Dexamethasone for the Treatment of Sore Throat in Children With Suspected Infectious Mononucleosis

A Randomized, Double-blind, Placebo-Controlled, Clinical Trial

Michel Roy, MD, FRCPC; Benoit Bailey, MD, MSc, FRCPC; Devendra K. Amre, MBBS, PhD; Jean-Bernard Girodias, MD; Jean-François Bussières, BPharm, MSc, MBA, FCSHP; Pierre Gaudreault, MD, FRCPC

Objective: To evaluate the efficacy of a single oral dose of dexamethasone for pain relief in acute exudative pharyngitis associated with infectious mononucleosis.

Methods: We conducted a randomized, double-blind, placebo-controlled pediatric emergency department–based clinical trial. Patients aged between 8 and 18 years with a sore throat from clinically suspected infectious mononucleosis were eligible. Patients were randomized to receive either an oral dose of 0.3 mg/kg (maximum, 15 mg) of dexamethasone or a placebo. Patients completed a diary of symptoms and rated their pain on a visual analog scale from 0 to 100 mm at 0 hours, 12 hours, 24 hours, 48 hours, 72 hours, and on day 7. An improvement of 20 mm from baseline on the visual analog scale was evaluated as the primary end point.

Results: Twenty patients were recruited in each group; mean±SD age was 13.5±2.8 years. In comparison with the placebo group, a significantly greater proportion of patients given dexamethasone achieved pain relief within the first 12 hours (12/20 vs 5/19; P=.03). On further follow-up, the proportions achieving pain relief were similar between groups: 11 of 20 vs 6 of 20 at 24 hours (P=.10); 11 of 20 vs 11 of 20 at 48 hours (P=.99); 15 of 20 vs 15 of 19 at 72 hours (P=.93); and 18 of 19 vs 19 of 20 at day 7 (P=.99), with dexamethasone vs placebo, respectively.

Conclusions: The short-lived relief of pain in acute exudative pharyngitis in children with suspected infectious mononucleosis may suggest that a single oral dose of dexamethasone may not be sufficient and that additional doses may be necessary for ensuring lasting relief.


Infectious mononucleosis (IM) causes significant morbidity. Tonsillopharyngeal symptoms are present in more than 75% of patients with IM.1 The acute exudative pharyngitis is usually painful and is maximal for 5 to 7 days, with subsequent resolution within 7 to 14 days, although longer persistence has been reported.2,3 Severe sore throat is the symptom that most frequently prompts patients to seek medical attention.3 Most patients who consult physicians wish to obtain pain relief so that they may return to their normal daily activities. However, presently, there is no recognized treatment for the acute exudative pharyngitis associated with IM despite the use of corticosteroids for faster amelioration of symptoms.2 Corticosteroids have been shown to reduce the upper airway obstruction caused by IM, but their efficacy for the treatment of the pain associated with the pharyngitis is unclear.4-8

To further evaluate the efficacy of corticosteroids for pain relief in acute exudative pharyngitis associated with IM, we conducted a randomized, double-blind, placebo-controlled, pediatric emergency department (ED)–based clinical trial. Our hypothesis was that patients treated with a single oral dose of dexamethasone would have better relief of sore throat compared with the placebo group.

METHODS

STUDY DESIGN AND ELIGIBILITY

All patients aged 8 to 18 years with a sore throat evaluated for clinically suspected IM in one large, urban, tertiary pediatric hospital ED with a mean annual visit rate of 69,000 patients per year were candidates for inclusion in the study. Because the monospot test to confirm the diagnosis of IM was only available during the daytime, all patients with clinical features suggesting IM according to the attending physician were eligible. Patients were therefore included in an intention-to-treat basis. Sore throat had to be present at enrollment but there was no minimum pain score. Patients were excluded from the study if corticosteroids were
indicated for upper airway obstruction or if they had any of the following conditions by history: pregnancy or suspected pregnancy, cancer, liver disease, human immunodeficiency virus or AIDS, current or past peptic ulcer disease, hypertension, tuberculosis, glaucoma, diabetes mellitus, immune deficiency, kidney disease, invasive bacterial infection, osteoporosis, varicella contact in patients without a history of chickenpox, active neurologic or psychiatric disease, malabsorption, immunosuppressor treatment, and patients who received corticosteroids in the 7 days preceding the visit to the ED. All patients gave consent to the study, and one of their parents or legal guardian had to sign the consent form prior to randomization. The ethical review board at our institution approved the study.

PROCEDURE

After the initial clinical diagnosis of IM by the attending physician, further confirmation was done by one of the investigators (M.R. or B.B.). Clinical diagnosis was based on the presence and duration of sore throat, odynophagia, respiratory distress, fatigue, and fever. In addition, information on general appearance, temperature, weight, tonsil size, tonsil redness, tonsil exudates, cervical lymphadenopathy, and the size of the liver and spleen were also recorded. The investigator also subjectively evaluated the severity of the pharyngitis (light, moderate, or severe). A bacterial throat culture, monitest, and Epstein-Barr virus were performed on each eligible patient to reach a final diagnosis of IM-induced acute exudative pharyngitis.

Participants were then asked to rate their sore throat pain at time 0 on a standardized visual analog scale (VAS) from 0 to 100 mm. Patients marked the VAS line with a pen, where 0 mm represents no pain and 100 mm represents the worst pain. Patients were then randomized into 1 of 2 groups: treatment or placebo. A computer random number generator was used to ensure unbiased allocation. The computer-generated list was drawn up a priori by the statistician and given directly to the pharmacy department. An independent pharmacist prepared either dexamethasone or a similar tasting and looking placebo in small opaque bottles identified by a number according to the list. These bottles were kept in the ED at all times. The investigator responsible for recruiting the patient allocated the next number on the list. A dose of 0.3 mg/kg of dexamethasone (1 mg/mL; maximum, 15 mg) or an equivalent amount of placebo was administered orally with a syringe by an attending nurse. All study personnel and participants were blinded to treatment assignment for the duration of the study. The randomization code was revealed to the researchers once recruitment, data collection, and laboratory analyses were complete for all patients.

When discharged from the ED, patients were provided with 5 copies of the visual analog scale, a chart for coanalgesia use (including type, timing, and dose), and a list of symptoms. Patients were encouraged on the consent form to use acetaminophen for coanalgesia. Other analgesics were not contraindicated; patients were simply asked to write down type (ie, acetaminophen, ibuprofen, or codeine), time, and dose if coanalgesia was used. Telephone reminders were made for completing the VAS at times 12, 24, 48, and 72 hours, and on day 7. To assess blinding, one of the investigators (M.R.) tried to guess if participants received dexamethasone or placebo once we had received the VAS. Patients were examined approximately 4 weeks after enrollment by one of the investigators (M.R.).

MEASUREMENTS

The main outcome with respect to the efficacy of dexamethasone was assessed by comparing the proportion of patients who achieved at least a 20-mm improvement on the VAS. We chose a 20-mm difference to be clinically important, a difference slightly higher than the 13-mm difference found to be clinically significant in previous VAS studies. Thus, for an α of .05, a β of .80, and an SD of 20 mm, we would need 20 patients in each group in this trial.

Differences in categorical outcomes (for example, proportions achieving pain relief) between groups were examined using the χ² test or Fisher exact test whenever appropriate. Survival analysis was done, and Kaplan-Meier survival curves were generated. Differences between groups in continuous variables (for example, the dose of acetaminophen used) were evaluated by a t test or Mann-Whitney rank sum test, whenever appropriate. The level of significance was set at P ≤ .05.

RESULTS

A total of 40 patients were recruited from October 2001 to November 2002 (Figure). There was no significant difference in the baseline characteristics of both groups (Table 1). Twenty-seven patients had a positive monitest and serologic test at the initial examination. Two patients had a positive monitest but negative serologic test at the initial examination. The follow-up serologic test was positive in those 2 cases. Two patients had a negative monitest and serologic test at the initial examination. The follow-up serologic test was positive in those 2 cases. Two patients had a negative monitest and serologic test at the initial examination but a positive serologic test at the follow-up. One patient had a negative monitest but a positive serologic test at the initial examination. One patient had only a monitest performed at the initial examination, and it was positive.

Table 2 presents the critical 20-mm difference in the VAS at different periods of time. In comparison with those given the placebo (group 1), a significantly greater proportion of patients given dexamethasone (group 2) achieved a 20-mm pain relief at 12 hours (12 [60%] of 20 vs 5 [26%] of 19, [95% CI, Δ 3%-57%], but this difference was not present at other times. The actual decrease in pain achieved by dexamethasone or placebo at different times is presented in Table 3. Again, dexamethasone achieved pain relief in a higher proportion of patients (group 2) when compared with the placebo (group 1) at all times.

<table>
<thead>
<tr>
<th>Table 1: Baseline Characteristics of Both Groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>----------</td>
</tr>
<tr>
<td>Treatment</td>
</tr>
<tr>
<td>Placebo</td>
</tr>
</tbody>
</table>

©2004 American Medical Association. All rights reserved.
methasone only decreased pain at 12 hours (P = .007). Kaplan-Meier survival curves did not reveal any significant differences overall in time to pain relief between the 2 groups (P = .71).

The frequency of use of acetaminophen was similar between the comparison groups: 12 (60%) of 20 in group 2 vs 16 (80%) of 20 in group 1 (P = .17). There were also no differences in the doses used (median, 12.4 in group 2 vs 35.6 mg/kg per day in group 1; P = .24). The overall frequency of use of any analgesic was similar between the 2 groups (16 [80%] of 20 for group 2 vs 17 [85%] of 20 for group 1; P = .68). Also, 11 patients used ibuprofen, 5 in group 2 and 6 in group 1 (P = .72). Two patients used codeine, both in group 2 (P = .49).

About 7 (44%) of 16 patients in the dexamethasone group had a fever (>38°C oral) after leaving the ED compared with 10 (67%) of 15 in the placebo group (P = .20). After 7 days, 9 (60%) of 15 of patients in group 2 had returned to their normal activities compared with 7 (41%) of 17 in group 1 (P = .39).

Four patients were hospitalized during the course of the study, all on subsequent visits to the ED, 3 patients in group 1 (15%) and 1 (5%) in group 2 (P = .30). The first patient in group 1 was hospitalized for decreased oral intake, vomiting, and dehydration. The second patient was hospitalized for dehydration and pneumonia. The last patient hospitalized in group 1 was admitted for severe pharyngitis, decreased oral intake, and dehydration. The patient from group 2 who was hospitalized was a 15-year-old girl who initially came to the ED with a sore throat and fatigue. On day 3 of the study, the research nurse advised her to consult the ED for evaluation of dehydration. Her physical examination demonstrated severe pharyngitis and dehydration. She did not have respiratory symptoms. She was hospitalized and received intravenous erythromycin and methylprednisolone for severe pharyngitis on day 3. In the next days, she developed respiratory distress and was later found to have pleural effusion and empyema. The culture was positive for Streptococcus constellatus. She later developed anemia and shock and was hospitalized in the pediatric intensive care unit for 2 weeks. She was seen in the infectious disease clinic 1 month after discharge. She was asymptomatic, and her hemoglobin level was normal.

The control physical examination was done in 39 of 40 patients approximately 1 month after inclusion in the study, and all physical examination findings were normal. One patient did not return; he was asymptomatic at the telephone follow-up. Blinding appears to have been successful, as one of the investigators was only able to correctly identify 10 of 20 and 12 of 20 participants who received dexamethasone and placebo, respectively.

Therapeutic options for the pain relief of acute exudative pharyngitis associated with IM are limited. Lymphoproliferative inflammation of the pharynx from the Epstein-Barr virus is responsible for the sore throat. Compared with other viral pharyngitis, Epstein-Barr virus exudative pharyngitis is more severe and lasts longer.³ The goal of short-term corticosteroid therapy is to reduce the acute inflammation and decrease the sore throat symptoms. Secondarily, one can postulate that patients with less pain can improve their oral intake and prevent dehydration and the need for hospitalization.

The results of our study suggest that dexamethasone is effective at providing greater relief of pain compared with a placebo at 12 hours. However, at 24 hours and later, there was no significant difference between dexamethasone and the placebo. Thus, more than 1 dose may be needed to achieve lasting relief of pain in IM-induced pharyngitis. The dose of dexamethasone used, 0.3 mg/kg, is equivalent to a prednisone or prednisolone dose of 1.8 mg/kg, with a longer duration of action.¹² A single oral dose of dexamethasone (0.6 mg/kg; maximum, 10 mg) was recently found to have no effect on pain induced by group A β-hemolytic streptococcus and non–group A β-hemolytic streptococcus pharyngitis in children.³¹ In adults, a single dose of 10 mg of dexamethasone has been found to be effective in group A β-hemolytic streptococcus and viruses other than Epstein-Barr.¹⁴-¹⁶

Previous studies that evaluated the efficacy of corticosteroids in IM are primarily based on data collected from inpatient health infirmaries and were done mostly in the 1960s. Schumacher et al ¹² found that oral prednisone, 60 mg/d for 5 days, had no effect on symptoms and signs of IM in a double-blind study of 13 patients with an average

**Table 1. Baseline Characteristics of Patients Included in the Study**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dexamethasone (n = 20)</th>
<th>Placebo (n = 20)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD, y</td>
<td>13.8 ± 2.7</td>
<td>13.2 ± 2.8</td>
<td>.48</td>
</tr>
<tr>
<td>Median duration of sore throat prior to initial examination, d</td>
<td>4.5</td>
<td>4.0</td>
<td>.74</td>
</tr>
<tr>
<td>Analgesic used prior to VAS</td>
<td>14</td>
<td>13</td>
<td>.74</td>
</tr>
<tr>
<td>Subjective tonsil size (1+/2+/3+)</td>
<td>7/9/5</td>
<td>7/9/4</td>
<td>.91</td>
</tr>
<tr>
<td>Initial intensity of sore throat mean ± SD, mm</td>
<td>71.3 ± 21.0</td>
<td>69.0 ± 16.0</td>
<td>.70</td>
</tr>
<tr>
<td>Investigator subjective pharyngitis assessment, light/moderate/severe</td>
<td>3/10/7</td>
<td>5/9/6</td>
<td>.73</td>
</tr>
</tbody>
</table>

Abbreviations: IM, infectious mononucleosis; VAS, visual analog scale.

**Table 2. Number of Patients With a 20-mm Decrease in Pain at Various Times After a Single 0.3-mg/kg Oral Dose of Dexamethasone or Placebo**

<table>
<thead>
<tr>
<th>Time</th>
<th>Dexamethasone (n = 20)</th>
<th>Placebo (n = 20)</th>
<th>95% CI Difference, %</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 h</td>
<td>12 (60)</td>
<td>5 (26) of 19</td>
<td>3 to 57</td>
<td>.03</td>
</tr>
<tr>
<td>24 h</td>
<td>11 (55)</td>
<td>6 (30)</td>
<td>−5 to 50</td>
<td>.10</td>
</tr>
<tr>
<td>48 h</td>
<td>11 (55)</td>
<td>11 (55)</td>
<td>−28 to 28</td>
<td>&gt;.99</td>
</tr>
<tr>
<td>72 h</td>
<td>15 (75)</td>
<td>15 (79) of 19</td>
<td>−29 to 22</td>
<td>.93</td>
</tr>
<tr>
<td>7 d</td>
<td>18 (95) of 19</td>
<td>19 (95)</td>
<td>−20 to 19</td>
<td>&gt;.99</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

*Data are given as number (percentage) of patients unless otherwise indicated.
Three patients from the placebo group were hospitalized, and only 1 patient from the dexamethasone group was hospitalized. This might suggest that dexamethasone could reduce the rate of hospitalization; however, definite conclusions cannot be reached due to the limited sample size. The dexamethasone-treated patient who was hospitalized had a complicated case of IM. Intravenous methylprednisolone was also administered to this patient because of the severe pharyngitis prior to the development of respiratory distress. The assessment of dexamethasone’s role, if any, is complicated by the use of methylprednisolone. However, empyema complicating IM was described in the literature in a patient who did not receive corticosteroids. It is a rare but known complication of IM. Therefore, a causal relationship between the empyema and the use of oral dexamethasone and intravenous methylprednisolone cannot be made. The safety issue of corticosteroids in IM remains a subject for discussion. Future studies with larger sample sizes could address that question.

The limitations of our study include the fact that all patients with or without (suspected) a confirmed diagnosis of IM were enrolled. The inclusion of clinically suspected IM pharyngitis in the study could have biased the study toward negative results since a single dose of dexamethasone (0.6 mg/kg; maximum, 10 mg) was found to have no effect in children with group A β-hemolytic streptococcal pharyngitis and non–group A β-hemolytic streptococcal pharyngitis. Another potential limitation of the study is that the VAS has not been previously validated for the assessment of sore throat in the ED. However, it has been used previously in similar studies and is likely to be quite accurate. This was also suggested by the observation that, in our study, there was a reasonable correlation between the subjective severity grading of the pharyngitis done by the investigator and the initial pain intensity obtained by the VAS (r = 0.39; P = .002). It is important to note that the study was not designed to have the power to detect differences in outcomes other than the primary outcome, which was pain associated with the sore throat.

In conclusion, the short-lived relief of pain in acute exudative pharyngitis in children with suspected IM may suggest that a single oral dose of dexamethasone may not be sufficient and that additional doses may be necessary for insuring lasting relief. However, it remains unclear if the benefit of corticosteroids in the treatment of IM-induced acute exudative pharyngitis can surpass the potential risk, if any, considering that 3 patients with suspected IM would have to be treated at least partly relieve the sore throat of 1 patient at 12 hours.

---

Table 3. Difference of VAS Score of Pain at Different Times Compared With Baseline for Dexamethasone and Placebo

<table>
<thead>
<tr>
<th>Time</th>
<th>Δ Dexamethasone vs Baseline, mm, Mean ± SD</th>
<th>Δ Placebo vs Baseline, mm, Mean ± SD</th>
<th>Δ Dexamethasone – Placebo (95% CI), mm</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 h</td>
<td>28 ± 26</td>
<td>8 ± 18</td>
<td>20 (6–34)</td>
<td>.007</td>
</tr>
<tr>
<td>24 h</td>
<td>29 ± 35</td>
<td>13 ± 20</td>
<td>16 (-2 to 35)</td>
<td>.19</td>
</tr>
<tr>
<td>48 h</td>
<td>30 ± 38</td>
<td>23 ± 26</td>
<td>7 (-13 to 28)</td>
<td>.62</td>
</tr>
<tr>
<td>72 h</td>
<td>41 ± 34</td>
<td>36 ± 32</td>
<td>5 (-16 to 26)</td>
<td>.64</td>
</tr>
<tr>
<td>7 d</td>
<td>62 ± 26</td>
<td>59 ± 25</td>
<td>2 (-14 to 19)</td>
<td>.50</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; VAS, visual analog scale.
Corticosteroids have been shown to reduce the upper airway obstruction caused by IM but their efficacy for the treatment of the pain associated with pharyngitis is unclear. Previous studies have not objectively measured the effect of corticosteroids on pain and were mostly done in hospitalized patients. In this pediatric emergency department–based study, a single dose of dexamethasone produced a short-lived reduction in the pain associated with IM-induced pharyngitis in adolescents. Additional doses may be necessary for ensuring lasting relief.

Accepted for publication October 2, 2003.
This project was funded by a grant from the Canadian Association of Emergency Physicians.

Corresponding author and reprints: Benoit Bailey, MD, MSc, FRCPC, Hôpital Ste-Justine, 3175 Chemin de la Côte-Sainte-Catherine, Montréal, Quebec, Canada, H3T 1C5 (e-mail: baileyb@med.umontreal.ca).

REFERENCES