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The Volume of Blood for Epidural Blood Patch in Obstetrics: A Randomized, Blinded Clinical Trial

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BACKGROUND: Our aim in this multinational, multicenter, randomized, blinded trial was to determine the optimum of 3 volumes of autologous blood for an epidural blood patch.

METHODS: Obstetric patients requiring epidural blood patch after unintentional dural puncture during epidural catheter insertion were allocated to receive 15, 20, or 30 mL of blood, stratified for the timing of epidural blood patch and center. Participants were followed for 5 days. The primary study end point was a composite of permanent or partial relief of headache, and secondary end points included permanent relief, partial relief, persisting headache severity, and low back pain during or after the procedure.

RESULTS: One hundred twenty-one women completed the study. The median (interquartile range) volume administered was 15 (15–15), 20 (20–20), and 30 (22–30) mL, with 98%, 81%, and 54% of groups 15, 20, and 30 receiving the allocated volume. Among groups 15, 20, and 30, respectively, the incidence of permanent or partial relief of headache was 61%, 73%, and 67% and that of complete relief of headache was 10%, 32%, and 26%. The 0- to 48-hour area under the curve of headache score versus time was highest in group 15. The incidence of low back pain during or after the epidural blood patch was similar among groups and was of low intensity, although group 15 had the highest postprocedural back pain scores. Serious morbidity was not reported.

CONCLUSIONS: Although the optimum volume of blood remains to be determined, we believe these findings support an attempt to administer 20 mL of autologous blood when treating postdural puncture headache in obstetric patients after unintentional dural puncture. (Anesth Analg 2011;113:126–33)

Unintentional dural puncture with an epidural needle or catheter is a common,[1–4] and arguably the most important, complication of obstetric epidural procedures. The risk of postdural puncture headache is high, and approximately half of those affected describe their symptoms as severe or incapacitating.[4–7] The duration of headache is often several days or more,[4,8] and it is occasionally accompanied by serious morbidity, such as cranial nerve palsy, subdural hematoma, or chronic headache.[4] The need to assess and manage the headache interferes with care of the newborn, often lengthens the hospital stay, and has significant cost implications for the health care budget.[9]

Although the headache eventually resolves without treatment in most patients, the results of expectant management with physical and pharmacological therapies to relieve symptoms are disappointing.[4,9,10] The value of epidural blood patch has been recognized for 50 years,[11,12] and this procedure is widely used to treat severe postdural puncture headache in the obstetric population,[2,4,6,10] but evidence supporting its efficacy is scarce.[8,13–15] The efficacy of a therapeutic epidural blood patch in obstetric patients may be less than among general surgical patients, possibly related to gender, age, or pregnancy/postpartum-specific differences. Observational studies have found that up to 95% of obstetric patients obtain short-term complete or partial relief of symptoms after an epidural blood patch, but only 35%–70% remain headache-free after several days.[4,6,16] Many procedural aspects of epidural blood patch have not been well studied. In particular, the optimal volume of autologous blood is not known.[10,17] Originally 2 to 3 mL[11] was injected, and subsequently 5 to 10 mL[18] or 15 to 20 mL were recommended.[19] Some anesthesiologists advocate 20 to 30 mL or as much volume as tolerated by the patient.[20] In the United States, practice varies, with two thirds of respondents to a survey reporting that they injected 16 to 20 mL, whereas the remainder injected a smaller or larger volume.[21] The first randomized controlled trial to investigate epidural blood patch volume compared 7.5 mL with 15 mL and found no difference in headache relief in Taiwanese women.[22]

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The aim of this study was to determine the optimum of 3 commonly used volumes of blood, injected for an epidural blood patch to treat postdural puncture headache, in obstetric patients who suffered unintentional dural puncture with an epidural needle. Our null hypothesis was that none of the volumes studied would be selected as preferable, on the basis of consideration of both efficacy (the relief of headache) and adverse effects. Our alternative hypothesis was that one of 15, 20, or 30 mL of blood would prove superior.

METHODS

Obstetric patients ages 18 or more years, with a diagnosis of postdural puncture headache after a confirmed (cerebrospinal fluid efflux) or likely (multiple attempts and typical headache) unintentional dural puncture by a 16- to 18-gauge epidural needle, and who had no contraindications to epidural blood patch, were eligible to participate in this study. The study received local institutional Ethics Committee approval at each participating center, and all women gave written informed consent for an epidural blood patch and study participation. The exclusion criteria were a previous epidural blood patch related to the same dural puncture (including a prophylactic epidural blood patch), an epidural blood patch scheduled <24 hours or >5 days after the dural puncture, a history of low or radicular back pain requiring treatment during the pregnancy, and another dural puncture at the time of the epidural blood patch.

A computer-generated randomization sequence, blocked for each study site and stratified for the timing of epidural blood patch (within versus at or beyond 48 hours from the time of dural puncture), was generated for 3 study arms. A numbered, opaque sealed envelope with group allocation was opened immediately before the intervention; the patient was allocated to receive 15 mL (group 15), 20 mL (group 20), or 30 mL (group 30) of autologous blood. Patients were warned that back discomfort might occur during injection of blood. At the discretion of the anesthesiologist performing the epidural blood patch, the final volume of blood injected could be limited if the patient complained of severe back pain during injection, but intention-to-treat analyses were performed. The person performing the epidural blood patch attempted to conceal the final volume of blood injected from all others present. The patient and all observers involved in data collection, an activity from which the proceduralist was excluded, were blinded to group allocation.

The technique was standardized only for performance with the patient in the flexed lateral position if possible and at a vertebral interspace either at or immediately below that at which the dural puncture occurred. Thirty milliliters of venous blood was collected by an assistant under sterile conditions, and the allocated volume of blood was injected at a rate of approximately 0.3 mL/s. After the procedure the patient rested supine for at least 2 hours while arterial blood pressure and temperature were observed. Patients were instructed to maintain good oral hydration and to avoid heavy lifting, abdominal straining, or coughing.

Demographic data collected included patient age, weight, height, ASA physical status, history of migraine, the circumstances of the dural puncture (reason for epidural insertion, gauge of needle, detection of cerebrospinal fluid, number of needle passes, intrathecal insertion of the epidural catheter after puncture), mode of delivery, the time to onset of postdural puncture headache, its severity including the degree of functional impairment, and the treatment received. Details of the epidural blood patch technique, including the presence of back pain and the actual volume of blood administered, were recorded. The presence and severity of headache were reassessed at 2, 4, 8, 24, 48, and 72 hours and 5 days postprocedure (by telephone if discharged). The headache was categorized as mild, moderate, or severe, and scored using a 0 to 10 numerical rating scale (NRS) after the patient had been standing erect for 1 minute. The 4 functional disability categories were no headache, mild headache when standing erect that did not interfere with normal activities, headache only when standing but interfering with normal activity, or headache interfering with normal activity when reclining in bed as well as when standing. If the relief of headache was partial after 4 hours or headache recurred after complete initial relief, an NRS for the average severity over the previous period of 24 hours was recorded at 48 and 72 hours. The severity of low back pain was assessed using an NRS immediately before the epidural blood patch, immediately after the epidural blood patch and at 4, 24, 48, and 72 hours and 5 days. Repetition of the epidural blood patch and the time to hospital discharge were noted.

The primary study end point was a composite of permanent or partial headache relief. Permanent relief was defined as full resolution of headache (pain score of zero 4 hours after the procedure), with no recurrence. Partial relief was defined either as a reduction of headache severity score by at least 50% at 4 hours or initial complete relief but a recurrence of postdural puncture headache (severity score >0 at any time in the study period). Secondary end points were the permanent headache relief rate alone, the partial relief rate (as defined above) alone, the severity of headache across the postprocedural time periods, the need for repeat epidural blood patch, and the incidence and severity of back pain in the postprocedural period.

The sample size calculation was based on selection theory (see online Appendix, Supplemental Digital Content 1, http://links.lww.com/AA/A260, and Web supplement, Supplemental Digital Content 2, http://links.lww.com/AA/A261, for explanations and calculations).[23,24] A selection theory approach may be used to reduce the number of required study subjects so that the trial conduct becomes feasible. In selection theory a treatment may be selected as superior even if, on the basis of an hypothesis test, it is actually equivalent to the other treatment(s).

Continuous data were summarized using median and range and interquartile range.

Univariate group comparisons of continuous outcomes were conducted using Kruskal–Wallis nonparametric analysis of variance. Categorical data were summarized using frequency distributions. Univariate comparisons of categorical outcomes were conducted using χ^2 or Fisher exact tests, as appropriate. Time to event outcomes, such as time of headache recurrence, were estimated using Kaplan–Meier survival probabilities and compared using log rank tests. Pain was analyzed on the basis of pain scores, with area under the NRS versus time curve (area under curve,

Table 1. Epidural Blood Patch Group Participants and Centers (n = 10)

Participant/center (country)	No. randomized	No. per group 15/20/30 mL
Paech MJ, Doherty DA, Christmas T: King Edward Memorial Hospital for Women (Australia)	39	14/13/12
Wong CA: Northwestern Memorial Hospital (USA)	26	10/9/7
Douglas MJ: BC Women's Hospital (Canada)	17	6/6/5
Van de Velde M: UZ Gasthuisberg Leuven (Belgium)	10	2/4/4
Elliot D: Westmead Hospital (Australia)	10	3/4/3
Brichant JF: CHR de la Citadelle Liege (Belgium)	8	2/2/4
Hill J: National Women's Hospital (New Zealand)	4	1/2/1
Teoh W: KK Women's and Children's Hospital (Singapore)	3	1/0/2
Angle P: Sunnybrook Hospital (Canada)	2	1/1/0
Caldwell C: Wellington Hospital (New Zealand)	2	1/0/1
Total	121	41/41/39

AUC) used as a summary measure. Logistic regression analysis was used to adjust comparisons of the outcomes permanent and partial relief on the basis of timing of epidural blood patch (less or >48 hours). The ability to determine the effects of these variables was limited because of sample size constraints. Odds ratios (OR) and their 95% confidence intervals (CI) were used to summarize the effects of the timing of performance of the epidural blood patch group. Analyses were conducted on the basis of intention to treat. SPSS statistical software was used for the data analysis (version 16.0, SPSS Inc., Chicago, IL). All hypothesis tests were 2 sided, and P values <0.05 were considered statistically significant.

RESULTS

We enrolled 121 women across 10 centers between September 2004 and August 2009, with 39 being the most women recruited from a single center (Table 1). Women were randomized to 1 of the 3 study groups, and 121 datasets were analyzed, including 2 protocol violations (Fig. 1). The patient characteristics are summarized in Table 2. The number in each group who received their allocated volume is shown in Table 3, as are details of headache and the epidural blood patch procedure.

The composite end point of permanent or partial headache relief occurred in 25 (61%), 30 (73%) and 26 (67%) women in groups 15, 20, and 30, respectively (Table 4). The OR for permanent or partial relief of headache if the timing of the procedure was equal to or >48 hours, in comparison with <48 hours from dural puncture, was 3.15 (CI: 1.39–7.15; P = 0.01). Permanent relief of headache occurred in 4 (10%), 13 (32%), and 10 (26%) women in groups 15, 20, and 30, respectively (Table 4). For all patients, the OR for permanent relief of headache if performing the procedure >48 hours in comparison with <48 hours after dural puncture was 2.35 (95% CI:

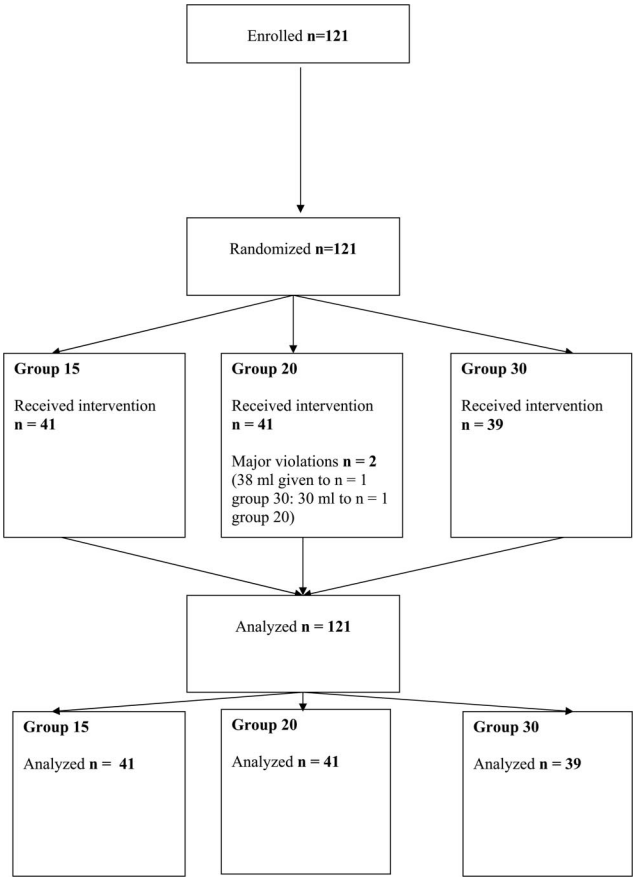

Figure 1. Flow chart of study participants.

0.84–6.56; P = 0.10). The incidence of repeat epidural blood patch is shown in Table 5.

Univariate logistic regression analyses of the effects of both patient characteristics and technique used for the epidural insertion on permanent or partial relief and on permanent relief alone were evaluated. Factors considered included maternal age, body mass index, needle gauge, number of needle passes, the level of epidural needle insertion, visual detection of cerebrospinal fluid, cesarean versus vaginal delivery, time to onset of headache from the dural puncture, and analgesic treatments received before epidural blood patch. No significant factors were identified (data not shown).

Headache pain scores after the epidural blood patch were generally of low intensity (Table 5). The area under the pain versus time curve for each group is shown in Figure 2. The functional assessments of impairment from headache (data not shown) appeared similar and the time to return of headache (overall mean 98 hours, 95% CI: 91–105 hours), time from the epidural blood patch to hospital discharge, and incidence of repeat epidural blood patch are shown in Table 5.

Back pain after the epidural blood patch was common but was usually of low intensity (Table 6). The time to onset of back pain after the epidural blood patch (Table 6) was an overall mean of 27 hours (95% CI: 20–35 hours). The area under the curve for back pain scores versus time for the first 48 hours after the epidural blood patch is shown in Figure 3. No serious morbidity was reported.

Table 2. Patient Characteristics

		15 mL *n*=41	20 mL *n*=41	30 mL *n*=39	*P* value
Age (years)		32 (28–34)	31 (26–34)	31(25–34)	0.77
BMI (kg · m^{-2})		26.5 (23.9–31.6)	27.3 (24.7–30.0)	28.0 (23.1–30.4)	0.91
ASA physical status	1	22 (54%)	29 (71%)	25 (66%)	
	2	19 (46%)	12 (29%)	13 (34%)	0.26
History of migraine		11 (27%)	6 (15%)	12 (32%)	0.19
Indication for epidural	Labor pain	35 (85%)	36 (88%)	34 (87%)	
	Cesarean	6 (15%)	5 (12%)	5 (13%)	0.94
Level of dural puncture	L1-2/L2-3	6 (15%)	6 (15%)	8 (21%)	
	L3-4	28 (68%)	28 (70%)	29 (74%)	
	L4-5	7 (17%)	6 (15%)	2 (5%)	0.52
	missing data		1		
Epidural needle gauge	16	16 (39%)	15 (37%)	14 (36%)	0.95
	17–18	25 (61%)	26 (63%)	25 (64%)	
Loss-of-resistance technique	Saline	28 (70%)	33 (82%)	30 (81%)	0.34
	Air	12 (30%)	7 (18%)	7 (19%)	
	missing data	1	1	2	
Catheter placed in subarachnoid space		12 (29%)	11 (27%)	15 (40%)	0.44
Intrathecal catheter duration (h)		24 (14–26) [0–43]	16 (7–29) [4–38]	21 (14–24) [5–41]	0.72
Delivery mode	Vaginal	29 (71%)	28 (68%)	28 (74%)	0.87
	Cesarean	12 (29%)	13 (32%)	10 (26%)	
	Missing data			1	

Values are median (IQR) or n (%). BMI = body mass index.

Table 3. Patient Characteristics in Relation to Headache and Epidural Blood Patch

	15 mL (*n* = 41)	20 mL (*n* = 41)	30 mL (*n* = 39)	*P* value
Time to onset of PDPH (hours)	15 (7–37)	28 (15–46)	16 (7–35)	0.05
Severity of PDPH (NRS) at time of EBP	8 (7–9)	8 (7–9)	8 (6–9)	0.85
PDPH intensity at time of EBP				
Mild	5 (12%)	2 (5%)	2 (5%)	
Moderate	11 (27%)	13 (32%)	10 (26%)	
Severe	25 (61%)	26 (63%)	27 (69%)	0.66
Severity of back pain (NRS) before EBP	0 (0–2)	0 (0–2)	0 (0–2)	0.94
Associated symptoms[a]	26 (63%)	33 (81%)	34 (87%)	0.03
Analgesic treatment before EBP	38 (97%)	39 (98%)	39 (100%)	0.61
Time from dural puncture to EBP (hours)	62 (49–85)	77 (48–86)	52 (40–80)	0.27
Time from dural puncture to EBP				
<48 hours	12 (29%)	13 (32%)	16 (41%)	0.51
≥48 hours	29 (71%)	28 (68%)	23 (59%)	
Time from onset of headache to EBP (hours)	41 (26–54)	39 (22–56)	31 (21–56)	0.64
Level of EBP				
L1–2/L2–3	5 (13%)	6 (15%)	1 (3%)	0.44
L3–4	22 (54%)	22 (55%)	24 (62%)	
L4–5/L5–S1	13 (33%)	12 (30%)	14 (36%)	
Missing data	1	1		
EBP at same level as dural puncture	27 (66%)	24 (59%)	18 (46%)	0.20
EBP loss-of-resistance technique				
Saline	30 (73%)	30 (73%)	28 (76%)	0.97
Air	11 (27%)	10 (24%)	9 (23%)	
Missing data		1	2	
Back pain during EBP	15 (37%)	20 (49%)	21 (54%)	
Worst back pain during EBP (NRS)	0 (0–4)	0 (0–5)	1 (0–6)	
Volume injected at onset of back pain (mL)	13 (10–15)	12 (10–18)	16 (9–25)	0.07
Severity of back pain immediately after EBP (NRS)	0 (0–3)	2 (0–5)	3 (0–5)	
Received allocated volume	40 (98%)	33 (81%)	21 (54%)	<0.01
Actual volume of EBP (mL)	15 (15–15)	20 (20–20)	30 (22–30)	<0.01

Values are median (interquartile range) or *n* (%). PDPH = postdural puncture headache; EBP = epidural blood patch; NRS = numerical rating scale score (0–10).
[a] Associated symptoms include visual or hearing disturbance, nausea.

Supplementary analyses based on actual treatment volume, that is the treatment received (up to 15 mL, 16 to 20 mL, or >20 mL: $n = 48$, $n = 40$, and $n = 33$, respectively), were performed. The results were consistent with those obtained with the intention-to-treat analyses (data not shown).

DISCUSSION

In this study we evaluated 3 volumes of blood for epidural blood patch in obstetric patients after unintentional dural puncture with an epidural needle. We found that 15, 20, and 30 mL of blood were of similar efficacy with respect to permanent or partial relief of postdural puncture headache.

Table 4. Incidence of Headache Relief After Epidural Blood Patch

	<48 hours	≥48 hours	Overall
Permanent or partial relief			
15 mL	33.3 (9.0–65.1)	72.4 (52.8–87.3)	61.0 (44.5–75.8)
20 mL	61.5 (31.6–86.1)	78.6 (59.1–91.7)	73.2 (57.1–85.8)
30 mL	56.3 (29.9–80.3)	73.9 (51.6–89.9)	66.7 (49.8–80.9)
Permanent relief[a]			
15 mL	0.0 (0–26.5)	13.8 (3.9–31.7)	9.8 (2.7–23.1)
20 mL	15.4 (1.9–45.5)	39.3 (21.5–59.4)	32.3 (18.1–48.1)
30 mL	25.0 (7.3–52.4)	26.1 (10.2–48.4)	25.6 (13.0–42.1)

Values are percentages (Clopper–Pearson binomial 95% confidence intervals). Summaries are shown for both strata and overall.

[a] Statistically significant differences in the rates of permanent relief were found between the groups on chi-square test ($P = 0.048$), with the less-than-expected number of permanent responses seen in the 15-mL group. Further comparisons using logistic regression analysis showed that the response achieved in the 20-mL group was significantly higher than that achieved in the 15-mL group (odds ratio [OR] = 4.49, confidence interval [CI] = 1.31–15.42; $P = 0.017$), while the higher response in the 30-mL group was not significantly different from that in the 15-mL group (OR = 3.56, CI = 0.99–12.73; $P = 0.051$).

Table 5. Headache After Epidural Blood Patch

	15 mL ($n = 41$)	20 mL ($n = 41$)	30 mL ($n = 39$)
Headache severity (NRS)			
2 hours ($n = 120$)	1 (0–4)	1 (0–3)	0 (0–3)
4 hours ($n = 120$)	0 (0–2)	1 (0–2)	0 (0–2)
24 hours ($n = 121$)	1 (0–4)	0 (0–2)	0 (0–1)
48 hours ($n = 114$)	2 (0–7)	0 (0–3)	0 (0–5)
72 hours ($n = 100$)	2 (0–6)	0 (0–4)	0 (0–5)
5 days ($n = 86$)	0 (0–2)	0 (0–0)	0 (0–0)
No analgesics required post-EBP	5 (12%)	17 (42%)	8 (21%)
Time from EBP to hospital discharge (hours)	24 (16–72)	26 (20–58)	28 (18–52)
Time to return of headache (hours)	100 (88–111)	100 (88–112)	95 (82–108)
Repeat EBP[a]	16 (39%)	9 (23%)	12 (31%)

Values are median (interquartile range) or *n* (%). NRS = numerical rating scale score (0–10); EBP = epidural blood patch.

[a] Mean (95% confidence interval) estimated using Kaplan–Meier survival probabilities.

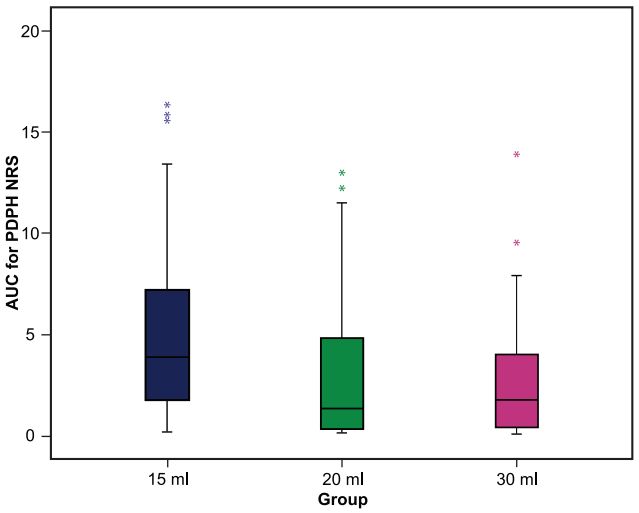

Figure 2. Area under the curve for postdural puncture headache scores between 0 and 48 hours after epidural blood patch. Box and whisker plot with median (interquartile range), 10th–90th percentiles, and outliers represented by asterisks. AUC for PDPH NRS = area under the curve for postdural puncture headache numerical rating scale scores. $P = 0.01$ for group 15 mL versus groups 20 and 30 mL.

Although the proportion of patients with full and permanent resolution of headache was smaller after 15 mL than after 20 mL and 30 mL, the 95% CIs overlapped and the study was not sufficiently powered to definitively conclude that there was a difference between 15 mL and higher volumes for this outcome. Post blood patch headache pain scores were higher in the 15-mL group. There were no differences in headache pain scores between the 20-mL and 30-mL groups. A postulated risk of large volumes is an increased incidence of back pain. We did not find this to be the case. However, we were unable to administer the planned epidural blood patch volume more often in the 30-mL group than in the lower-volume groups because of patient complaints of back pain during the procedure.

There were no serious complications from the procedure in any group. Taken together, we believe that these findings support an attempt to administer 20 mL of autologous blood when treating postdural puncture headache in obstetric patients after unintentional dural puncture.

Approximately 1% of obstetric patients experience an unintentional dural puncture during attempted insertion of an epidural catheter,[1] of whom 55%–80% develop a postdural puncture headache and approximately two thirds receive an epidural blood patch.[2,4–7] The nature of the headache is such that it is often severe enough to prevent ambulation or effective interaction between mother and baby. This also increases nursing and anesthetic workload, prolongs hospitalization, and adds substantially to health care costs. These headaches usually persist for a week or more, are moderate to severe in 50% of cases,[8] and occasionally persist as chronic headache. Randomized controlled trials have confirmed the greater efficacy of an epidural blood patch in comparison with conservative treatment (bed rest and IV fluid).[8,14,15] Unfortunately, in obstetric patients the efficacy varies and is often modest; complete resolution of symptoms, and no recurrence, after

Table 6. Back Pain After Epidural Blood Patch

	15 mL (n = 41)	20 mL (n = 41)	30 mL (n = 39)
Incidence of back pain	34 (83%)	34 (85%)	35 (87%)
Lower back pain severity (NRS)			
4 hours (n = 120)	1 (0–3)	2 (0–4)	2 (0–3)
24 hours (n = 121)	2 (0–4)	1 (0–3)	1 (0–3)
48 hours (n = 114)	1 (0–4)	1 (0–2)	1 (0–2)
72 hours (n = 104)	2 (0–4)	0 (0–2)	1 (0–3)
5 days (n = 86)	2 (0–3)	0 (0–1)	0 (0–2)
Time to onset of back pain after EBP (hours)[a]	28 (15–42)	27 (14–39)	27 (15–39)

Values are median (interquartile range) or n (%). NRS = numerical rating scale score (0–10). EBP = epidural blood patch.
[a] Mean (95% confidence interval) estimated using Kaplan–Meier survival probabilities.

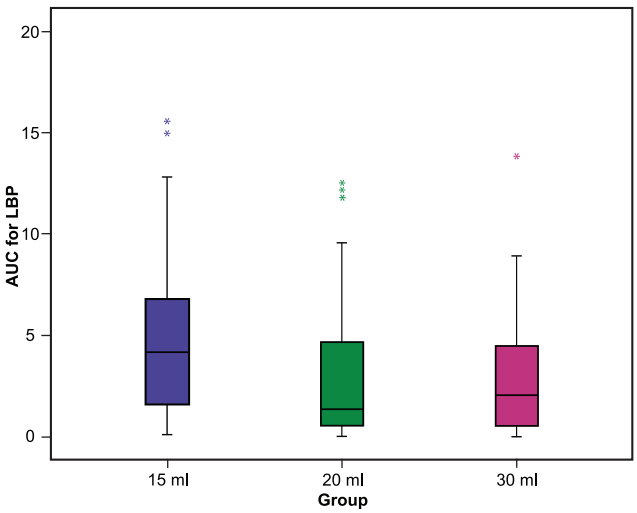

Figure 3. Area under the curve for lumbar back pain scores between 0 and 48 hours after epidural blood patch. Box and whisker plot with median (interquartile range), 10th–90th percentiles, and outliers represented by asterisks. AUC = area under the curve for numerical rating scale scores; LBP = lumbar back pain. P = 0.02 for group 15 mL versus groups 20 and 30 mL.

a single therapeutic epidural blood patch occurs in only 35%–70% of cases, mainly because of the high rate of recurrence.[6,16,25] A number of questions about the method, outcomes, and side effects of epidural blood patch remain unanswered and practice varies substantially.[17,21]

The volume of blood that would optimize outcomes, including an acceptable incidence of procedural and postprocedural back pain, is controversial. In 1960, Gormley[11] claimed a 100% response using 2 to 3 mL of blood, and in 1970 DiGiovanni and Dunbar[18] reported a 90% response to 5 to 10 mL. Szeinfeld et al.[26] found that an average of 15 mL (range 12 to 18 mL) was effective and spread extensively over 7 to 14 spinal intervertebral segments, but others reported no advantage from 10 to 15 mL rather than 10 mL.[27] In 1980, Crawford[19] described almost complete success using 20 mL and subsequently claimed even better results with >20 mL.[28] Other observational studies have failed to clarify the situation, some reporting better efficacy from volumes larger than 20 mL and others not finding volume to be predictive of outcome.[6,29] Most studies were retrospective, and follow-up was not standardized. In the only randomized controlled trial, 7.5 mL and 15 mL produced similar relief, but pain during injection was less with the smaller volume.[22]

A clinical problem associated with the injection of an increasing volume of blood is back pain. This occurs during and after injection and is attributed to direct nerve root irritation or the acute and sustained neuraxial canal pressure increase that is transmitted to nerve roots,[30] meninges, or medullary tissue. This back pain may limit the volume that can be injected. Discomfort often commences after 5 to 7.5 mL,[30] and the incidence of pain increases as the volume of blood injected increases. Approximately 50% of women experience pain from injection of 15 mL.[22] Our study confirms that this problem is clinically important, because the percentage of women in whom the assigned volume could be injected decreased substantially in the group allocated the highest volume of 30 mL. Detailed studies of the period after an epidural blood patch are scarce, and none evaluated postprocedural pain as a primary outcome, but some report back pain for up to 3 days.[5,6,8,22,31] We found a higher overall incidence, probably due to better surveillance, but a similar incidence of clinically relevant lower back pain to previous studies. One quarter of our participants described moderate or severe pain for up to 5 days but most had very low scores, suggesting that this side effect of epidural blood patch should not be a deterrent to performing the procedure. An unexplained finding was that this postprocedural back pain was more intense among women treated with 15 mL of blood, although pain scores were usually very low. The study was not powered to detect differences in serious complications or morbidities, which appear rare but have not been quantified. None was reported in this study, but severe back pain, subdural hematoma, pneumocephalus, cranial nerve palsies, meningism, and epidural abscess continue to be reported sporadically.[17]

We attempted to control several possible confounding technique variables such as rate of blood injection, vertebral level of the epidural blood patch, and its timing. The relevance of these factors to response to epidural blood patch is uncertain and the intensity of headache at the time of epidural blood patch was similar across groups. Evidence from observational studies suggests that earlier intervention in relation to dural puncture is associated with a higher epidural blood patch failure rate. Banks et al.[16] found epidural blood patch was unsuccessful when performed within 24 hours of dural puncture, and Taivenen et al.[27] noted that the risk of failure was doubled if epidural blood patch was performed within 4 days of the puncture. It is unclear whether the timing of the procedure actually influences the success rate, or whether patients who require an epidural blood patch later are inherently different from those who require an early blood patch. In our study,

univariate logistic regression suggested that a better response was likely if the procedure was delayed until 48 hours or more from the time of dural puncture, but this finding requires confirmation in a randomized trial.

This study has a number of limitations. Recruitment to such a trial is difficult, and it is possible that there were undetected differences in outcomes in different centers and changes across the 5-year study duration. The findings may not apply to treatment of postdural puncture headache resulting from spinal needles, for which epidural blood patch appears to have greater efficacy.[14,27,29,31] The results may not be valid in the nonobstetric population, and there may be differences depending on the epidural needle size or design. The attending anesthesiologist was not blinded, and different anesthesiologists are likely to have had different attitudes to continuing injection of blood when the patient complained of back pain. It is likely that the study was underpowered with respect to a number of outcomes. The sample size was derived using selection theory, which allows a treatment to be ranked and selected as superior even if it is actually equivalent to the other treatment considered. This approach allows for smaller sample sizes in comparison with conventional statistical designs used in clinical research and is appropriate when the study would not be feasible on the basis of conventional sample size calculation.[32,33] The concepts of significance level and power do not have direct analogs in the methodology based on selection theory, but the probability of selecting a superior treatment can be interpreted as the study power. Using conventional statistical methods for the selection of the number of patients required, the study did not appear feasible. For example, a 3-arm trial in which the primary end point was a permanent response to the epidural blood patch, evaluated using a χ^2 test (that is, not accounting for pairwise comparisons), required 360 per group ($n = 1080$) to detect a complete response in 50% rather than 40% ($\alpha = 0.05$, $\beta = 0.8$). A published randomized trial of epidural blood patch volume, involving only 33 obstetric patients, took 7 years to complete.[22] We argue that design based on selection theory was justified, given that it took >5 years to recruit sufficient patients in 10 busy maternity units. Another important criterion to be met in applying this statistical approach is that choosing the wrong arm should not have unacceptable consequences. This criterion applies to this study, because all study volumes are currently used clinically. We considered that between-groups differences were likely to be modest and that even modest benefit or disadvantage of one particular volume could be acknowledged as clinically relevant.

Although the optimum volume of blood remains to be determined, we believe that these findings support an attempt to administer 20 mL of autologous blood when treating postdural puncture headache in obstetric patients after unintentional dural puncture.

RECUSE NOTE

Cynthia Wong is the section Editor for Obstetric Anesthesiology for the *Journal*. This manuscript was handled by Steve Shafer, Editor-in-Chief, and Dr. Wong was not involved in any way with the editorial process or decision.

DISCLOSURES

Name: Michael J. Paech, DM.
Contribution: This author helped design the study, conduct the study, and write the manuscript.
Attestation: Michael J. Paech has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Name: Dorota A. Doherty, PhD.
Contribution: This author helped design the study, analyze the data, and write the manuscript.
Attestation: Dorota A. Doherty has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Tracey Christmas, FRCA.
Contribution: This author helped conduct the study and write the manuscript.
Attestation: Tracey Christmas has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Cynthia A. Wong, MD.
Contribution: This author helped design the study, conduct the study, and write the manuscript.
Attestation: Cynthia A. Wong has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Epidural Blood Patch Trial group (see Table 1).
Contribution: These authors helped design the study and conduct the study.
Attestation: Epidural Blood Patch Trial group approved the final manuscript.

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