

Cosyntropin for Prophylaxis against Postdural Puncture Headache after Accidental Dural Puncture

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ABSTRACT

Background: The aim of the current study was to investigate the effect of administration of cosyntropin after accidental dural puncture (ADP) on the incidence of postdural puncture headache (PDPH) and the need for therapeutic epidural blood patch (EBP).

Methods: Ninety parturients who suffered an ADP were studied. After delivery, patients were randomly assigned to one of two equal-sized groups. In group I (cosyntropin group), patients received cosyntropin in a dose of 1 mg intravenously. In group II (control group), patients received an equal volume of normal saline.

Results: Fifteen patients (33%) in the cosyntropin group suffered from PDPH, compared with 31 patients (68.9%) in the control group ($P = 0.001$). Significantly fewer patients in the cosyntropin group required an EBP, compared with the control group (5 patients [11.1%] *vs.* 13 patients [28.9%], respectively; $P = 0.035$). The Kaplan–Meier curves for the occurrence of PDPH showed a hazard ratio of 0.32 (95% CI = 0.16–0.55, $P < 0.0001$). The time from ADP to occurrence of PDPH was significantly longer in the cosyntropin group (27.2 [7.7] h) in comparison with the control group (17.5 [4.9] h; $P < 0.001$). However, there were no statistically significant differences among patients who developed PDPH in both groups with regard to the severity or duration of PDPH or with regard to the need for EBP or for repeat EBP ($P > 0.05$).

Conclusions: Administration of cosyntropin after ADP in parturients was associated with significant reduction in the incidence of PDPH and need for EBP and significant prolongation of the time from ADP to occurrence of PDPH.

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What We Already Know about This Topic

- ❖ Adrenocorticotrophic hormone or its analogues have been used to treat postdural puncture headache, but they have not been studied for prophylaxis

What This Article Tells Us That Is New

- ❖ In 90 parturients with accidental dural puncture during epidural needle placement for labor analgesia, the incidence of postdural puncture headache was halved, from 69% with placebo to 33% by prophylaxis with 1 mg cosyntropin
- ❖ Cosyntropin also reduced the need for epidural blood patch from 30% to 11%

THE incidence of inadvertent dural tap at attempted epidural placement in obstetric patients has been reported to be on the order of 0.4–6%,¹ and it is associated with an alarmingly high occurrence of postdural puncture headache (PDPH), which complicates 75–86% of the incidents.^{1,2} Management of accidental dural puncture (ADP) is largely expectant,^{1,2} and it is associated with a significant increase in the hospital length of stay.³ The strikingly high rate of PDPH that complicates ADP^{1,2} and the increase in the hospital length of stay associated with expectant management of ADP³ may warrant that more specific measures be undertaken to prevent PDPH after ADP has been sustained, in much the same way as patients at high risk for other anesthesia-related complications, for example, postoperative nausea and vomiting, receive prophylactic treatment well before the occurrence of complications.

Reports do exist of successfully treating refractory cases of PDPH with adrenocorticotrophic hormone (ACTH) or its analogues.^{4–8} However, the role of prophylactic administration of this form of intervention is unclear.

The aim of the current study was to investigate the effect of prophylactic administration of cosyntropin, an ACTH analogue, after ADP on the incidence of PDPH and the need for therapeutic epidural blood patch (EBP). A secondary aim was to study the effect of this intervention on the severity of PDPH and the need for repeat EBP.

Materials and Methods

This study was conducted during the period from October 2006 to September 2009. After approval of the institutional

review board (Research Ethics Committee, Faculty of Medicine, Ain Shams University, Cairo, Egypt) and obtaining an informed consent, 95 parturients, who had epidural analgesia for normal vaginal delivery and who suffered an inadvertent dural tap, were included in this study. Exclusion criteria were contraindication to steroid or ACTH therapy (*e.g.*, hypertension or diabetes mellitus), preeclampsia, or contraindication to EBP (*e.g.*, fever or leukocytosis).

Technique of Epidural Analgesia

Epidural attempts were conducted by staff obstetric anesthesiologists using 18-gauge or 16-gauge Tuohy-type epidural needles and loss of resistance to saline. Anesthesiologists had the freedom of choosing the patient position (sitting or lateral), intervertebral space, approach to the epidural space (midline or paramedian), and the needle size as deemed convenient.

On recognition of dural tap, the epidural needle was withdrawn, and the replacement was attempted at another intervertebral space. The catheter was threaded 3 cm into the epidural space and tested with 3 ml of 2% lidocaine with 1:200,000 epinephrine. A loading dose of 8–15 ml of 0.125% bupivacaine, to which 50 μ g of fentanyl was added, was given, followed by a continuous infusion of 0.125% bupivacaine with fentanyl 2 μ g/ml at a rate of 8–15 ml/h.⁹

Patient Randomization

Thirty minutes after delivery, the epidural catheter was removed, and patients were randomly assigned to one of two groups using a computer-generated random number list. The list was created using the GraphPad StatMate version 1.01i software (GraphPad Software Inc., San Diego, CA) and was accessible to anesthesiologists attending to patients in labor through the computer database. In group I (cosyntropin group), patients received a single intravenous injection of cosyntropin (Cortrosy[®], Amphastar Pharmaceuticals Inc., Rancho Cucamonga, CA) in a dose of 1 mg. Four vials of cosyntropin, each containing 0.25 mg of the drug, were reconstituted in 0.9% sodium chloride, using 1 ml of solvent for each vial. The reconstituted solution was injected intravenously over 5 min. In group II (control group), patients received an equal volume of normal saline. Injections were prepared by assistants not participating in the study, and both the patients and those involved in the study were blinded as to the patients' groups.

Management of ADP

Patients were admitted to hospital for 48 h during which they were managed expectantly. The incidents were explained to the patients, who were informed to report any headache, and were encouraged to ambulate and to drink plenty of fluids, with prescription of stool softeners. The staff nurse in charge was asked to inquire the patients whether they had any headache at 8-h intervals. A resident anesthesi-

ologist visited the patients twice a day, inquired specifically about headache, and reviewed the patients' charts. Patients reporting headache were asked about its time of onset, character, aggravating and alleviating factors, and severity. Severity was assessed using a 5-point verbal rating scale as follows: no headache = 0, mild headache = 1, moderate headache = 2, severe headache = 3, and unbearable headache = 4. The highest score recorded on each day from the onset of headache until headache remitted completely was taken, and these scores were averaged and entered for analysis. Nurses and anesthesiologists involved in headache assessment were blinded as to the patients' groups.

Patients were diagnosed as having PDPH if they developed headache within 5 days after dural puncture, which worsened within 15 min of sitting or standing, and improved within 15 min after lying, with at least one of the following criteria: neck stiffness, tinnitus, hypacusia, photophobia, or nausea.¹⁰ Other features, such as a throbbing character, a fronto-occipital location, radiation to the neck and shoulders, or exacerbation by head movement or by maneuvers that increased intracranial pressure (*e.g.*, coughing, sneezing, straining, or ocular compression)^{11–13} were not essential for the diagnosis.

Patients who did not develop PDPH for 48 h after ADP and who were ambulating normally were discharged from the hospital with the instruction to come back for reassessment if they experience any headache. Discharged patients were contacted daily by phone for 14 days and were asked about symptoms suggestive of PDPH. Patients who developed PDPH after discharge would be readmitted. All patients with PDPH were managed conservatively. They were instructed to lie flat in a supine position and to drink plenty of fluids. For mild-to-moderate headache, 1 g paracetamol and 400 mg ibuprofen orally every 6 h were prescribed. For severe headache, 1 mg/kg meperidine was given by intramuscular injection, in addition, and could be repeated every 6 h as required. If nausea or vomiting was prominent, 10 mg metoclopramide orally every 8 h was allowed. EBP was performed for patients who reported a persistently severe headache after 48 h of conservative treatment. The epidural space was approached at the level of the dural puncture or at a lower space, using loss of resistance to saline. Under strict aseptic technique, 20 ml of the patient's own blood was drawn from a large vein and was injected into the already accessed epidural space over 1 min. If the patient experienced pain in the back or lower extremities, the injection would be terminated after administration of 2 more ml of blood. Thereafter, the patient was kept in the supine position for 2 h, before allowing ambulation. A second EBP would be performed if headache did not improve in 24 h. Patients were discharged after they were ambulating normally without experiencing any headache. After discharge, patients were followed up by phone calls for 14 days from the incident. The hospital length of stay, the occurrence of PDPH, and the need for EBP were noted.

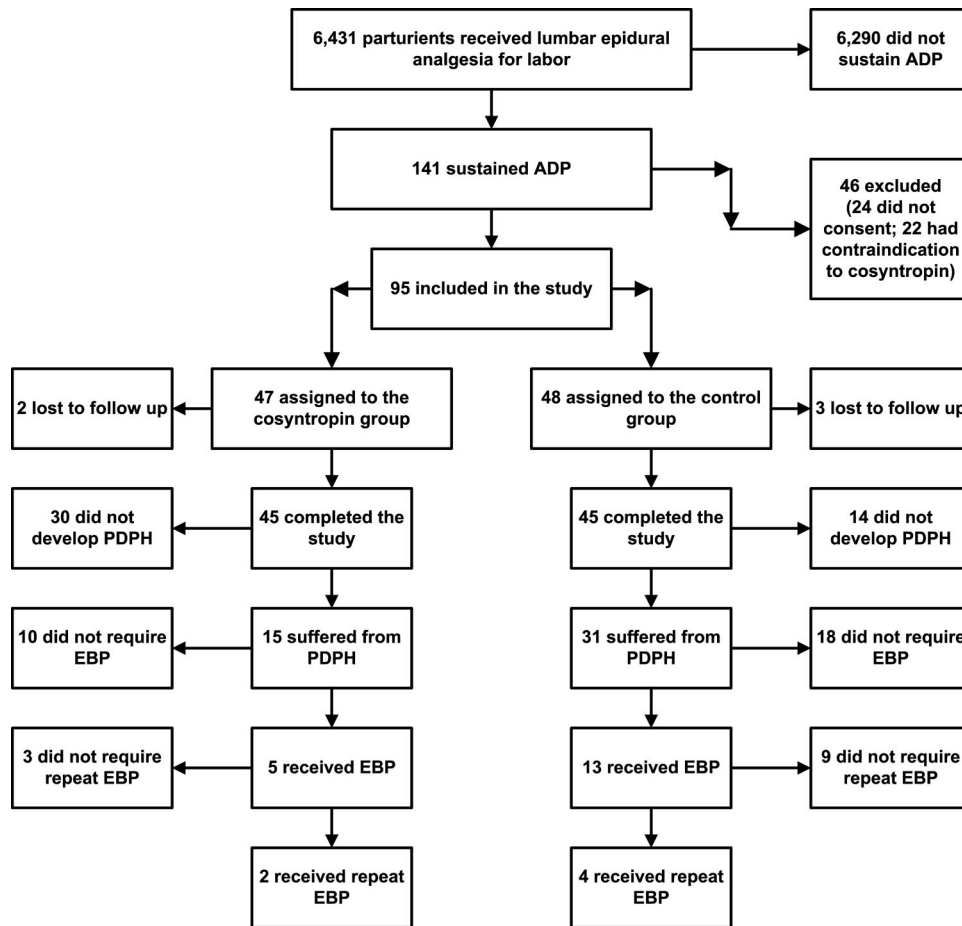


Fig. 1. Flow chart showing incidence of accidental dural puncture (ADP), patient recruitment and randomization, incidence of postdural puncture headache (PDPH), and need for epidural blood patch (EBP) and repeat EBP.

Statistical Analysis

Sample size was estimated using the G*Power[®] software version 3.1.0 (Institut für Experimentelle Psychologie, Heinrich Heine Universität, Düsseldorf, Germany). The primary outcome measure was the incidence of PDPH. Considering two-tailed α -error of 0.05, β -error of 0.2, and degree of freedom of 1, it was estimated that a minimum of 44 patients had to be included in each study group to detect a 30% difference in the incidence of PDPH.

Statistical analysis was done on a personal computer using the Statistical Package for Social Sciences[®] version 17 (SPSS[®], SPSS Inc., Chicago, IL). Kolmogorov–Smirnov goodness-of-fit test was performed initially to test the hypothesis that numerical data were normally distributed. Normally distributed numerical data were presented as mean (SD), and between-group differences were compared parametrically using the independent-samples Student *t* test. Nonnormally distributed numerical data were presented as median (interquartile range), and intergroup differences were compared nonparametrically using the Mann–Whitney *U* test. Nominal data were presented as ratio or number (percentage), and the differences between the two groups were compared using the Pearson chi-square test, with application of Fisher exact test when appropriate. Kaplan–Meier

curves for occurrence of PDPH were constructed using GraphPad Prism[®] version 5 (GraphPad Software Inc.), and the difference between the two groups was compared using the log-rank test. A *P* value of less than 0.05 was regarded as statistically significant.

Results

During the study period, 6,431 parturients received epidural labor analgesia, 141 (2.19%) of whom sustained an ADP. Ninety-five (67.4%) of those who suffered an ADP were entered into the study and were randomized into the cosyntropin group ($n = 47$) or the control group ($n = 48$). Two patients in the cosyntropin group and three in the control group were discharged after 48 h from the ADP and were lost to follow-up thereafter. None of these patients had PDPH while in hospital; they were included in the Kaplan–Meier analysis as censored data, but they were excluded from other analyses. Ninety patients (45 in each group) completed the study (fig. 1).

Table 1 shows the demographic characteristics of both study groups, and table 2 shows the details of the epidural attempts. There were no statistically significant differences between the two groups as regards any of these variables ($P > 0.05$).

Table 1. Demographic Data

Variable	Cosyntropin Group (n = 45)	Control Group (n = 45)	P Value
Age, yr	31.3 (4.8)	29.7 (4.9)	0.111
Weight, kg	71.7 (7.6)	68.2 (9.8)	0.062
ASA-PS I/II	32/13	29/16	0.499
Gestational age, wk	38 (37–40)	38 (37–39)	0.197

Data are presented as mean (SD), ratio, or median (interquartile range).

ASA-PS = American Society of Anesthesiologists physical status.

Sixty-seven patients (74.4%) of those recruited suffered a dural puncture with an 18-gauge Tuohy needle, whereas 23 patients (25.6%) had it with a 16-gauge needle. Significantly, more patients in the 16-gauge category had PDPH compared with the 18-gauge category (16 [69.6%] *vs.* 30 [44.8%], respectively, $P = 0.04$). However, no such difference was observed within any of the two study groups separately ($P > 0.05$; table 3).

Fifteen patients (33.3%) in the cosyntropin group suffered from PDPH when compared with 31 (68.9%) patients in the control group ($P = 0.001$). Significantly fewer patients in the cosyntropin group required an EBP when compared with the control group (5 [11.1%] *vs.* 13 [28.9%], respectively; $P = 0.035$). However, the number of patients who required a repeat EBP was comparable (2/5 [40%] in the cosyntropin group *vs.* 4/13 [30.8%] in the control group, $P = 1.0$; table 4). All patients who developed PDPH did so while still in hospital within 48 h from the occurrence of ADP. Likewise, all EBP and second patches were received before discharge after delivery.

Figure 2 shows the characteristics of the Kaplan–Meier curves for the occurrence of PDPH. They had a hazard ratio of 0.32 with a 95% CI of 0.16–0.55 ($P < 0.0001$). The median time to occurrence of PDPH was 21.5 h in the control group. However, because more than 50% of the patients

in the cosyntropin group had not developed PDPH by day 14, the median time to occurrence of PDPH could not be defined in this group.

Table 5 shows the characteristics of PDPH in affected patients in both groups. The time from ADP to occurrence of PDPH was significantly longer in the cosyntropin group (27.2 [7.7] h) in comparison with the control group (17.5 [4.9] h; $P < 0.001$). However, there were no statistically significant differences between these two subgroups as regards the severity or duration of PDPH or as regards the number of patients who required an EBP or a repeat EBP ($P > 0.05$).

Two (4.4%) patients in the cosyntropin group developed mild reactions compatible with hypersensitivity to cosyntropin. These consisted in urticarial wheals confined to the face ($n = 1$ [2.2%]) or to the upper half of the body ($n = 1$ [2.2%]) that appeared shortly after the injection (average 6 min). The reactions were self-limiting and required no treatment. None of the patients in the control group developed such reactions. This difference was not statistically significant ($P = 0.494$). None of the patients in either group developed untoward hemodynamic reactions related to the injection.

Discussion

The current study showed that the administration of cosyntropin after ADP was associated with a significant reduction in the incidence of PDPH and the need for therapeutic EBP. The use of ACTH and its analogues for the treatment of refractory PDPH has been described previously in isolated case reports.^{4–8} However, evidence from randomized controlled trials is sparse. In one prospective randomized controlled trial, Rucklidge *et al.*¹⁴ administered a long-acting ACTH analogue (tetracosactrin zinc phosphate) or placebo to a series of parturients with PDPH after deliberate or ADP and failed to demonstrate a difference either in the severity of PDPH or in the requirement of EBP. However, that study,

Table 2. Data of Epidural Attempts

Variable	Cosyntropin Group (n = 45)	Control Group (n = 45)	P Value
Patient's position (sitting/lateral)	34/11	37/8	0.438
Needle size (18-gauge/16-gauge)	35/10	32/13	0.468
Level of dural tap			
L2–L3	11 (24.4)	17 (37.8)	0.390
L3–L4	20 (44.4)	16 (35.6)	
L4–L5	14 (31.1)	12 (26.7)	
Level of epidural catheter placement			
L2–L3	5 (11.1)	7 (15.6)	0.784
L3–L4	15 (33.3)	13 (28.9)	
L4–L5	22 (48.9)	20 (44.4)	
L5–S1	3 (6.7)	5 (11.1)	
Approach used at level of dural tap (median/paramedian)	33/12	35/10	0.624
Approach used at level of epidural catheter placement (median/paramedian)	31/14	36/9	0.227

Data are presented as ratio or n (%). Sum of percentages may not equal 100 owing to approximations.

Table 3. Size of Tuohy Needle and Incidence of Postdural Puncture Headache (PDPH) within Each of the Two Study Groups and among All Participants

	Cosyntropin Group (n = 45)		Control Group (n = 45)		All Patients (n = 90)	
	18-gauge (n = 35)	16-gauge (n = 10)	18-gauge (n = 32)	16-gauge (n = 13)	18-gauge (n = 67)	16-gauge (n = 23)
No PDPH	26 (74.3)	4 (40)	11 (34.4)	3 (23.1)	37 (55.2)	7 (30.4)
PDPH	9 (25.7)	6 (60)	21 (65.6)	10 (76.9)	30 (44.8)	16 (69.6)
P value	0.062		0.724		0.04	

Data are presented as n (%).

may have been underpowered, owing to the small number of patients studied (18 patients).

Other reports do exist on the successful use of hydrocortisone for treatment of intractable PDPH,^{15,16} and at least one randomized controlled trial¹⁷ showed that hydrocortisone did significantly reduce the severity of PDPH in parturients who underwent cesarean delivery with spinal anesthesia. Hydrocortisone has also been used prophylactically to prevent PDPH after ADP.¹⁶ However, no such reports exist for ACTH or its analogues.

The pathogenesis of PDPH is not clear. After dural tap, excessive leakage of cerebrospinal fluid may lead to reduction of cerebrospinal fluid volume and intracranial pressure. This may exert a traction effect on the pain-sensitive intracranial structures when the erect posture is assumed. In addition, reduction of cerebrospinal fluid volume tends to induce compensatory venodilation to keep the intracranial volume constant, which could contribute to the headache.¹⁸ In fact, radioisotope-enhanced magnetic resonance imaging did show sagging of intracranial structures, sometimes with meningeal enhancement denoting meningeal vasodilatation, in patients suffering from PDPH.¹⁹

In this respect, the mechanism whereby ACTH or related compounds could benefit PDPH is not precisely known. It has been proposed that ACTH stimulates the release of aldosterone, which enhances salt and water retention and affects an expansion of blood volume. This could favor the closure of the dural tear by inducing dural edema or by simple overlap of the edges of the dural hole.²⁰ Other proposed mechanisms are an increase in

cerebrospinal fluid production involving active transport of sodium ions or an increase in brain β endorphin that could modulate the perception of pain.^{4,6} Notably, both ACTH and β endorphin are derived from the same precursor, proopiomelanocortin,²¹ and there is evidence that fragments derived from ACTH interact with opioid receptors.^{22,23} In addition, ACTH-derived fragments were shown to mimic the effects of morphine *in vitro*.²⁴ Although the clinical implication of this interaction is unclear, it may confer putative mechanisms for ACTH in PDPH, and in this regard, an ACTH analogue could be more effective than a direct-acting glucocorticoid. This postulation has not been founded, but it would be ideally examined with prospective randomized trials comparing the efficacy of ACTH with that of glucocorticoids in PDPH.

Natural ACTH is a 39-amino acid polypeptide. Its hormonal activity resides in the first (*N*-terminal) portion of the peptide (amino acid sequence 1–24), which is common to other animal species. Conversely, most antigenic properties of the polypeptide reside in the *C*-terminal portion (remaining 15 amino acids).²⁵ ACTH exerts its effects by interacting with specific G-protein-coupled receptors. The result of this interaction is activation of adenylyl cyclase with increased intracellular cyclic adenosine monophosphate, which acts as a second messenger for ACTH. Cosyntropin is a synthetic ACTH analogue comprising the initial 24 amino acid sequence of the parent chain. Therefore, the drug exhibits full hormonal activity of the endogenous peptide with much less antigenicity. At

Table 4. Incidence of Postdural Puncture Headache (PDPH) and Need for Epidural Blood Patch (EBP) in Both Groups

Variable	Cosyntropin Group (n = 45)	Control Group (n = 45)	P Value
Incidence of PDPH			
PDPH occurred	15 (33.3)	31 (68.9)	0.001
PDPH did not occur	30 (66.7)	14 (31.1)	
Need for EBP			
EBP needed	5 (11.1)	13 (28.9)	0.035
EBP not needed	40 (88.9)	32 (71.1)	
Need for repeat EBP (number received second EBP/number received EBP)	2/5 (40)	4/13 (30.8)	1.0

Data are presented as n (%) or ratio (%).

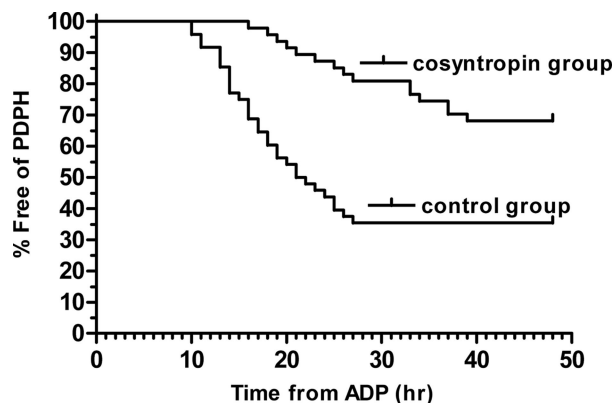


Fig. 2. Kaplan–Meier curves for the occurrence of postdural puncture headache (PDPH) in cosyntropin group and control group. Hazard ratio = 0.32 (95% confidence interval = 0.16–0.55, $P < 0.0001$). Median time to occurrence of PDPH = 21.5 h in control group and is undefined in cosyntropin group. ADP = accidental dural puncture.

present, the main clinical application of cosyntropin is to test the integrity of the hypothalamic-pituitary-adrenal axis. Cosyntropin in a dose of 0.25 mg is equipotent with 25 units of natural ACTH in stimulating the adrenal cortex. The main untoward effects of cosyntropin are related to excessive glucocorticoid output and to rare hypersensitivity reactions.²⁶

To screen for adrenal function, the manufacturer of Cortrosyn® (Amphastar Pharmaceuticals, Inc.) recommends that 0.25 mg of the drug be administered by the intramuscular or intravenous route. Because no sufficient data exist on the use of ACTH for the prevention of PDPH after ADP, any dosage recommendation would be arbitrary. Taking into consideration the dosages cited by other authors for treating refractory PDPH (0.25–1.0 mg of cosyntropin or equivalent),^{4,6,7} the current study opted for the higher dose in the range, assuming that a higher dose might be more effective in demonstrating an effect, if any. However, other prospective randomized trials specifically addressing this issue are strongly recommended to validate this postulation.

In the current study, the incidence of PDPH was significantly higher when the dural puncture was sustained with a 16-gauge needle when compared with an 18-gauge needle. This is in concord with meta-analyses²⁷ and reviews,^{28,29} demonstrating a higher incidence of PDPH associated with larger-sized needles. This difference was observed when all the population that completed the study ($n = 90$) was considered. However, no such difference was detected within either of the two study groups ($n = 45$) separately. This could be explained in terms of larger β error (*i.e.*, reduced power) associated with the smaller sample size (estimated power = 0.52 for a sample size of 45 patients *vs.* 0.81 for 90 patients).

The alarmingly high rate of PDPH after ADP,^{1,2} and the attendant increase in the hospital length of stay associated with expectant management,³ may warrant more proactive strategies. Evidence for the efficacy of prophylactic EBP after ADP is at best controversial.^{30,31} The largest study on the effectiveness of prophylactic EBP³² showed that prophylactic EBP did not reduce the incidence of PDPH or the need for therapeutic EBP after ADP, although it did shorten the duration of the headache. In addition, EBP is an invasive procedure that is not without drawbacks,³³ some of which could be quite serious.^{34–36} In this regard, administration of ACTH after ADP may offer an attractive option in terms of safety, convenience, and burden on attending physicians and the hospital's resources.

In concurrence with local institutional practice, therapeutic EBP was performed in the current study after 48 h of conservative therapy had proved unsatisfactory. This may account for the overall low rate of applying epidural patches in this series (28.9% in the control group and 11.1% in the cosyntropin group). The timing of therapeutic EBP has been the subject of much debate. Some investigators³⁷ suggested that patching be performed early for patients who remained bed-ridden for longer than half a day, despite receiving expectant treatment for their PDPH. However, there is good evidence that the earlier the EBP is applied, the higher the failure rate.^{38–40}

Table 5. Characteristics of Postdural Puncture Headache (PDPH) in Affected Patients of Both Groups

Variable	Patients with PDPH in Cosyntropin Group (n = 15)	Patients with PDPH in Control Group (n = 31)	P Value
Time from ADP to occurrence of PDPH, h	27.2 (7.7)	17.5 (4.9)	<0.001
Severity of PDPH	3.0 (2.0–3.75)	3.0 (2.0–3.0)	0.831
Duration of PDPH, days	2.0 (2.0–3.0)	2.0 (2.0–3.0)	0.628
Need for EBP			
EBP needed	5 (33.3)	13 (41.9)	0.575
EBP not needed	10 (66.7)	18 (58.1)	
Need for repeat EBP (number received second EBP/number received EBP)	2/5 (40)	4/13 (30.8)	1.0

Data are presented as mean (SD), median (interquartile range), n (%), or ratio (%). ADP = accidental dural puncture; EBP = epidural blood patch.

In the current study, 4.4% of patients who received cosyntropin developed mild reactions compatible with hypersensitivity to the drug. Their appearance shortly after injection and their evanescent character suggested their nature. However, these incidents were not statistically significant, and none of the patients in the cosyntropin group developed any untoward hemodynamic reactions related to the injection.

Conclusions

The administration of a single intravenous dose of cosyntropin after ADP was associated with the significant reduction in the incidence of PDPH and the need for EBP. Cosyntropin administration was also associated with significant prolongation of the time from ADP to occurrence of PDPH, although it did not influence either the duration or the severity of the headache. In patients who developed PDPH, prophylactic administration of cosyntropin did not seem to influence the need of either EBP or repatching.

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ANESTHESIOLOGY REFLECTIONS

“Anesthesia about 1850” at the 1939 World’s Fair



Planned by prominent American physician-anesthetists, “Modern Anesthesia” was advertised as “the *hit show* in the Medicine and Public Health Building” of the New York World’s Fair of 1939. Postcards depicted early practice of this “fully developed and important specialty of medicine,” including “life size models” demonstrating “Anesthesia about 1850” (see above). Sponsored by a local-anesthetic giant, New York’s Winthrop Chemical Company, the exhibit celebrated “the training, skill, and resourcefulness of the anesthetist of today [to] render modern anesthesia wonderfully efficient and remarkably safe.” (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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