Comparison of cosyntropin versus caffeine for post-dural puncture headaches: A randomized double-blind trial

Wesley Zeger¹, Bradley Younggren², Lynette Smith¹

¹ Department of Emergency Medicine, University of Nebraska Medical Center, Omaha, NE 68198, USA
² Department of Emergency Medicine, Madigan Army Medical Center, Tacoma, WA, USA

Corresponding Author: Wesley Zeger, Email: wzeger@unmc.edu

INTRODUCTION
Post-dural puncture headache is a common complication of lumbar puncture. Its incidence has been reported to be 30% in patients undergoing a diagnostic lumbar puncture,¹ but a wide range has been reported.²,³ Although the exact cause of pain is unclear, intracranial hypotension is likely the underlying problem.⁴ Post-dural headaches are postural, usually occur within 72 hours, and can be severe.⁵ They usually resolve on their own, but it may take 7 days or longer for the dura to repair itself.⁶ Patients frequently present to the emergency department for pain relief because of the severe and refractory nature of the headaches.

Treatment options for post-dural puncture headaches consist of medical or interventional therapies.²,³ Epidural blood patching (EBP) is the most frequent interventional treatment and has a high frequency of success.⁵-⁷ Unfortunately, blood patching is isky, and an initial trial of medical therapy is often preferred.²,³,⁵-⁹ Caffeine is the best medical therapy,²,³,⁵-⁹ and has an effective rate of 70%.¹⁴ In 1994, Collier¹⁵ first described ACTH for successful treatment of a post-dural puncture headache. Since its mechanism of action is not entirely clear, it is thought to have some effect on the increasing production of cerebrospinal fluid (CSF).¹⁵-¹⁷ Cosyntropin, an ACTH analog, has been reported in case series and case reports.
to have some benefit in treatment of the headaches.\textsuperscript{[16,18]} But there have been no studies comparing these two pharmacologic modalities.

We compared cosyntropin with caffeine in the treatment of post-dural puncture headaches in patients presenting to an emergency department.

\section*{METHODS}

This study was a double-blind, randomized controlled trial conducted in the emergency department of Madigan Army Medical Center, a tertiary medical center with an annual census of 70,000 patients. All patients presenting to the emergency department were eligible for inclusion. Inclusion criteria required patients to present within seven days of a lumbar puncture and meet the diagnostic criteria for a post-dural puncture headache. The diagnostic criteria for a post-dural puncture headache (PDPH) were a headache clinically consistent with a PDPH, the presence of a postural component, and other serious etiologies of headache that had been excluded as clinically appropriate. There was no one particular location or symptom (i.e., nausea, optic, vestibular, or otic) used as inclusion criteria. Patients were excluded from the study if they had a life-threatening etiology for their headache, an evidence of elevated intracranial pressure (e.g. papilledema), pregnancy, and a history of congestive heart failure, severe hypertension, allergy to caffeine, ACTH or its analogs. Patients were also excluded if they elected a blood patch as an initial therapeutic intervention. The study was approved by the institutional review board of the hospital.

There were two study arms, one receiving caffeine and the other receiving cosyntropin. Each drug was pre-mixed, coded, and randomized by the hospital pharmacy without the knowledge of the health care provider. All patients received 975 mg of tylenol and 2 liters of normal saline over a 2-hour period.

\subsection*{Treatment study arms}

The caffeine arm received 500 mg caffeine in 1 liter of normal saline (NS) given intravenously over 60 minutes followed by a repeated dose of 500 mg caffeine in 1 liter of NS over 60 minutes. The cosyntropin arm received 0.75 mg cosyntropin in 1 L NS over 60 minutes followed by 1 L NS given over 60 minutes.

\subsection*{Pain assessment}

A 100 mm visual analog scale (VAS) was filled out with the patient sitting upright to facilitate a maximal score. This assessment was performed at baseline (time 0) and after the first liter of saline and study drug were infused (60 minutes). The patient was then returned to the supine position and the second liter of fluid was infused. A third VAS was completed in a similar fashion at 120 minutes. If the drug was effective (adequate pain control), the patient was discharged from the emergency department without a rescue therapy. If pain control was inadequate (drug ineffective) after infusion of the second liter of saline, rescue therapy was provided at the discretion of the treating physician. The primary endpoint was drug efficacy rate. Mean VAS pain scores at 0, 60, and 120 minutes were measured as secondary endpoints.

\subsection*{Statistical analysis}

The primary endpoint of drug efficacy was calculated as the proportion of patients not requiring rescue therapy with 95% confidence intervals. Repeated-measures analysis of variance was utilized to compare mean VAS pain scores between the treatment arms and over-time intervals. We included fixed effects for drug, time and drug-time interaction. A random subject effect was included in the model to take into account the correlation of measurements within a subject. \(P\) values for pairwise comparisons were adjusted for multiple comparisons with Tukey’s method. Diagnostic methods, including residual plots and influence statistics, were examined to check the distributional assumptions of the repeated-measures model. The assumptions appeared to be met. \(P\) values less than 0.05 were considered to be statistically significant. Descriptive data were analyzed with Student’s \(t\) test or the Chi-square test.

An initial power analysis performed based on a desired effect size of 10\%, \(\beta=0.2\) and two-tailed \(\alpha=0.5\) required 270 patients would be in each arm. Since data on cosyntropin were lacking, an interim analysis was made to present the interim results.

\section*{RESULTS}

After 37 patients were enrolled, we performed an interim analysis. Three patients had a protocol violation and one patient withdrew from the study, leaving a total of 33 patients available for analysis of the primary endpoint. In the 33 patients, one had an incomplete pain VAS assessment, thus 32 patients were available for secondary endpoint analysis. The interim analysis revealed no adverse events in the patients. The study was terminated after the interim analysis because of feasibility. This analysis was based on intention to treat.
### Table 1. Demographic data of the patients

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Caffeine (n=16)</th>
<th>Cosyntropin (n=17)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years, mean ±SD)</td>
<td>33 (11)</td>
<td>25 (8)</td>
<td>0.04</td>
</tr>
<tr>
<td>Sex (n, %)</td>
<td></td>
<td></td>
<td>0.83</td>
</tr>
<tr>
<td>Male</td>
<td>6 (37%)</td>
<td>7 (41%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>10 (63%)</td>
<td>10 (59%)</td>
<td></td>
</tr>
<tr>
<td>Initial pain score (mm, mean±SD)</td>
<td>82 (15)</td>
<td>78 (16)</td>
<td>0.53</td>
</tr>
<tr>
<td>Time from procedure (days, mean±SD)</td>
<td>2.5 (1.6)</td>
<td>2.3 (0.8)</td>
<td>0.78</td>
</tr>
</tbody>
</table>

Figure 1. VAS graph.

Demographic data of the patients are shown in Table 1. Treatment with caffeine required rescue medication in 3 of 15 patients, with an overall efficacy rate of 80% (95% CI 60%–100%). Cosyntropin required rescue medication in 8 of 18 patients, with an overall efficacy rate of 56% (95% CI 33%–79%).

Repeated-measures ANOVA for pain VAS assessments did not show a statistically significant interaction between time and drug ($P=0.34$). While there was no significant difference in VAS scores between the drugs ($P=0.66$), a significant change was observed in VAS scores over time ($P<0.0001$), with times 60 and 120 minutes having significantly smaller VAS scores than time 0 ($P<0.001$ when averaging over the drugs). Mean VAS scores were not significantly changed from time 60 to 120 minutes ($P=0.20$). Figure 1 summarizes the VAS results with confidence intervals.

### DISCUSSION

In our study, the efficacy rates for caffeine and cosyntropin were 80% and 56%, respectively. Although caffeine’s efficacy was comparable to the reported efficacy rates $^{[8,14]}$ and appeared to be better than cosyntropin, wide confidence intervals for both drugs make them statistically similar. Given the sample size of our interim analysis, a type II error could be present, and a larger sample size would be needed to evaluate the rate of rescue medication requirement as an outcome measure. However, both groups showed statistically similar improvements in the overall degree of pain at 60 and 120 minutes. Based on the degree and statistically similar changes in the VAS assessment over time, both drugs showed a similar improvement in the level of patient’s overall pain.

Post-dural puncture headaches can be disabling. The pathophysiology of post-dural puncture headaches is not well delineated, and there are several theories. One is related to the traction of the pain-sensitive anchoring structures of the dura produced by the decreased amount of CSF.$^{[16]}$ Reports of relief with epidural saline infusion substantiate this theory.$^{[19,20]}$ Cosyntropin is theorized to act by increasing CSF volume, thereby decreasing the amount of traction and producing mild beta-endorphin effects.$^{[15,16]}$ Cosyntropin (or analog) which was used to treat the headaches has shown mixed results.$^{[15,16,18,21]}$

The other theory suggests that vasodilatation of cerebral blood vessels occurs to compensate for the space created by the relative CSF deficit. Caffeine is thought to act on vascular dilation, with an efficacy rate of 70%–75%.$^{[8,14]}$

There are several limitations to the present study. Needle size and type are reported to be factors in preventing post-dural puncture headaches.$^{[2,3,22,23]}$ The typical kits we used have 20 gauge cutting needles, but some of the lumbar punctures in this study were done with 22 gauge cutting needles. We were unable to control this potential confounder. In addition, since increasing volume of CSF is thought to be one of the mechanisms, through which cosyntropin works, we did not study potential delayed effects and/or may not have allotted enough time to maximize its effectiveness.

In conclusion, despite early termination, this study represents the largest randomized trial to compare caffeine and cosyntropin in the treatment of post-dural puncture headaches. In the study caffeine and cosyntropin provided a similar degree of pain relief over time when measured by VAS. Although there was no statistical difference, a higher proportion of cosyntropin treated patients required rescue therapy.

### Funding:
None.

### Ethical approval:
The study was approved by the Ethical Committee of the University of Nebraska Medical Center, Omaha, USA.

### Conflicts of interest:
There is no conflict of interest in this study.

### Contributors:
Zeger W collected and analyzed data, and wrote the manuscript. Younggren B entered data, and edited the manuscript. Smith analyzed data, and edited the manuscript.
REFERENCES


Received March 17, 2012
Accepted after revision June 28, 2012