to be caused by entesopathies within the shoulder girdle, such as tendinitis, bursitis and capsulitis. An inflammatory reaction due to subacromial soft-tissue impingement appears to be the common pathological mechanism behind these entesopathies. About 50% of all patients with shoulder disorders consult a physician. They constitute the third most largest group of patients with locomotor disorders in primary care, after patients with low back and neck disorders. In the majority of all newly presented episodes in general practice symptoms disappear within a few weeks, while some episodes may last over 6 months and result in substantial limitation of daily activities, even up to a year or more.

Although patients with shoulder disorders are believed to benefit considerably from common primary care treatments for shoulder disorders, such as NSAIDs, steroid injections and physiotherapy, controversy on their efficacy persists. The evidence on their efficacy has been evaluated in 3 separate reviews (Chapters 2 through 4). Extensive searches for relevant publications yielded 20 randomized clinical trials on physiotherapy, 16 on steroid injections and 19 on NSAIDs. Most trials lack statistical power due to small sample sizes. In general, the systematic assessments revealed the rather poor quality of their methods. Methods assessment was frequently hampered by insufficient information about randomization procedures, prognostic similarity of groups at baseline, and contamination by co-interventions or poor compliance. The validity of many trials is jeopardized by treatment withdrawals, missing values, poor blinding of patients and therapists for treatment identity and poor blinding during outcome assessments. Therefore, conclusions on the efficacy of these treatments can only be based on the trials with high quality of methods.

While for both steroid injections and NSAIDs for shoulder disorders 3 trials with acceptable methods favour their efficacy, the effects are rather small. None of the 6 trials on physiotherapy with acceptable methods showed physiotherapy to be effective for shoulder disorders.

From the systematic review on physiotherapy (Chapter 2) it appears that ultrasoundtherapy is inefficacious, while electrotherapy (ET) so far has not been demonstrated to be effective. Nevertheless, physiotherapists from various countries frequently use US and ET in the treatment of shoulder disorders, commonly as adjuvants to exercise therapy. Therefore, it would be interesting to see the results of a new trial with an acceptable quality of methods and sufficient sample size.

The primary goal of the main study of this thesis (Chapter 5) was to examine whether US and ET add to the effect of exercise therapy for shoulder disorders. A secondary goal was to study possible placebo-effects. Between 1 May 1992 and 1 November 1994 180 patients with shoulder pain or restricted shoulder mobility, without underlying systemic disorders, were enrolled in our study. They all received a maximum of 12 sessions of exercise therapy over a 6 week period and additionally were randomized in a 2 by 2 factorial design: (1) active ET plus active US; (2) active ET plus dummy US; (3) dummy ET plus active US; (4) dummy ET plus dummy US. In order to estimate the placebo effect of adjuvant US and ET, an extra group was added that received (5) no adjuvants. Both active and dummy treatments were given to 73 and 72 patients, respectively, while 35 patients received no adjuvants. The prognosis of groups appeared to be similar at baseline. Blinding of patients for treatment identity was successfully maintained. Outcome measurements were blinded for treatment identity. Measurement at 6 weeks and 3, 6, 9 and 12 months follow-up revealed no differences. At 6 weeks 20% of the patients without adjuvants, 23 and 22% with active and dummy ET, and 26 and 19% with active and dummy US reported complete recovery or substantial improvement. These proportions increased up to 3 months to approximately 40% and remained stable thereafter. In all follow-up measurements, however, the absence of any large effect was consistent for all outcome measures.

During the design and conduct of the clinical trial it was also possible to overcome the most important potential threats to validity. Consequently, the results allow a clear conclusion: neither ultrasoundtherapy nor electrotherapy prove to be effective as adjuvants to exercise therapy for shoulder disorders. Neither have both treatments been shown to have a large placebo effect.

Chapter 6 describes the design of the shoulder disability questionnaire (SDQ), a novel functional status measure for shoulder disorders. The SDQ appears to be a clinically relevant and responsive measure for evaluating disability in our trial population. The general discussion (Chapter 7) provides a review of the findings that are presented in this thesis. Special attention is given to our clinical trial. Since we could not demonstrate any favourable effect of US and ET, it is recommended to refrain from further use of ultrasoundtherapy and electrotherapy in the treatment of shoulder disorders. Given the frequent use of exercise therapy, we would suggest to exclusively focus future trials on its efficacy and cost-effectiveness. In view of the results of our systematic reviews such trials should give priority to steroid injections and NSAIDs as comparators. In view of the cost-effectiveness of exercise therapy, other important alternatives for comparison would be analgesics, advice and no treatment (e.g. rest, waiting list).

Samenvatting

Dit proefschrift gaat over schouderaandoeningen in de eerstelijnsgezondheidszorg. Het centrale onderwerp is een gerandomiseerde placebo-gecontroleerde effectstudie naar het effect van ultrageluidtherapie en elektrotherapie als aanvulling op bewegings-therapie bij patiënten in de eerstelijnsgezondheidszorg met aandoeningen van de weke delen van de schouder.

In Hoofdstuk 1 wordt de belangrijkste achtergrondinformatie over aandoeningen van de schouder samengevat. Pijn en stijfheid in de schoudergordel blijken de belangrijkste klachten van patiënten met schouderaandoeningen te zijn. Ongeveer 10% van de populatie in een huisartsenpraktijk blijkt gedurende hun leven een of meer episoden met schouderklachten door te maken. De meest frequent gerapporteerde oorzaak voor schouderklachten is een ontstekingsreactie van de weke delen (entesopathiën) in de schoudergordel, zoals tendinitiden, bursitiden en capsulitiden. Een subacromiale inklemming van weke delen lijkt het meest waarschijnlijke oorzakelijke mechanisme voor deze ontstekingsreacties.

Na rugklachten en nekkklachten vormen schouderklachten de derde grootste groep van alle aandoeningen aan het bewegingsapparaat in de eerstelijnsgezondheidszorg. In de meeste gevallen verdwijnen de klachten binnen enkele weken, maar in een beperkt aantal gevallen blijven de klachten 6 maanden tot meer dan een jaar bestaan, en leiden deze tot forse beperkingen in de dagelijkse bezigheden.

Aangenomen wordt dat patiënten met schouderklachten baat hebben bij gebruikelijke behandelingen in de eerstelijnsgezondheidszorg, zoals NSAIDs, steroïde injecties en fysiotherapie. Tot op heden bestaat er echter geen duidelijkheid over de effectiviteit van deze behandelvormen. In 3 afzonderlijke literatuurstudies (Hoofdstuk 2 tot en met 4) worden de beschikbare gerandomiseerde effectstudies samengevat en hun onderzoeksmethoden beoordeeld.

Uitgebreide zoekacties naar gerandomiseerde onderzoeken leverden 20 effectstudies op over fysiotherapie, 16 studies over steroïde injecties en 19 studies over NSAIDs. Vanwege hun kleine populatieomvang hebben vrijwel al deze studies een geringe statistische bewijskracht. Uit de systematische evaluatie van de onderzoeksmethoden bleek dat er frequent onduidelijkheid bestaat over bepaalde aspecten van de opzet en uitvoering van de studies. Zo ontbrak zeer frequent informatie over de randomisatieprocedure, prognostische vergelijkbaarheid van de groepen na randomisatie, en bestond er onduidelijkheid over toepassing van co-interventies en trouw aan het onderzoeksprotocol. Voorts vertoonden de opzet en uitvoering van de

meeste studies belangrijke tekortkomingen, waardoor de interne validiteit van de studies werd aangetast. De meest frequent geconstateerde tekortkomingen betreffen het voortijdig staken van de toegewezen behandeling, ontbrekende waarden voor uitkomstmetingen, gebrekkige blinding van patiënten en behandelaars voor de identiteit van de toegewezen behandeling en gebrekkige blinding tijdens effectmetingen.

Over zowel steroïde injecties (Hoofdstuk 3) als NSAIDs (Hoofdstuk 4) zijn 3 studies met een acceptabele kwaliteit van onderzoeksmethoden beschikbaar waarvan de uitkomsten de effectiviteit van deze behandelvormen ondersteunen. De waargenomen effecten zijn echter nogal klein.

De 6 effectstudies over fysiotherapie bij schouderaandoeningen (Hoofdstuk 2) met een acceptabele kwaliteit van onderzoeksmethoden geven geen ondersteuning voor de effectiviteit ervan. Ultrageluidtherapie (UG) lijkt niet effectief te zijn, terwijl de effectiviteit van elektrotherapie (ET) bij patiënten met schouderaandoeningen tot op heden niet is aangetoond. Toch worden UG en ET in veel landen veelvuldig toegepast ter behandeling van patiënten met schouder-aandoeningen, gewoonlijk als aanvulling op bewegingstherapie. Derhalve is het interessant om een nieuwe gerandomiseerde studie uit te voeren.

Het doel van onze gerandomiseerde placebo-gecontroleerde effectstudie (Hoofdstuk 5) was om te onderzoeken of UG en ET als aanvulling op bewegingstherapie bijdragen aan het herstel van schouderaandoeningen. Een secundair doel was de bestudering van eventuele placebo-effecten. Tussen 1 mei 1992 and 1 november 1994 werden 180 patiënten voor deelname geselecteerd. Zij waren 18 jaar of ouder en hadden schouderpijn of glenohumerale bewegingsbeperking, alsmede klinische verschijnselen van entesopathiën (tendinitis, bursitis of capsulitis) van de schouder zonder aanwijsbaar onderliggend lijden. Deze patiënten ontvingen in 6 weken maximaal 12 sessies bewegingstherapie, en werden via een aselecte procedure toegewezen aan: actieve ET plus actieve UG; (2) actieve ET plus dummy UG; (3) dummy ET plus actieve UG; (4) dummy ET plus dummy UG. Om eventuele placebo-effecten van ET en UG te onderzoeken werd een extra groep gevormd zonder aanvullende therapievormen. Beide actieve en dummy therapievormen werden aan respectievelijk 73 and 72 patiënten toegewezen, terwijl 35 patiënten geen aanvullende therapievormen toegewezen kregen. Na randomisatie bleek de prognose van de groepen goed vergelijkbaar te zijn. Tijdens de effectmeting 6 weken na randomisatie bleken de patiënten goed geblindeerd te zijn ten aanzien van de identiteit van de aanvullende behandelvormen. Zes weken na randomisatie bleek 20% van de patiënten zonder aanvullende behandelvormen, 23 en 22% met actieve en dummy ET, en 26 en 19% met actieve and dummy UG geheel hersteld of zeer veel verbeterd te zijn. Drie maanden na randomisatie bleken deze proporties ongeveer verdubbeld te zijn. Tot aan het einde van de follow-up na 12 maanden bleven deze proporties stabiel. De afwezigheid van effecten van enige omvang was de gehele follow-up consistent voor alle uitkomstmaten. Omdat tijdens de opzet en de uitvoering van dit onderzoek vertekening werd voorkomen, laat het duidelijke conclusies toe: noch ET noch UG blijken effectief te zijn als aanvulling op bewegingstherapie ter behandeling van patiënten met schouderaandoeningen. Een placebo effect blijkt voor beide therapievormen eveneens afwezig te zijn.

Hoofdstuk 6 beschrijft de samenstelling van de Schouder Beperkingen Vragenlijst (SDQ), een nieuwe effectmaat ter bepaling van de functionele status van patiënten met schouderandoeningen. Tijdens ons effectonderzoek blijkt de SDQ een klinisch relevante en responsieve effectmaat te zijn.

In de afsluitende discussie (Hoofdstuk 7) worden de resultaten besproken van de hoofdstukken van dit proefschrift. Daarbij wordt extra aandacht geschonken aan de gerandomiseerde placebo-gecontroleerde studie naar de effectiviteit van UG en ET (Hoofdstuk 5). Aanbevolen wordt af te zien van verdere toepassing van ET en UG ter behandeling van personen met schouderandoeningen.

Gegeven de frequente toepassing van bewegingstherapie, wordt aanbevolen toekomstig effectonderzoek inzake fysiotherapie bij schouderandoeningen uitsluitend te richten op de werkzaamheid en doelmatigheid van deze therapievorm. Vanwege de indicaties inzake hun werkzaamheid vormen steroïde injecties en NSAIDs daarbij relevante interventies ter vergelijking met bewegingstherapie. Voor onderzoek naar de doelmatigheid van bewegingstherapie bij schouderandoeningen zijn analgetica, adviezen en geen behandeling (bijvoorbeeld rust tijdens een wachtlijstperiode) eveneens relevante alternatieve interventies.

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Curriculum vitae

Geert J.M.G. van der Heijden werd op 12 april 1958 te Oisterwijk geboren. Hij is in 1992 gehuwd met Meta de Graaff. Zij hebben twee kinderen, Eva en Thijs.

In 1974 behaalde hij het MAVO-diploma en in 1976 het HAVO-diploma, te Tilburg. Zijn opleiding fysiotherapie te Utrecht en Amsterdam werd in 1979 onderbroken door militaire dienst. Na het behalen van het diploma fysiotherapie in 1985, werkte hij korte tijd als fysiotherapeut in Engeland.

Vanaf 1986 studeerde hij aan de Faculteit der Gezondheidswetenschappen (GW) aan de Rijksuniversiteit Limburg (RL), te Maastricht. In 1990 behaalde hij in de afstudeerrichting Bewegingswetenschappen het GW-diploma met aanvullende examens. Tijdens de laatste 2 jaar van zijn studie publiceerde hij als student-assistent bij de vakgroep Epidemiologie enkele artikelen inzake literatuuronderzoek naar de effectiviteit van fysiotherapie.

Voor zijn afstudeerproject, een *placebo-gecontroleerd onderzoek naar de effecten van tractie bij lage rugklachten*, kreeg hij in 1992 de GW studentenprijs van de Stichting Wetenschapsbeoefening van de RL. Zijn voorstel voor het vervolg van dit onderzoek werd door het Fonds Ontwikkelingsgeneeskunde gesubsidieerd. Zijn projectvoorstel voor een onderzoek naar de werkzaamheid van ultrageluidtherapie en elektrotherapie bij schouderklachten werd door de Ziekenfondsraad gesubsidieerd. Sinds 1990 voerde hij dit *schouderonderzoek* uit bij de vakgroep Epidemiologie van de RL. Daarnaast was hij als docent verbonden aan de GW afstudeerrichting *Verkort Bewegingswetenschappen* voor fysiotherapeuten.

Hij kreeg zijn epidemiologische scholing binnen de vakgroep Epidemiologie. Ook volgde hij cursussen over epidemiologisch onderzoek bij Rothman, Lanes, Lemeshow (1992) en Miettinen (1993). In 1993 volgde zijn registratie als Epidemioloog A.

Hij was voorzitter van de Maastrichtse Studenten Alpen Club (1986-1987) en lid van de gebruikersraad van het RL bureau studentensport 'Lichamelijke vorming en sport' (1987-1988). Ook was hij lid van de GW faculteitsraad (1994-1995).

Sinds augustus 1996 werkt hij bij het Instituut voor Revalidatie Vraagstukken te Hoensbroek.

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Shoulder disorder treatment

Efficacy of ultrasoundtherapy and electrotherapy

Geert J.M.G. van der Heijden

Shoulder disorders constitute a serious health problem. After low back and neck disorders, they constitute the third most largest group of all disorders of the locomotor system in primary care. Non-steroidal anti-inflammatory drugs (NSAIDS), steroid injections and physiotherapy are believed to promote their recovery.

This thesis reports on a randomized placebo-controlled clinical trial on the efficacy of ultrasoundtherapy and electrotherapy as adjuvants to exercise therapy for shoulder disorders in primary care physiotherapy in the Netherlands.

Furthermore, this thesis describes systematic reviews of randomized clinical trials on the efficacy of NSAIDS, steroid injections and physiotherapy for shoulder disorders, and it reports on the design and responsiveness of the Shoulder Disability Questionnaire.

Schouderaandoeningen vormen een veel voorkomend gezondheidsprobleem. In de groep met aandoeningen aan het bewegingsapparaat in de eerstelijnsgezondheidszorg nemen schouderaandoeningen dan ook een derde plaats in na aandoeningen van de lage rug en nek. Verondersteld wordt dat injecties met steroïden, niet-steroïde ontstekingsremmende medicatie (NSAIDS) en fysiotherapie werkzame behandelvormen zijn voor schouderaandoeningen.

In dit proefschrift wordt een gerandomiseerd placebo-gecontroleerd effectonderzoek gerapporteerd naar de werkzaamheid van ultrageluidtherapie en elektrotherapie als aanvulling op bewegingstherapie bij schouderaandoeningen in de eerstelijnsfysiotherapie. Voorts worden systematische literatuurstudies inzake de werkzaamheid van injecties met steroïden, NSAIDS en fysiotherapie bij aandoeningen van de schouder, alsmede de ontwikkeling van de schouder beperkingen vragenlijst beschreven.