A Randomized Clinical Trial of Oral versus Intramuscular Delivery of Steroids in Acute Exudative Pharyngitis

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Abstract. Previous study has shown that the use of intramuscular (IM) steroid leads to improved symptoms in patients with group A beta-hemolytic streptococcus (GABHS). Objective: To compare oral with IM steroids as an adjunct to antibiotic therapy in the treatment of acute exudative pharyngitis. The null hypothesis was that there would be no difference in effectiveness of oral versus IM steroids. Methods: The study was a randomized, double-blind outpatient clinical trial. After consent was obtained, each patient was asked to rate his or her pain on a 10-cm numbered visual analog scale (VAS; 0–10). All of the patients received injectable benzathine penicillin or, if allergic to penicillin, a ten-day course of polyenteric-coated erythromycin. Each patient was randomized to receive either injectable steroid plus oral placebo or injectable placebo plus oral steroid. All medications were given in the emergency department. All patients were contacted by telephone at 24 hours (first follow-up) and 48 hours (second follow-up) by one of the study investigators and asked to rate their pain based on another VAS. If their pain was not resolved by 48 hours, they were called again daily for the third to seventh day after the initial visit. The time to total resolution of the sore throat was documented. The main outcome measures were time to complete relief of pain and VAS scores. Pain medication was not controlled; however, use of pain medications and amounts were recorded. Results: A total of 78 patients were initially enrolled in the study. Eight patients were excluded from the statistical analysis because of inability to follow up. A total of 70 were entered, with 35 randomized to IM steroid plus oral placebo and 35 to IM placebo plus oral steroid. There was no difference in pain scores for the oral versus IM group at first follow-up (p = 0.13) and second follow-up (p = 0.82), and in number of hours to relief of pain (p = 0.06). Using repeated-measures analysis of variance, no difference in the effects of the two medications over time was detected (p = 0.83). Conclusions: The results of this clinical trial suggest that oral steroid and IM steroid provide similar levels of pain relief in acute exudative pharyngitis. Key words: pharyngitis; corticosteroids; emergency department; oral; intramuscular; drug delivery.
There is abundant literature on the benefits of steroids in the treatment of the inflammatory component in conditions such as croup and bronchial asthma. For years physicians in our institution have used the combination of betamethasone or dexamethasone with an antibiotic for the treatment of acute exudative pharyngitis. However, this treatment regimen requires an IM injection of steroid, causing pain, necessitating more nursing care, and potentially lengthening ED stays. The purpose of the present study was to compare injected with oral steroids in a one-time dose in patients with acute exudative pharyngitis. Our null hypothesis was that there would be no difference in time of complete pain relief and in visual analog scale (VAS) pain scores by using IM versus oral steroid as adjunct to antibiotics in acute exudative pharyngitis.

METHODS

Study Design. The study was a randomized double-blind clinical trial in a convenience sampling of patients. The university institutional review board for protection of human subjects approved the study. Written prospective informed consent was obtained from all participants.

Study Setting and Population. The study took place in the adult section of an inner-city ED with an emergency medicine residency program and an annual census of 150,000. Subjects aged 18–65 years were included. The attending physician ultimately determined eligibility in the study.

Study Protocol. Patients were included if they had a complaint of all of the following: sore throat, odynophagia, dysphagia, and fever by history. Only patients with visible evidence of pharyngeal infection including enlarged tonsils and purulent exudates were entered. For inclusion in the study, a minimum initial pain score of 5 on a 10-cm VAS was necessary to establish existence of odynophagia. In an attempt to exclude other sources for the sore throat such as allergic or viral causes, patients entered into the study had exudative pharyngitis as opposed to only erythematous changes. Patients were also required to have a working telephone in order to ensure follow-up.

Subjects were excluded from the study if they had AIDS or immunocompromise, a peritonsillar abscess, thrush, recent steroid use (within the last three months), diabetes, an ulcerative pharyngitis, a pharyngitis without exudates, known allergic reactions to steroids, or the inability to provide meaningful informed consent. Pregnant women were also excluded.

Patients who agreed to participate in the study were asked to rate their pain on a standardized visual pain scale. The scale was a 10-cm line-graded VAS from 0 to 10 at 1-cm increments, with 0 representing no pain and 10 the worst pain ever. Subjects were asked to mark the line at the point corresponding to their pain. Once this first assessment was complete, patients no longer had access to this initial visual pain scale.

Patients were prospectively randomized to one of two groups, one receiving antibiotic and 2 mL of injectable dexamethasone (10 mg) and oral placebo and the other receiving antibiotic and 2 mL of injectable saline and oral prednisone (60 mg). Patients weighing more than 90 lb received 1.2 million units of IM benzathine penicillin, whereas those with a weight less than 90 lb received 900,000 units IM. Those subjects allergic to penicillin were supplied with samples of polyenteric-coated erythromycin (PCE) 500 mg twice a day for 10 days. Randomization into each study group was done using a computerized random numbers table. Once the patient was entered in the study, the treating physician wrote the order for the antibiotic, and recorded the patient’s study number. The principal investigator wrote an order for “study # X” and the nurse prepared the medication, either saline or dexamethasone, according to the random table. Another researcher who was not aware of the randomization administered the medication. Neither the person giving the injection nor the patient was aware of which medication was being administered. The oral medications were prepared by pharmacy in a numbered bag corresponding to the study number. The prednisone (60 mg) and placebo looked exactly alike. The antibiotic used was not blinded and was administered in the usual manner.

Before discharge from the ED, each subject was given a copy of the consent form and a copy of the pain scale similar to the one used to rate the pain initially. This was used for the observational home trial follow-up of pain. A follow-up questionnaire was completed with the subject’s name, address, telephone number, hospital number, and the study number. Each patient was then called at 24 and 48 hours. The endpoint of the study was time to complete relief of pain, based on the patient’s self-report. Patients were asked to rate their pain in follow-up in the same way they had rated their pain in the initial visit. Patients who did not have the pain scale available at the time of follow-up were reminded what number they rated their pain initially and asked to compare their pain on that particular day with the previous pain severity. Investigators making follow-up phone calls were unaware of treatment assignment. Side effects and days missed from school or work were documented as number of days of each. No pain medications
were given as part of the study protocol, but ibuprofen or acetaminophen was recommended for fever or pain control at the discretion of the physician. At follow-up, patients were asked about pain medication use, salt-water gargles, spray anesthetics, and amount of use.

**Data Analysis.** Statistical models were considered with variables grouped as follows:

1. Response variables included initial pain scores, pain scores at first follow-up, pain score at second follow-up, hours until initial relief began, number of hours until being pain-free, and number of days of work or school missed.

2. Demographic data of age, gender, side effects, medication used for pain at home, and amount used were compared using descriptive statistical analysis.

Statistical analysis was performed using t-tests and the Mann-Whitney U test for comparing scores and times to complete relief between groups. The Mann Whitney U test was used because the data were nonparametric. Chi-square was used to test categorical data for treatment group differences at baseline. P-values of <0.05 were considered statistically significant.

Repeated-measures analysis of variance (ANOVA) was used to test differences between the groups over time.

**Sample Size Determination.** It was determined that with 30 subjects in each group, the study had a power of 0.9 to detect a significant difference using repeated-measures ANOVA. Additionally, the study had a power of at least 0.8 to detect a 12-mm difference in VAS scores. This is in concordance with previous studies of clinically significant differences.10

**RESULTS**

A total of 78 patients were initially enrolled in the study. Follow-up was not obtained for eight patients due to inability to contact patients after multiple attempts. Of the 70 total, there were 35 in the IM dexamethasone group and 35 in the IM placebo group. All patients received IM penicillin. A summary of patient enrollment is shown in Figure 1. The mean ± SD initial pain score for the dexamethasone group was 7.9 ± 2 cm (median score 8 cm) and that for the prednisone group was 7.5 ± 2 cm (median score 8 cm). The numbers of males and females, mean ages (32 versus 29 years), and initial pain scores were comparable in the two treatment groups and were not statistically different. Pain medications use at home and amounts used were not statistically different in the IM dexamethasone versus oral prednisone groups.

These results are summarized in Table 1. The measure of variability between groups is standard deviation. Differences are expressed as percent differences in means, with 95% confidence intervals (95% CIs) around these differences.

On phone follow-up, approximately 50% of patients were reminded of previous scores on the VAS. The median pain scores at first phone follow-up (p = 0.13 using Mann-Whitney U) were not significantly different in the dexamethasone and the prednisone groups (mean difference between groups at first follow-up: 0.8; 95% CI = −0.4 to 2). The median pain scores at second follow-up were also not significantly different (mean difference between groups: 0.3; 95% CI = −1.4 to 0.9). Using the Mann-Whitney U test for nonparametric anal-
ysis, the numbers of hours until no pain (0.06) were not significantly different in the two groups. The numbers of days of school or work missed were not significantly different in the two groups (1.2 versus 0.83 days, p = 0.1). These results are summarized in Table 1.

Using repeated-measures ANOVA to determine effect of medication on time, no difference was detected (p = 0.83). No difference was detected in tests of within-subjects effects (p = 0.84) or between-subjects effects (p = 0.88) (Table 2).

Twelve patients reported pain at the injection site, six in the dexamethasone and six in the prednisone group. There was no difference in number of side effects reported in the two groups (p = 0.55). Other complaints at telephone follow-up included dizziness in four patients, headache in four, stomachache in two, and upper respiratory infection symptoms in three. No other side effects, complaints, or complications were reported.

**DISCUSSION**

Patients with sore throats often present to the ED with a chief complaint of pain. They may have difficulty swallowing and thus be unable to maintain desired hydration. Their main goal in presenting to the ED is to obtain relief of pain. In addition to pain relief, a major goal in the ED is to treat potential GABHS to prevent complications.

Evaluation and treatment of pharyngitis remain controversial and vary widely. Antibiotics have been shown to have an effective role in the treatment of acute exudative pharyngitis caused by GABHS, and in the prevention of rheumatic fever and other delayed complications. Clinical prediction rules considering the use of antibiotics for presumed GABHS include physical examination and historical findings. Recommendations for treating pharyngitis with antibiotics include three or four of the following: presence of exudates, anterior cervical node enlargement or pain, absence of cough, and history of fever. Penicillin is a very effective treatment for GABHS because it prevents acute rheumatic fever and the ensuing complications. Prompt relief of the patient’s pain is also of concern. The purpose of this study was to show whether oral prednisone worked as well as injectable dexamethasone in the treatment of the pain of exudative pharyngitis.

Dexamethasone (Decadron) is a rapid-acting steroid with a short duration of action. Response is noted within 12–24 hours of administration. Prednisone also acts rapidly. Intramuscular injections lead to high concentrations of steroids, although there is systemic absorption with oral dosing as well. Glucocorticoids act on the inflammatory process, leading to a decreased number of certain white blood cells. After treatment with prednisone, these cells decline within four to six hours, and lower numbers persist for 24 hours or more.

O’Brien et al. also studied patients with acute exudative pharyngitis. In that study, patients rated their pain on a 15-cm VAS (not validated). The steroid of choice in the O’Brien study was dexamethasone, 10 mg IM. Unlike our present study, the O’Brien study provided only oral antibiotics, and patients were followed at different posttreatment intervals than in our study. Patient compliance was not a problem in those receiving penicillin IM in our previous study or the present study, but it may have been an issue in the O’Brien study. Time to relief of pain was significantly shorter in those patients receiving dexamethasone in our study compared with those receiving placebo.

### Table 1. Demographics of the Dexamethasone versus Prednisone Groups

<table>
<thead>
<tr>
<th></th>
<th>Dexamethasone (n = 35)</th>
<th>Prednisone (n = 35)</th>
<th>p-value (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>19 (27%)</td>
<td>20 (29%)</td>
<td>p = 0.81</td>
</tr>
<tr>
<td>Female</td>
<td>16 (23%)</td>
<td>15 (21%)</td>
<td></td>
</tr>
<tr>
<td>Age—mean ± SD</td>
<td>32 ± 11</td>
<td>29 ± 12</td>
<td>Diff 3%; 95% CI = −2 to 8</td>
</tr>
<tr>
<td>VAS 1*—mean ± SD</td>
<td>7.9 ± 2</td>
<td>7.5 ± 2</td>
<td>p = 0.32</td>
</tr>
<tr>
<td>Analgesics used—mean number ± SD</td>
<td>0.7 ± 0.4</td>
<td>0.5 ± 0.5</td>
<td>p = 0.083</td>
</tr>
<tr>
<td>Amount of analgesics—mean number of doses ± SD</td>
<td>2 ± 2</td>
<td>3 ± 3</td>
<td>Diff 0.6%; 95% CI = −1 to 2</td>
</tr>
<tr>
<td>Side effects—mean ± SD</td>
<td>0.4 ± 0.5</td>
<td>0.4 ± 0.5</td>
<td>p = 0.76</td>
</tr>
<tr>
<td>Hours to begin relief—median</td>
<td>5</td>
<td>3</td>
<td>p = 0.5</td>
</tr>
<tr>
<td>Hours to complete relief—median</td>
<td>43</td>
<td>36</td>
<td>p = 0.06</td>
</tr>
<tr>
<td>Days of work/school missed—median</td>
<td>1.2</td>
<td>0.83</td>
<td>p = 0.1</td>
</tr>
</tbody>
</table>

*Score on the first visual analog pain scale.
# Table 2. Results of the Visual Analog Scale (VAS)

<table>
<thead>
<tr>
<th>Time = 0</th>
<th>Dexamethasone</th>
<th>Prednisone</th>
<th>p-value (nonparametric*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VAS median</td>
<td>8.0 cm</td>
<td>8.0 cm</td>
<td>0.32</td>
</tr>
<tr>
<td>IQR</td>
<td>6.0–10.0 cm</td>
<td>6.0–9.0 cm</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time = 24 hours</th>
<th>VAS median change</th>
<th>VAS median</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>3.0 cm</td>
<td>1.0 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.0 cm</td>
<td>7.0 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0–4.5 cm</td>
<td>1.0–3.0 cm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Time = 48–72 hours</th>
<th>VAS median change</th>
<th>VAS median</th>
<th>IQR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0 cm</td>
<td>0 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.0 cm</td>
<td>1.0 cm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0–2.0 cm</td>
<td>0–1.5 cm</td>
</tr>
</tbody>
</table>

*Repeated-measures analysis of variance p = 0.83; within-subjects effects p = 0.84; between-subjects effects p = 0.88.
†IQR = interquartile range.

in the O’Brien study. The numbers of hours to complete relief of pain in the O’Brien study were substantially lower for both groups compared with those in our studies. The reasons for this are unknown. The uses of analgesics were reported as similar in the two groups by types of pills, numbers, and strengths.

Our previous study of inner-city ED patients compared IM betamethasone with placebo for the treatment of exudative pharyngitis. Patients entered into that study had exudative pharyngitis as opposed to only erythematous changes. Patients receiving betamethasone had more relief of pain and therefore a lower pain scale score sooner than the placebo group. Those receiving betamethasone also reported a more rapid onset of pain relief and total relief of pain compared with the placebo group; patients receiving betamethasone started to feel better five hours earlier and were pain-free on an average of approximately 14 hours earlier than the placebo group. There was no difference in the number of days missed from work or school between the two groups in that study.

To the best of our knowledge, our present study is the first to examine oral compared with IM steroids for pain reduction in exudative pharyngitis. Since it has been established in two studies that IM injections of steroids are effective in reducing the pain of exudative pharyngitis, our goal was to determine whether the steroid could be given as a single oral loading dose, instead of necessitating an IM injection. Since VAS scores, numbers of days of work or school missed, and uses of pain medications were statistically similar in the two groups, our study suggests that in our patient population, oral steroids in a single dose resulted in an equal pain reduction response to an IM dose of steroid and may therefore be of benefit for pain relief in acute exudative pharyngitis.

It is unknown whether steroids may adversely affect or exacerbate pharyngitis. Considering use of much higher doses in asthmatic patients and in those with other infectious diseases such as bronchitis or pneumonia, this does not appear to be a significant issue. No infectious complications were observed in previous studies in which single IM doses of steroids were used, or in our present study. A larger sample size is necessary to determine whether complications of pharyngitis such as peritonsillar abscess may increase because of steroid use. Cultures posttreatment could determine whether bacterial pathogens are still present after treatment with steroid, but this is beyond the scope of this study.

There are many potential advantages to the use of oral rather than IM steroids. Injections usually are more costly than orally administered drugs. Exposure of personnel to needles is risky. Patients also complain frequently about the pain of injection. In our study, many continued to have pain at the time of telephone follow-up. There is also a risk of formation of sterile abscesses at injection sites, which would require further medical care and cause more pain to the patient. Administration of a single oral dose of prednisone may therefore be of increased benefit and eliminates an additional injection in patients with exudative pharyngitis.

## Limitations and Future Questions

This study did not require throat cultures to establish a bacterial cause of pharyngitis. In recent literature, however, cultures are not recommended in adults and treatment should be based on physical examination and historical findings.

The VAS used for the study was a standard 10-cm VAS. Gradations were used for the telephone follow-up portion of the study, and it is not certain
that a verbal report of a VAS has the same meaning as its traditional application. These measures had been successfully used in our previous study of patients with exudative pharyngitis, however.9

Another potential limitation was the unavoidable necessity of having to remind patients of previous VAS scores if they did not have their copies with them at the time of telephone contact. They were then able to quantify whether their pain was less than it had been previously. Approximately 50% of patients had to be reminded of their previous scores (with about equal representation in the two groups). The possible effect of this limitation is uncertain.

Pain medication use, although recorded, was not controlled. It is unknown whether use of adjunctive pain medications, such as codeine or hydrocodone, could have resulted in equal or better results for improving symptoms in this group.

Our placebo group was not compared with the group receiving oral steroids. However, previous studies have shown IM steroids to be a significant contribution to pain relief when compared with placebo.8,9 It is likely that the same holds true for oral steroids, and this question might be an important future study topic.

Only those with exudates were entered in the study. The effect of steroids on those without exudates is not established.

A comparison of opioid pain medication with and without steroids may establish the optimal method for pain control in the setting of acute exudative pharyngitis.

CONCLUSIONS

There was no difference in single-dose oral prednisone compared with IM dexamethasone in relieving the pain of exudative pharyngitis. With the added benefit of lower cost and no pain from the injection, oral steroids may provide effective adjunctive therapy to patients with painful exudative pharyngitis. The safety of steroid use without antimicrobial use has not been studied; therefore, use should be limited to those receiving antimicrobial therapy.

References