

HEADACHE & FACIAL PAIN SECTION

Original Research Article

Intravenous Cosyntropin Versus Epidural Blood Patch for Treatment of Postdural Puncture Headache

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Abstract

Objective. This study evaluated the efficacy of IV cosyntropin as an alternative to epidural blood patch (EBP) for refractory or severe post-dural puncture headache (PDPH).

Methods. Twenty-eight patients were randomized to receive EBP or intravenous cosyntropin after diagnosis with post-dural puncture headache. Efficacy was evaluated immediately after treatment and at 1 day, 3 days, and 7 days following treatment using self-reported verbal reported scores for pain and function related to their headache on a 10-point scale using two-way repeated measures analysis of variance (ANOVA) with multiple comparisons.

Results. Baseline information for the control and study cohorts showed no difference based on intent

to treat analysis. EBP showed significant improvement over cosyntropin at day 1 ($P < 0.001$) for VRS pain and function scores; however, cosyntropin demonstrated similar efficacy to EBP immediately after treatment and days 3 and 7 post treatment (respectively, $P = 0.459$, $P = 0.391$ and 0.925 for pain and $P = 0.189$ and 0.478 for function). Treatment effects remained at day 1 after multivariate analysis ($P < 0.001$ and $P = 0.002$ for pain and function, respectively).

Conclusions. It is reasonable to consider IV cosyntropin as the treatment of choice for patients in whom EBP is contraindicated or in austere environments where there is limited or no access to anesthesia trained providers. Future research should compare efficacy and cost of prophylaxis to treatment of PDPH with intravenous cosyntropin and evaluate the most effective dosing regimen, including duration, number, and strength of doses.

Key Words. Epidural Blood Patch; Postdural Puncture Headache; Adrenocorticotrophic Hormone; Technique

Introduction

Epidural blood patch (EBP) is currently the standard treatment for severe post-dural puncture headache (PDPH) or for mild cases refractory to conservative measures [1]. EBP was originally thought to be 90% effective with repeat treatment efficacy approaching >96%; however, studies with increased patient follow up showed persistent relief of symptoms in 61–75% of treatments [2–4]. Treatment with EBP requires trained personnel to perform [5] and has numerous contraindications [6] including: increased ICP, coagulopathies, possible CNS or systemic infections, local infection at the site of the EBP, certain malignancies, or inability to access the epidural space. Additionally, it has been associated with serious complications to include severe back pain, bradycardia, neurologic deterioration, post-partum seizures, and cranial nerve paresis [4,7–11].

Other treatments such as sumatriptan, gabapentin, intravenous hydrocortisone, epidural morphine, and aminophylline have shown potential efficacy including prophylaxis for patients at higher risk of developing PDPH [12–15], but none have emerged as equivalent alternatives to EBP. Among these candidates, adrenocorticotrophic hormone (ACTH) and synthetic analogues have shown efficacy in both treatment [16–21] and prophylaxis [22] of PDPH compared with placebo. Contraindications to the ACTH analogue cosyntropin are more limited, but include hypersensitivity to the medication, acute psychosis, untreated infections, peptic ulcer disease, refractory heart failure, Cushing's syndrome, treatment of primary adrenocortical insufficiency, and adrenogenital syndrome. Despite its potential efficacy, research directly comparing effectiveness ACTH analogues to EBP is lacking.

This prospective, randomized, multi-center study hypothesized no difference in efficacy of EBP and the intravenous administration of the ACTH analogue, cosyntropin, in the treatment of PDPH.

Methods

After receiving approval by the Institutional Review Boards at two United States Naval Military Treatment Facilities, 28 patients were enrolled in the study from 2006 to 2013. Patients were enrolled after being diagnosed with severe PDPH based on the clinical judgment of the consulting anesthesia provider and meeting inclusion criteria on a standardized intake form. Patients were excluded if they were pregnant at the time of enrollment, had a diagnosis of congestive heart failure, showed signs of increased intracranial pressure, had local infection at the proposed injection site, were hemodynamically unstable or markedly hypovolemic as determined by the provider's assessment, had signs or symptoms of systemic infection, or were not deemed to be a suitable candidate for another reason not named above by the diagnosing provider. Patients were given written informed consent per institutional protocols and were randomized to receive EBP or intravenous cosyntropin.

Patients receiving EBP were pretreated with one liter of intravenous normal saline given over 1 hour. Using aseptic technique, an anesthesia provider injected up to 20 milliliters of autologous blood into the lumbar epidural space using an 18 gauge Touhy needle. Volume was limited to 20 milliliters or a volume that produced low back pain or pressure, whichever was less. Patients randomized to intravenous cosyntropin received 500 micrograms in 1 liter of normal saline over 1 hour. Dosing was based off of previous reported dosing of ACTH and cosyntropin (actual or equivalent doses ranging from 500–1000 mcg [16–22]). All patients were required to remain supine for 30 minutes following treatment.

Efficacy was evaluated on the day of treatment prior to discharge and 1 day, 3 days, and 7 days posttreatment for pain and 1, 3, and 7 days post treatment for function

using verbal self-reported scores for pain and function related to their headache. A 10-point scale was utilized with a score of 0 representing no pain and no impairment of function and a score of 10 representing maximum pain and full impairment of function. Scores were reported at each time point as noted above along with return trips to the ED and any alternative pain interventions required after receiving study treatments. Patients who received cosyntropin could opt to receive EBP treatment if pain persisted after their initial treatment.

Statistical analysis was completed using Stata/IC 12.0 (StataCorpLP, College Station, TX). Basic patient demographics, headache characteristics, and partum status were compared using Student's t-test for continuous variables and Fisher's exact test for categorical variables. Self-reported pain and functional scores were compared using two-way repeated measures analysis of variance (ANOVA) with multiple comparisons. Incidence of Emergency Department (ED) follow up or additional treatment were compiled and compared from treatment to control group using Student's t-test. Statistical analysis of patients was based on intent to treat, but reanalysis was done retrospectively to analyze the effect of subjects who received both treatments.

Results

Twenty-nine individuals were consented for the trial. Of these, 28 patients met study criteria and were randomized to receive EBP ($n=13$) or to receive intravenous cosyntropin injection ($n=15$). One patient randomized to receive EBP experienced resolution of headache symptoms prior to receiving the blood patch. All other patients received treatment and follow up for 7 days with the exception of two patients who were unable to be contacted at 7 days post treatment. Descriptive statistics of the sample are given in Table 1. In total, four individuals from the cosyntropin group also received EBP between their first and third day post treatment, with one patient receiving two EBPs. Baseline information for the control and study cohorts showed no difference based on intent to treat for demographics, medical history, headache symptoms, or baseline pain and function scores.

Mean outcome scores at the various time points along with standard deviation are shown for pain (Figure 1) and function (Figure 2). ANOVA revealed that there was a statistically significant improvement of EBP over cosyntropin at day 1 ($P<0.001$) for VRS Pain and Function Rating Scores (Table 2). However, cosyntropin demonstrated similar efficacy to EBP day of procedure prior to discharge and at days 3 and 7 (respectively, $P=0.459$, $P=0.391$ and 0.925 for pain and $P=0.189$ and 0.478 for function). ANOVA additionally indicated that there was significant effect of time with improvements from treatment to day 1 ($P<0.001$) in the EBP group and from day 1 to day 3 in the cosyntropin group. Even though there was a significant effect over time with both treatments, treatment effects remained at day 1 after

Table 1 Characteristics shown between control and study groups with *P* values listed to the nearest hundredth. Numbers in parentheses are percentages. HA history was considered positive if the patient reported any previous diagnosis of recurrent headaches or previous post-dural puncture headache.

	Treatment		<i>P</i> value
	EBP	Cosyntropin	
Demographics			
Sex			0.47
Female	8 (61.5)	9 (66.7)	
Male	5 (38.5)	6 (33.3)	
Age	26.9	29.2	0.28
Race			0.10
African American	1/13 (7.7)	4/15 (26.7)	
Asian/Pacific Islander	1/13 (7.7)	1/15 (6.7)	
Caucasian	7/13 (53.9)	9/15 (60)	
Hispanic	1/13 (7.7)	1/15 (6.7)	
Not reported	2/13 (15.4)	0/15 (0)	
Other	1/13 (7.7)	0/15 (0)	
Medical History			
HA History	2/13 (15.4)	5/15 (33.3)	0.28
Postpartum	3/13 (23.1)	3/13 (23.1)	0.425
HA Characteristics			
Baseline Pain	8.50	8.53	0.47
Baseline Function	7.17	7.40	0.39
Nausea/Vomiting	11/13 (84.6)	10/15 (66.7)	0.28
Neck Stiffness	10/13 (76.9)	10/15 (66.7)	0.28
Treatment			
Symptom onset (days post puncture)	1.23	1.33	0.43
Study treatment (days post puncture)	3.23	3.87	0.2

multivariate analysis ($P < 0.001$ and $= 0.002$ for pain and function, respectively). When adjusted for those patients who received EBP following cosyntropin, there was still no difference between the day of treatment (data not shown), day 3, and day 7 reported scores (Table 2).

Finally, the frequency with which patients returned to the ED for treatment and utilized additional pain medications after receiving the treatment was compared (Table 3). Sixty percent of patients who received cosyntropin were found to return to the ED versus only 8% for those treated with EBP ($P = 0.004$). Sixty-six percent of patients treated with cosyntropin received additional treatment, including blood patch (4), acupuncture (2), hydrocodone/acetaminophen (2), hydromorphone (1), oxycodone/acetaminophen (1), and gabapentin (1). Seventeen percent of EBP patients received additional treatment, which included repeated EBP (1) or caffeine (1). Including pre- and post-study treatment interventions, there was no difference between the EBP and cosyntropin groups in the number of patients treated with intravenous fluids ($P = 0.11$), caffeine ($P = 0.06$), non-steroidal anti-inflammatory drugs ($P = 0.33$), or opioids ($P = 0.23$).

Discussion

This prospective study of 28 patients randomized to receive IV cosyntropin or EPB demonstrated no difference in immediate post-procedure pain scores and 3- and 7-day post-procedure pain scores based on intent to treat or by retrospective analysis excluding patients who received both treatments. There were significantly more individuals who returned to the ED for treatment in the cosyntropin group compared with the epidural blood patch group, which could be explained by a bimodal response to cosyntropin. Counseling patients about the potential for this type of response could mitigate the return to the ED for additional treatment. Prophylactic treatment in cases of suspected dural puncture could hasten persistent pain relief if lasting treatment effect is

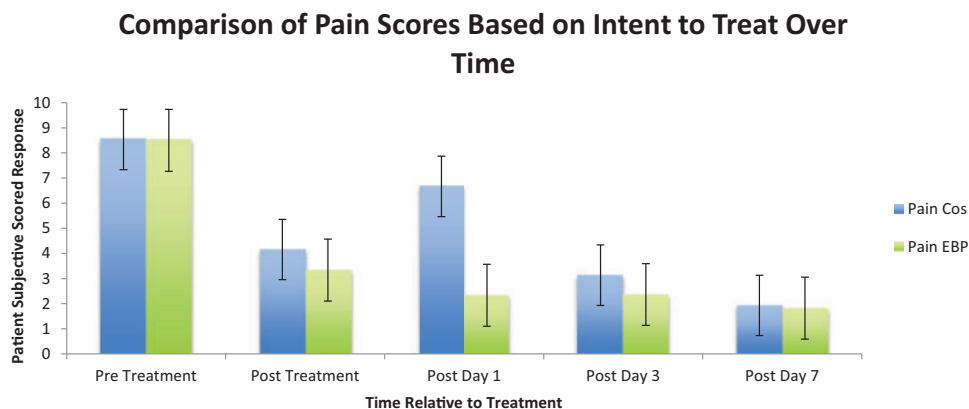


Figure 1 Control (EBP) and experimental (Cos) treatments are compared by patients' self-reported pain scores with 10 representing the greatest pain. Scores were reported post treatment prior to ED discharge, 1, 3, and 7 days after receiving the initial treatment.

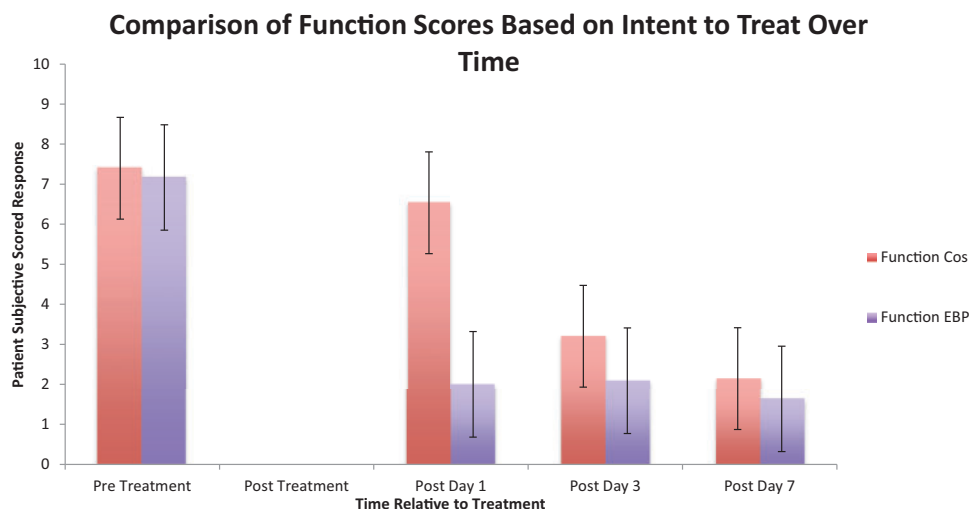


Figure 2 Control (EBP) and experimental (Cos) treatments are compared by patients' self-reported function scores with 10 representing the greatest impairment to function. Scores were reported 1, 3, and 7 days after receiving the initial treatment. No scores were reported immediately post treatment.

Table 2 Effect of each treatment, time and treatment adjusted for time effect (tx#time). Analysis was done first with cohorts based on intent to treat and then repeated retrospectively with patients who received both treatments removed. The same relationships still held. All of the effect on treatment is attributable to the difference in day 1 treatment scores.

Variable	Treatment	
	Intent to treat	Multiple treatments
Time	$P < 0.001$	$P < 0.001$
Treatment	0.006	0.022
Tx#Time	0.019	0.017

typical for most patients 1–3 days post treatment. Alternatively, the response could be the combination of multiple types of responders (early, late, or non-responders) with those late and non-responders representing those returning for treatment. Finally, this response could be the result of immediate improvement only with the 3- and 7-day responses resulting from a combination of other pain treatments and/or the natural course of post-dural puncture headache resolving. Based on the results of this study, it is reasonable to consider IV cosyntropin as the treatment of choice for patients in whom EBP is contraindicated. Additionally, IV cosyntropin represents a viable treatment option to EBP for treatment of PDPH in austere environments where there is limited or no access to anesthesia trained providers.

Table 3 Percentage of patients who returned to the ED as a result of their headache symptoms and percentage of individuals with any documented or self-reported treatment for their headache in addition to the study treatment.

Treatment	Percentage of patients returning to the ED	Percentage of patients requiring additional treatment
EBP	0	16.7
Cosyntropin	60	66.7
P value	<0.001	<0.001

Proposed mechanisms of cosyntropin include stimulated endorphin release, anti-inflammatory action, fluid and electrolyte retention, as well as direct stimulation of cerebral spinal fluid production [19,21]. These mechanisms could reasonably account for a bimodal response to treatment with cosyntropin. Additionally, the observed response could be related to the administration of the medication. Delivery route, total dose, number of doses administered, and time of infusion has varied greatly in previous reports [16–20,22]. The prescribed regimen was chosen based on previous reports [16–22], with our dose in the moderate to conservative range of all measures except that it was administered intravenously instead of intramuscularly. This suggests the possibility of a better dose response with longer infusion times [20], increased total doses [22], or ability to repeat dose [19].

Previous studies have shown a difference in rates of dural puncture headache based on needle size and

design [23]. While this was not recorded for each patient, it is standard practice at the study institutions to use 21g Quinke needles for diagnostic lumbar puncture, which was the cause of dural puncture in most of our cohort ($n=22$). Twenty-five gauge Whitacre needles and 25g Pencan needles are generally used for spinal anesthesia and 18g Touhy needles for epidural anesthesia. Spinal anesthesia was responsible for four headaches and suspected wet tap on epidural in two cases, respectively. There were no statistically significant differences in spinal and epidurals as the cause of dural puncture between the treatment and study groups.

One of the main limitations of the study was that subjects initially treated with cosyntropin had the ability to also receive EBP, thereby receiving both treatments. In comparing study to control groups, but excluding subjects receiving both treatment modalities, we were effectively able to rule out EBP treatment as the cause for improvement in the study group. Patients who received both treatments may have experienced improvement in symptoms by day 3 post treatment had they received no additional treatment on follow up and may have been less likely to return to the ED if educated on the potential for a bimodal treatment response. Day 7 treatment responses may be largely attributable to the natural history of post-dural puncture headache as 72% of individuals have symptoms resolve within 7 days [24]. Another potential limit was the lack of description of patient activity level on follow up. Though the functional score was meant to capture this component, there may be significant variation in the time patients spent supine or were less active in the study and control groups, which could have affected pain scores. Additionally, this functional scoring tool was not previously validated and may not have accurately captured participants' functional status. Cost analysis and total system utilization are other descriptive measures of pain treatment efficacy that were not captured in this cohort but would have likely demonstrated increased cost and time of treatment in the cosyntropin group. Additionally, variations in clinical judgment could have resulted in selection bias among different providers. Finally, lack of blinding could have resulted in potential treatment bias.

Future research should compare efficacy and cost of prophylaxis to treatment of PDPH with intravenous cosyntropin, given the possibility of delayed sustained response demonstrated by our data. Though rare, serious adverse effects have been associated with EBP administration [8–11]. Larger populations could be evaluated for comparison of serious adverse effects of EBP and IV cosyntropin. Additionally, patients with contraindications to EBP could be studied in their response to intravenous IV cosyntropin in a larger cohort to validate the results demonstrated by this study. Finally, future work could re-evaluate the most effective dosing regimen of cosyntropin, including duration, number of doses, and strength of dose.

In conclusion, this prospective study demonstrated no difference between intravenous cosyntropin and EBP in reducing self-reported PDPH pain scores prior to ED discharge and at 3 and 7 days following treatment. Further studies are needed to fully elucidate the role of this treatment in the care of PDPH.

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