A double-blind randomised controlled study comparing subacromial injection of tenoxicam or methylprednisolone in patients with subacromial impingement

S. Karthikeyan, H. T. Kwong, P. K. Upadhaya, N. Parsons, S. J. Drew, D. Griffin

From Warwick Medical School, Coventry, England

We have carried out a prospective double-blind randomised controlled trial to compare the efficacy of a single subacromial injection of the non-steroidal anti-inflammatory drug, tenoxicam, with a single injection of methylprednisolone in patients with subacromial impingement. A total of 58 patients were randomly allocated into two groups. Group A received 40 mg of methylprednisolone and group B 20 mg of tenoxicam as a subacromial injection along with lignocaine. The Constant-Murley shoulder score was used as the primary outcome measure and the Disability of Arm, Shoulder and Hand (DASH) and the Oxford Shoulder Score (OSS) as secondary measures. Six weeks after injection the improvement in the Constant-Murley score was significantly greater in the methylprednisolone group (p = 0.003) than in the tenoxicam group. The improvement in the DASH score was greater in the steroid group and the difference was statistically significant and consistent two (p < 0.01), four (p < 0.01) and six weeks (p < 0.020) after the injection. The improvement in the OSS was consistently greater in the steroid group than in the tenoxicam group. Although the difference was statistically significant at two (p < 0.001) and four (p = 0.003) weeks after the injection, it was not at six weeks (p = 0.055). Subacromial injection of tenoxicam does not offer an equivalent outcome to subacromial injection of corticosteroid at six weeks. Corticosteroid is significantly better than tenoxicam for improving shoulder function in tenodesis of the rotator cuff after six weeks.

Tendonitis of the rotator cuff due to subacromial impingement is caused by encroachment of the coracoacromial arch on the underlying tendons which constitute the rotator cuff.1 Tendonitis can progress to partial- or full-thickness tears of the cuff, and in some patients massive tears can lead to secondary osteoarthritis of the glenohumeral joint. A wide spectrum of options for treatment have been suggested, ranging from rest to total acromionectomy.1-7 The use of drugs such as non-steroidal anti-inflammatoryatories (NSAIDs), corticosteroids and injections of local anaesthetic have remained controversial owing to conflicting evidence in the literature supporting their anti-inflammatory properties.14,15 However, if steroids are effective because of their anti-inflammatory properties, there is an argument to try an alternative drug designed specifically as an anti-inflammatory, such as an NSAID, which might be a more effective therapeutic intervention.

NSAIDs have potent anti-inflammatory properties, and several have been used to treat tendonitis of the rotator cuff.2,8,13,18 These are most commonly administered as an oral preparation and are not often used as an injection because of local irritation and poor tolerability.19 Tenoxicam, a long-acting NSAID, is available as an injection for local administration. It is water soluble and comes without irritant preservatives which might cause local irritation. Patients who have had tenoxicam as an intramuscular or intravenous injection have tolerated it well.19 Tenoxicam was found to be useful in treating painful shoulders.19
Our objective in this double-blind randomised controlled trial was to evaluate the efficacy of subacromial injection of tenoxicam (Mobiflex, Roche, Welwyn Garden City, United Kingdom) in improving shoulder function and compare it to an injection of corticosteroid (methylprednisolone) (Depomedrone, Pharmacia NV/SA, Puurs, Belgium) in patients with subacromial impingement.

**Patients and Methods**

The study protocol was approved by the local research ethics committee and by the Research and Development Department in the host hospital. For the use of tenoxicam as subacromial injection in this study, the clinical trial licence for doctors (MLA 162, DDX) was obtained from the Medicines Control Agency. Guidelines according to the CONSORT statement were used to report the trial. All patients gave informed consent for participation in the trial. Patients not wishing to participate were treated according to existing protocols.

**Table I.** Baseline characteristics for the steroid and non-steroidal anti-inflammatory drug (NSAID) groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Steroid (n = 27)</td>
<td>NSAID (n = 31)</td>
</tr>
<tr>
<td>Mean age in years (range)</td>
<td>60 (36 to 88)</td>
<td>58 (36 to 75)</td>
</tr>
<tr>
<td>Gender (M:F)</td>
<td>16:11</td>
<td>16:15</td>
</tr>
<tr>
<td>Mean duration of symptoms in months (range)</td>
<td>8 (2 to 12)</td>
<td>10 (2 to 12)</td>
</tr>
<tr>
<td>Side</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dominant</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Non-dominant</td>
<td>11</td>
<td>16</td>
</tr>
<tr>
<td>Cause</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Traumatic</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Atraumatic</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>Median Constant-Murley score (range)</td>
<td>44.0 (18 to 86)</td>
<td>41.50 (25 to 92)</td>
</tr>
<tr>
<td>Median DASH* score (range)</td>
<td>45.0 (11.7 to 89.2)</td>
<td>36.7 (4.2 to 64.2)</td>
</tr>
<tr>
<td>Median Oxford Shoulder Score (range)</td>
<td>32.5 (21 to 62)</td>
<td>32.0 (17 to 48)</td>
</tr>
</tbody>
</table>

* DASH, Disability of the Arm, Shoulder and Hand

**Recruitment.** Patients were recruited from a specialist upper limb clinic in a university hospital. Over a two-year period, 58 patients satisfied the inclusion and exclusion criteria and were enrolled in the study, of whom 27 were randomised to the methylprednisolone group and 31 to the tenoxicam group (Fig. 1). The two groups were comparable with respect to age, gender, mode of onset (traumatic or atraumatic), duration of symptoms and the affected side. There were no significant differences in shoulder scores between the two groups before the injection. These data are summarised in Table I.

Two patients (one in each group) were lost to follow-up. The remaining 56 were seen for review six weeks after injection.

**Sample size calculation.** Patient numbers were calculated, assuming an approximate normal distribution for the primary outcome measure and a SD of 12 points, to detect a ten-point difference in the Constant-Murley Shoulder score between treatment groups at a 5% level of significance with 80% power. Allowing for some losses to follow-up (10%), this gave a minimum sample size of 25 patients for each arm of the trial.

**Inclusion and exclusion criteria.** All patients over the age of 18 years with a clinical diagnosis of subacromial impingement were considered eligible to participate in this study. The diagnosis was made by an upper limb orthopaedic consultant (SJD, ST) based on the history and clinical examination. The patients presented with a history of pain around the shoulder and/or lateral deltoid area, which worsened with overhead activity.

Examination of the affected shoulder showed a painful arc of movement on abduction, tenderness over the insertion of the cuff, and a positive Hawkins-Kennedy impingement sign. All patients had an anteroposterior (AP)
shoulder radiograph to rule out other causes of shoulder pain, such as arthritis of the glenohumeral or acromioclavicular joint. The trial was designed to mimic the typical presentation of a patient with an impingement syndrome to an orthopaedic clinic, and therefore advanced imaging tests such as ultrasound or MRI were not considered as part of the initial evaluation.

All patients had symptoms that had been present for at least three months, and had already undergone a period of conservative therapy consisting of rest, physiotherapy and/or oral anti-inflammatory medications.

Patients were excluded if any of the following criteria were present:
1. Evidence of other pathology causing shoulder pain, such as arthritis of the glenohumeral or acromioclavicular joints, adhesive capsulitis, fracture or a major tear of the rotator cuff presenting with weakness and muscle wasting.
2. Injection in the same shoulder within the previous six months.
3. Patients taking regular systemic NSAIDs or steroids, or in whom those drugs were contraindicated.
4. If their shoulder condition was currently the subject of any legal proceedings or insurance claims.
5. Pregnant and breastfeeding mothers.

Randomisation and preparation of medication. Random numbers for allocating patients to treatment groups were generated using a computer program. Before the study started, a set of sealed, consecutively numbered envelopes containing the random allocation details for each patient was prepared by colleagues not involved in the study. The patients were randomised to have either a single injection of 20 mg tenoxicam mixed with 5 ml 1% lignocaine, or 40 mg methylprednisolone mixed with 5 ml 1% lignocaine. The injection was prepared by the researcher and the syringes were kept by an independent clinic nurse. When a patient was recruited, the nurse was instructed to open one sealed envelope according to the individual patient’s recruitment number. The nurse took one prepared syringe containing the appropriate injection according to the details inside the envelope. Two opaque labels were applied to cover the whole syringe body, so that no other person could identify the medication inside it. It was then handed back to the researcher ready for injection into the patient’s affected subacromial space by one of the two orthopaedic consultants (SJD, ST). Throughout the preparation and follow-up, all patients, outcome assessors and treating consultants were blinded to the medication used; only the nurse who was responsible for opening the envelope and covering the appropriate syringe with labels was aware of the treatment allocated. The independent clinic nurse discarded all unused medication at the end of each clinic.

Procedure. The consultant gave the injection, using a 21-gauge needle with the covered syringe, into the patient’s subacromial bursa via the anterolateral approach applying an aseptic technique. A reduction in pain of at least 50% with full active abduction ten minutes after injection (Neer’s impingement test)26 confirmed accurate placement of the injection in the subacromial bursa. Patients were advised to take simple analgesia if required, but to avoid any preparation containing NSAIDs. All had standardised outpatient physiotherapy provided by an experienced specialist shoulder physiotherapist which was tailored to meet the needs of each patient and was aimed at correcting posture, associated muscle spasm or imbalance, posterior capsular tightness and restoring normal scapulothoracic movements.

Outcome assessment. The primary outcome measure was the Constant-Murley Shoulder Score.24 This consists of subjective assessments of pain and activities of daily living, as well as objective measurements of the range of active shoulder movement and strength of abduction. The latter measurement was recorded using a Nottingham Mecmesin Myometer (Atlantech Medical Device Ltd, Harrogate, United Kingdom).

The Disability of the Arm, Shoulder and Hand score (DASH)27 and the Oxford Shoulder score (OSS)28 were used as secondary outcome measures. The former is a self-administered region-specific outcome instrument developed as a measure of self-rated upper-limb disability and symptoms. It consists primarily of a 30-item disability/symptom scale, scored 0 (no disability) to 100. It has been validated29,30 and is shown to be useful in assessing the effectiveness of treatment of the impingement syndrome.

The OSS is a shoulder-specific self-administered questionnaire consisting of 12 items scored on a five-point ordinal scale. Scores are summed to give a single score, with a range from 12 (best) to 60 (worst). It has been shown to be consistent, valid, reproducible, and sensitive to clinical change.28

All patients completed the primary and secondary outcome measures scores before the subacromial injection. Each was followed up at 14 and 28 days, and the two outcome questionnaires (OSS, DASH) were completed via telephone by the researcher. At six weeks, patients were followed up in the outpatient clinic and all the outcome measures were collected. Patients were also asked about their use of oral analgesia during the study period, and gave a global assessment of their shoulder condition, rating it as much better, slightly better, no change, slightly worse or much worse.

Statistical analysis. Data on the scores were analysed using the non-parametric Mann-Whitney U test, and the subjective assessments of pain and shoulder function were analysed using chi-squared test. The null hypothesis was that there was no difference between test treatment groups, and for both tests a p-value ≤ 0.05 was considered significant. Box plots expressed the median and the interquartile ranges (IQR) for each group.

Results
Primary outcomes. Both groups showed an improvement in their Constant-Murley scores six weeks after the injection. However, the improvement was more pronounced in the steroid group. The median improvement in the Constant-Murley score at six weeks was 19.5 (IQR 8.75 to 33) for
patients in the steroid group and 6.5 (IQR: 3 to 15.75) for patients in the non-steroidal group (Fig. 2 and Table II). This difference was found to be statistically significant (Mann-Whitney, p = 0.003). In all, 25 of the 26 patients who were followed up in the steroid group showed an improvement in the Constant-Murley score, whereas in the non-steroid group 21 patients showed an improvement and nine a reduced score after six weeks.

Secondary outcomes. Patients in the steroid group showed significantly more improvement in the DASH and the OSS than patients in the NSAID group throughout the study period at two, four and six weeks after the injection. The results are given in Table III and illustrated in Figures 3 and 4.

Subjective assessment. In the Subjective Categorical Assessment (with one patient lost to follow-up in each group) more patients in the steroid group (23 of 26) felt that the injection helped with their pain, compared to the NSAID group (15 of 30) (chi-squared, p = 0.003). In all, eight patients in the steroid group decided to take additional oral analgesia during the study period compared with 15 in the NSAID group; this difference was not significant (chi-squared, p = 0.235). No patient in either group took supplementary NSAIDs during the study period. Overall, 12 patients in the steroid group felt their shoulder was much better, and eight felt it was slightly better than before the injection. In the NSAID group seven patients reported their shoulder to be much better and eight thought it was slightly better. The differences for shoulder function were not significantly different from the steroid group (p = 0.091, p = 0.771 Fishers exact test). In the NSAID group 15 patients reported their shoulder condition to be either unchanged or slightly worse than before injection. No adverse events or complications, either locally or systemically, were reported in either group.

Discussion

Few clinical studies have directly compared injection of steroid with NSAIDs by mouth in the treatment of rotator cuff tendinitis. The available evidence does not conclusively prove that one treatment is better than the other.8,13,18

Adebajo et al8 conducted a prospective double-blind placebo-controlled study comparing triamcinolone hexacetonide injection with oral diclofenac 50 mg tds. At four weeks both treatments were found to be superior to the placebo in reducing pain, improving active abduction and reducing functional limitation. However, improvement with triamcinolone was significantly better than with diclofenac. Similar results were found by Petri et al13 when they compared triamcinolone injection with treatment with oral naproxen. However, White et al18 found that there was no difference in the short-term efficacy of oral non-steroidal therapy compared to local corticosteroid injection after conducting a prospective double-blind randomised trial comparing a subacromial injection of 40 g of triamcinolone acetonide with oral indometacin (100 mg/day).
A systematic review conducted by the Cochrane Collaboration also concluded that although the available evidence from randomised controlled trials supports the use of subacromial corticosteroid injection for disease of the rotator cuff, the effect may be small and short-lived and no better than NSAIDs.

Our study suggests that a single subacromial injection of 20 mg tenoxicam does not have the same efficacy as corticosteroids, as measured by improvement in pain and function at six weeks. The difference was significant even at two weeks after the injection, and was maintained throughout the study period. One possible explanation could be that tenoxicam may have a shorter duration of action than methylprednisolone. Tenoxicam is a long-acting NSAID, and a double-blinded placebo controlled trial of 80 patients by Itzkowitch et al found that locally administered tenoxicam was effective in alleviating pain and improving shoulder mobility compared to a placebo. However, in that study patients had weekly injections of tenoxicam for up to four weeks. In our series, the first evaluation of functional response took place two weeks after injection and may have missed any therapeutic effect of tenoxicam, simply leaving the placebo effect. In order to maintain the double-blinded nature of our study, the protocol was based on our normal practice where patients receive a single subacromial injection of methylprednisolone and have an outpatient follow-up six weeks later.

This study has limitations. The treatment for subacromial impingement continues for a longer time, and patients could have multiple injections during the course of their treatment. The follow-up in the present study was limited to six weeks and consequently the results do not address long-term outcome or the occurrence of adverse events. However, a recent study by Cummins, Sasso and Nicholson on the temporal outcomes of non-operative treatment for impingement syndrome, suggests that the outcome at six weeks following a subacromial injection can predict the long-term outcome. Moreover, many patients with subacromial impingement may be taking regular oral NSAIDs, which would have excluded them from this study, making it difficult to extrapolate the results to all patients seen in clinical practice.

In our group of patients with cuff-related pain, a single subacromial corticosteroid injection of 40 mg of methylprednisolone provided a significantly better outcome than a single injection of 20 mg of tenoxicam when shoulder function was assessed at two, four and six weeks.

We wish to thank Mr S. Turner, Consultant Orthopaedic Surgeon at University Hospitals Coventry and Warwickshire NHS Trust, for his help in conducting this study. We also thank Mr M. Costa and Dr J. Achten for their help in preparing this manuscript.

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

Acknowledgements

We are grateful to the patients who participated in this study.

Funding

This study was supported by a grant from the NHS Research and Development Programme.

A controlled study comparing subacromial injection of tenoxicam or methylprednisolone

References


