Factors associated with failed epidural blood patch after accidental dural puncture in obstetrics: a prospective, multicentre, international cohort study

Gupta, A.; Velde, M. van de; Magnuson, A.; Heymann, C. von; Guasch, E.; Alahuhta, S.; ... ; European Practices Management Acci

BJA

British Journal of Anaesthesia, 129 (5): 758–766 (2022)

doi: 10.1016/j.bja.2022.06.040
Advance Access Publication Date: 3 September 2022
Pain

Factors associated with failed epidural blood patch after accidental dural puncture in obstetrics: a prospective, multicentre, international cohort study

Anil Gupta[1,*], Marc Van de Velde[2,3], Anders Magnuson[4], Christian von Heymann[5], Emilia Guasch[6], Seppo Alahuhta[7], Frédéric J. Mercier[8], Alexandra M. J. V. Schyns-van den Berg[9,10], and the European Practices in the Management of Accidental Dural Puncture in Obstetrics Investigators[†]

[1]Department of Perioperative Medicine and Intensive Care and Institution of Physiology and Pharmacology, Karolinska Hospital and Karolinska Institutet, Stockholm, Sweden, [2]Department of Cardiovascular Sciences, KZ Leuven, Belgium, [3]Department of Anesthesiology, UZ Leuven, Leuven, Belgium, [4]Clinical Epidemiology and Biostatistics, School of Medical Sciences, Örebro University, Örebro, Sweden, [5]Department of Anaesthesia, Intensive Care Medicine, Emergency Medicine and Pain Therapy, Vivantes Klinikum Im Friedrichshain, Berlin, Germany, [6]Department of Anaesthesia and Reanimation, Hospital Universitario La Paz, Madrid, Spain, [7]Department of Anaesthesiology, Medical Research Centre Oulu, University of Oulu, Oulu University Hospital, Oulu, Finland, [8]Departement of Anaesthesia, Hôpital Antoine Béclère, AP-HP Université Paris-Saclay, France, [9]Department of Anesthesiology, Albert Schweitzer Ziekenhuis, Dordrecht, the Netherlands and [10]Department of Anesthesiology, Leiden University Medical Centre, Leiden, the Netherlands

*Corresponding author. E-mail: anil.gupta@regionstockholm.se
[†]For the complete list of the European Practices in the Management of Accidental Dural Puncture in Obstetrics collaborators, please see the Supplementary Appendix.

Abstract

Background: Epidural blood patch is commonly used for management of post-dural puncture headache after accidental dural puncture. The primary aim was to determine factors associated with failed epidural blood patch.
Methods: In this prospective, multicentre, international cohort study, parturients ≥18 yr receiving an epidural blood patch for treatment of post-dural puncture headache were included. Failed epidural blood patch was defined as headache intensity numeric rating scale (NRS) score ≥7 in the upright position at 4, 24, or 48 h, or the need for a second epidural blood patch, and complete success by NRS=0 at 0–48 h after epidural blood patch. All others were considered partial success. Multinominal logistic regression was used for statistical analyses with $P<0.01$ considered statistically significant.
Results: In all, 643 women received an epidural blood patch. Complete data to classify failure were available in 591 (91.9%) women. Failed epidural blood patch occurred in 167 (28.3%) patients; 195 (33.0%) were completely successful and 229 (38.7%) partially successful. A total of 126 women (19.8%) received a second epidural blood patch. A statistically significant association with failure was observed in patients with a history of migraine, when the accidental dural puncture occurred between lumbar levels L1/L3 compared with L3/L5 and when epidural blood patch was performed <48 h compared with ≥48 h after accidental dural puncture. In patients having radiological investigations, three intracranial bleeds were diagnosed.
Conclusions: Failed epidural blood patch occurred in 28.3% of women. Independent modifiable factors associated with failure were higher lumbar level of accidental dural puncture and short interval between accidental dural puncture and epidural blood patch. A history of migraine was associated with a higher risk of second epidural blood patch.
Clinical trial registration: NCT02362828.

Received: 5 July 2021; **Accepted:** 22 June 2022

Keywords: accidental dural puncture; epidural analgesia; epidural blood patch; obstetric anaesthesia; post-dural puncture headache

Editor's key points

- Epidural blood patch for post-dural puncture headache after accidental dural puncture shows limited efficacy.
- This prospective, multicentre, international cohort study of 643 patients in the European Practices in the Management of Accidental Dural Puncture in Obstetrics trial examined factors associated with failed epidural blood patch.
- Epidural blood patch failed in 28.3% of patients; 33.0% were completely successful and 38.7% partially successful, while 19.8% received a second blood patch.
- Risk factors identified for failure include a history of migraine headache, accidental dural puncture at higher lumbar levels, and injection of epidural blood patch <48 h after accidental dural puncture.
- These associations with modifiable risk factors should be confirmed in large randomised studies.

Accidental dural puncture (ADP), whilst performing epidural labour analgesia, occurs in 0.5–1.5% of procedures.[1,2] This iatrogenic injury causes leakage of CSF and can result in an intense post-dural puncture headache (PDPH), which is commonly postural.[3] PDPH often results in the patient being bedridden, thus delaying maternal recovery and mother–child bonding.[4,5] Several treatment options exist for the management of PDPH, but an epidural blood patch (EBP), where autologous blood is injected into the epidural space near the ADP site, is usually considered to be the best therapeutic option, although up to 30% of patients required a second EBP because of recurrent symptoms.[6–9] An EBP is believed to have a two-fold effect: immediate restoration of the reduced intracranial CSF pressure and a secondary effect resulting from clot formation and reparation of the dural tear.[10] Although EBP is an invasive procedure, serious complications have rarely been described.[7,11]

The European Practices in the Management of Accidental Dural Puncture in Obstetrics (EPiMAP) was an international cohort study that described current practices in the management of PDPH and studied risk factors of failure of EBP. In the first part of the study, we identified factors associated with the preference for use of EBP or conservative management after diagnosis of PDPH.[12] The main objective of the present study was to determine factors associated with failure of EBP. Some of these factors have been described previously, such as injection of lower volumes of blood during EBP and early application of EBP after ADP.[8,9,13,14] However, a causal relationship between timing of EBP and failure has not been proven. It has been suggested that an attempt to inject up to 20 ml of autologous blood should be made, as higher volumes have not been shown to improve success rates even when height adjusted.[7–9,15] An association between risk of intracranial bleeding and delay in application of EBP has been suggested, but early application of EBP may be associated with failure.[13,16] The primary aim of the present EPiMAP study was to determine risk factors associated with failure of the first EBP in women having PDPH after obstetric neuraxial anaesthesia and analgesia.

Methods

This was a prospective, multicentre cohort study. Data were collected from January 1, 2016 to December 31, 2018, with a follow-up period of 3 months ending March 31, 2019. The study was registered on ClinicalTrials.gov (NCT02362828), and ethical committee approval was obtained in each participating country, either locally or nationally, depending on country requirements. Signed informed consent was obtained from each patient before inclusion when requested by the local/national ethics committee. Inclusion and exclusion criteria were the same as those described in EPiMAP I except only women who received an EBP were included in the present study.[12]

Post-dural puncture headache was diagnosed by a board-certified anaesthesiologist according to the prevailing International Classification of Headache Disorders (ICHD-II 2d).[17] The ICHD-II describes PDPH as a headache that worsens within 15 min in the upright position and improves within 15 min after lying down, which develops within 5 days after suspected or confirmed dural puncture, and which may or may not be accompanied by neck stiffness and vestibular, visual, or auditory symptoms.[17] Headache intensity was measured in the upright (sitting/standing) and supine (lying) positions using a numeric rating scale (NRS), with 0=no pain and 10=worst imaginable pain, and classified as none (NRS=0), mild (1–3), moderate (4–6), and severe (7–10) in the upright position.

The need for an EBP was ascertained by a certified anaesthesiologist immediately before its application, depending on headache intensity during the previous 6–12 h, accompanying symptoms and local traditions and guidelines in each centre/country. The timing of the EBP, the position of the patient, the lumbar level chosen for the EBP, the volume of blood injected, the duration of bed rest, the timing of home discharge, and the need for a second or third EBP were at the discretion of the anaesthesiologist. CT, MRI, or Doppler ultrasonography was used when needed to exclude other pathological processes, in accordance with existing clinical practice. An open source clinical data management system (OpenClinica™), was used by the European Society of Anaesthesiology and Intensive Care (ESAIC), to collect data in accordance with the general data protection regulations. Patients were followed up during hospital stay, by telephone after discharge, and after 7 days and 3 months by a standardised telephone interview.

The primary outcome was failed EBP, defined as a headache intensity with NRS $\geq$7 in the upright position at 4, 24, and or 48 h after application of EBP or the need for a second EBP. A complete success was defined as no headache (NRS=0) at 4, 24, and 48 h after EBP in the upright position and no subsequent

Table 1 Characteristics of study population. Data presented as *n* (%) unless otherwise stated. ADP, accidental dural puncture; EBP, epidural blood patch; IQR, inter-quartile range; NRS, numeric rating score; PDPH, post-dural puncture headache. *Includes underweight (six patients). †BMI ≥35 kg m^{-2} (45 patients). ‡<24 h between epidural needle insertion and EBP (25 patients). ¶Orthostatic headache was classified as delta pain intensity ≥2 NRS higher upright than lying 6–12 h before EBP.

Epidural blood patch group (*n*=643)	*n* (%)
Patient characteristics	
Mother's age (yr), median (IQR; min–max)	31 (28–34; 18–46)
BMI (kg m^{-2}), median (IQR) (*n*=642)	26.7 (24.0–30.1)
<25 normal (+underweight*)	219 (34.1)
25.0–29.9 (pre-obesity)	251 (39.1)
≥30.0 (obesity)†	172 (26.8)
Previous history of	
PDPH headache	17 (2.6)
Chronic headache	30 (4.7)
Migraine	98 (15.2)
Vertebral column pathology	49 (7.6)
University as highest education (*n*=641)	308 (48.0)
Mode of delivery	
Spontaneous	452 (70.3)
Instrumental	79 (12.3)
Caesarean delivery	112 (17.4)
Characteristics of epidural insertion	
Needle size at accidental dural puncture	
18–20G	518 (80.6)
16–17G	125 (19.4)
Method for detecting loss of resistance (*n*=642)	
Saline	560 (87.2)
Air	71 (11.1)
Both	11 (1.7)
Position of patient at accidental dural puncture (*n*=640)	
Sitting	519 (81.1)
Lying	121 (18.9)
Level of accidental dural puncture (*n*=642)	
L3/L5	421 (65.6)
L1/L3	221 (34.4)
Multiple attempts at different levels	304 (47.3)
Intrathecal catheter placed after accidental dural puncture	91 (14.2)
Experience of operator providing epidural analgesia (yr)	
≥1	502 (78.1)
<1	141 (21.9)
How accidental dural puncture was determined	
CSF in epidural needle	321 (49.9)
CSF in catheter or positive aspiration test or positive intrathecal test dose, without CSF in needle	85 (13.2)
Only classical signs of PDPH postpartum	237 (36.9)
Second accidental dural puncture occurring when new epidural needle was inserted (*n*=641)	
No	429 (66.9)
Yes	64 (10.0)
Not applicable	148 (23.1)
Time for first symptoms of PDPH after accidental dural puncture (h) (*n*=639), median (IQR; min–max)	16 (8–28; 0–120)
Symptoms other than classical PDPH, before/after confirmed PDPH	
Nausea/vomiting	178 (27.7)
Auditory symptoms	172 (26.7)
Diplopia	18 (2.8)
Dizziness	181 (28.1)
Other visual symptoms	106 (16.5)
Tinnitus	90 (14.0)
Neck	69 (10.7)
Others	66 (10.3)
Characteristics of EBP management	
Hours from ADP to EBP, median (IQR; min–max)‡	68 (47–97; 0.5–270)
Patient initially refused EBP	13 (2.0)
Experience of the operator in performing EBP (yr), *n*	
<1	52 (8.1)
1–10	224 (34.8)
>10	367 (57.1)

Continued

Table 1 Continued

Epidural blood patch group (n=643)	n (%)
Position of patient during EBP	
Sitting	344 (53.5)
Lying	299 (46.5)
Worst pain intensity upright 6–12 h before EBP (NRS), median (IQR; min–max) (n=630)	9 (8–10; 0–10)
Orthostatic headache classified 6–12 h before EBP[¶] (n=630)	555 (88.1)
Level of insertion of EBP (n=642)	
L3/L5	444 (69.2)
L1/L3	198 (30.8)
Technical difficulties in performing EBP	60 (9.3)
Volume of blood injected during EBP (ml), median (IQR; min–max)	20 (18–20, 8–40)
First mobilisation after EBP (h) (n=640), median (IQR; min–max)	2 (2–4; 0–24)
Country	
Spain	110 (17.1)
France	84 (13.1)
Sweden	84 (13.1)
Portugal	57 (8.9)
Germany	56 (8.7)
Netherlands	46 (7.2)
Belgium	42 (6.5)
Israel	25 (3.9)
Finland	22 (3.4)
Norway	22 (3.4)
Switzerland	22 (3.4)
Other	73 (11.3)

EBP application, and partial success included all other patients not categorized as success or failure. If the patient had no headache at 4 or 24 h and was discharged before 48 h and not readmitted with headache, the EBP was also considered a complete success. The terms *chronic headache*, *vertebral column pathology*, and technical difficulty in insertion of epidural were not defined *pre hoc*, but left to the discretion of the attending anaesthesiologist.

ESAIC was the sponsor and coordinated the study, ensuring quality assurance and control systems using standard operating procedures. Data were generated, documented, and reported in compliance with the protocol Good Clinical Practice, and the local regulatory requirements. The sponsor ensured agreement from all involved parties and access to all trial-related sites, source data/documents, reports for monitoring and auditing, and inspection by domestic and foreign regulatory authorities. The local principal investigator verified data quality and registration and was controlled by the sponsor with random assessments of centres to confirm correctness of data.

Statistical analysis

Because of the limited number of randomised studies to estimate potential risk factors for EBP failure, we used low volume of blood injected into the epidural space during EBP as one potential risk factor for failure to determine sample size. An absolute reduction of failure rates from 39% to 27% was found by Paech and colleagues[9] when comparing women who were allocated to receive 15 ml *vs* 20 ml of blood during EBP. Using these data, we estimated that 636 patients receiving an EBP would be needed for 90% statistical power when using a 5% significance level. Multinominal logistic regression was used with the outcome categorized as EBP resulting in a complete success (the reference), partial success, or failure.

Independent variables identified *a priori* as potential causes of failure from the literature included intensity of headache before EBP, experience of the anaesthesiologist performing the EBP, epidural needle size, position of the patient during EBP, volume of blood injected, time from ADP to EBP, and duration of rest before mobilisation after EBP. Other variables listed in Table 1 were included as potential risk factors after discussion within the steering committee and before data analyses. The unadjusted models were adjusted for country of residence, with countries including fewer than 15 patients collapsed into one category. The adjusted model was estimated with all variables in the model to evaluate each variable's independent association with the outcome.

Continuous variables were categorised in tertiles, with some exceptions. Hours from ADP to EBP were categorised <48, 48 to <72 h, and ≥72 h. Body mass index (BMI) was categorised as BMI <25, 25–29.9, or ≥30 kg m^{-2}.[18] Needle size used during ADP was characterised as large (16G or 17G) or small (18G, 19G, or 20G) bore; vertebral interspace during ADP and at EBP insertion as high (L1/L3; L1–L2 or L2–L3 interspace) or low (L3/L5; L3–L4 or L4–L5 interspace); and mobilisation time after EBP as early (<2 h), intermediate (2–4 h), or late (>4 h). Experience of the anaesthesia operator during ADP was categorised as experience <1 or ≥1 yr. Orthostatic headache was defined as NRS pain intensity in the upright position–supine position ≥2.

Regression diagnostics and sensitivity analysis were performed by excluding outliers, and influential subjects were identified using Pearson residuals, deviance residuals, and Pregibon leverage statistics, but there were no different

findings. We evaluated the potential collinearity issues by estimating the variance inflation factor (VIF); the variables showed a VIF score between 1 and 2, much lower than 10, which is a rule of thumb for collinearity. Because of missing data on some independent variables and outcomes, multiple imputation was performed using logistic and multinominal regression with chained equations based on the concept of Rubin.[19] All variables in the adjusted model and the outcome were used as independent variables for the imputation, which was repeated 10 times. Variables showing statistical significance in the adjusted model were further evaluated by comparing the NRS pain intensity at different time points pre-EBP and post-EBP with Kruskal–Wallis and Mann–Whitney tests, and by comparing the frequency of second EBP with χ^2 or Fisher's exact test when appropriate and differences in orthostatic headache with χ^2 test. Multinominal logistic regression gives odds ratios (ORs) with 95% confidence intervals (CIs) as association measures. To reduce the risk of false-positive findings because many independent variables were hypothesised as risk factors, a *P*-value <0.01 was set as statistically significant. All statistical calculations were done in Stata release 14 (StataCorp, College Station, TX, USA).

Results

From a total of 1001 patients with PDPH who were included in the EPiMAP database, 647 patients from 24 countries and 125 centres received an EBP (64.6%).[12] Of these, four patients receiving an EBP >2 weeks after ADP were excluded from the present analysis, and a total of 643 women from 24 countries were included in the final analyses (Fig 1). The number of patients included and the rates of failures, partial success, and complete success varied considerably in different countries (Supplementary Fig 1S). Patient characteristics with missing data on some variables are shown in Table 1.

Headache intensities before and after application of EBP are shown in Table 2, and the numbers (%) of completely successful, partially successful, and failed EBP are shown in Fig 1. A total of 52 of 643 (8.1%) patients could not be classified for the primary outcome because of some missing pain intensity data. In all, failure of first EBP was seen in 167 of 591 (28.3%; 95% CI: 24.6–32.1%) patients, partial success in 229 of 591 (38.7%; 95% CI: 34.8–42.8%), and 195 (33.0%; 95% CI: 29.2–36.9%) of EBP were completely successful. Severe headache was reported by an increasing proportion of women between 4 and 24 h after

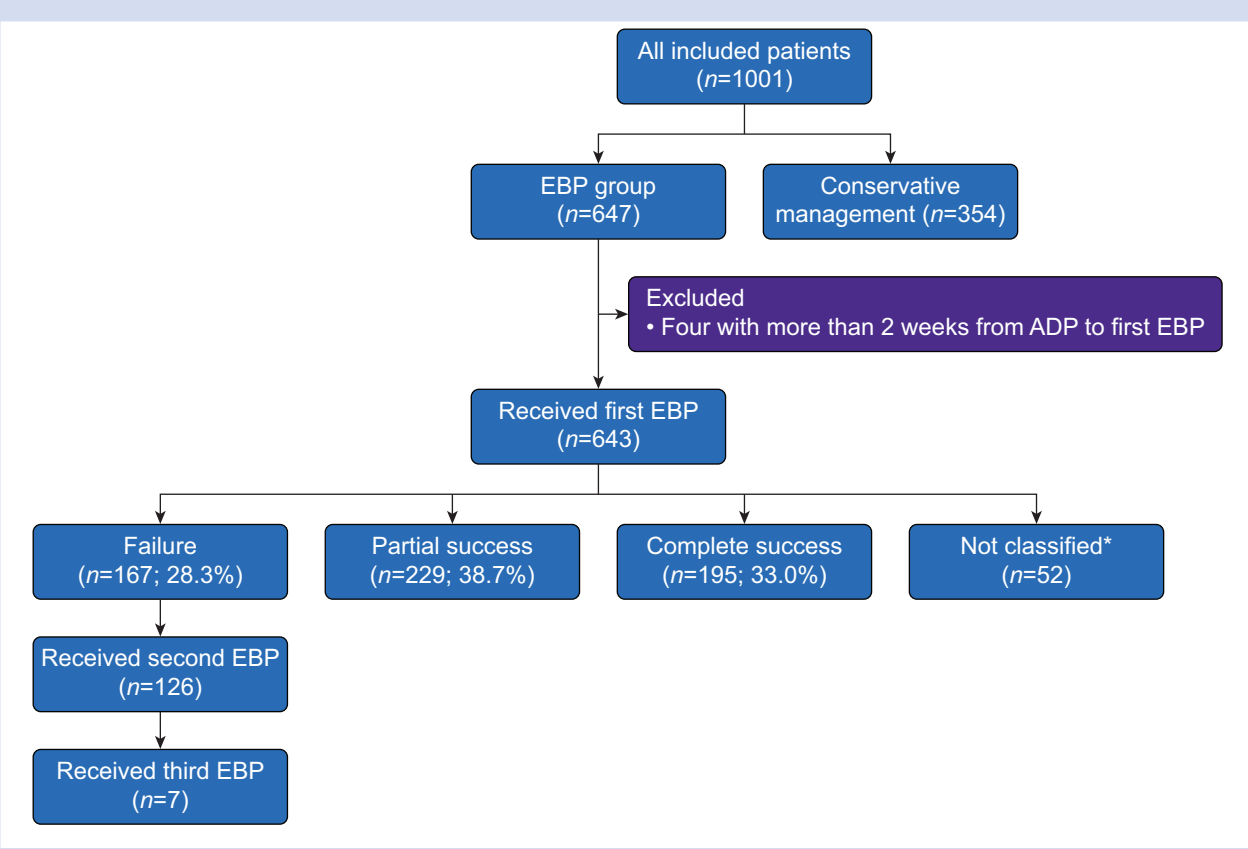

Fig 1. Strengthening the Reporting of Observational Studies in Epidemiology diagram for inclusion or exclusion of patients. *Primary outcome not classified in 52 patients because of missing pain intensity data. EBP, epidural blood patch. Please see text for definitions of failure, partial success, and complete success. ADP, accidental dural puncture.

Table 2 Analgesia outcomes. EBP group, *n*=643. EBP, epidural blood patch; IQR, inter-quartile range; NRS, numeric rating score; PDPH, post-dural puncture headache.

Pain intensity in the upright position	*n*	None (NRS 0), *n* (%)	Mild (NRS 1–3), *n* (%)	Moderate (NRS 4–6), *n* (%)	Severe (NRS 7–10), *n* (%)
6–12 h before EBP	630	1 (0.2)	3 (0.5)	74 (11.7)	552 (87.6)
After EBP	641	250 (39.0)	249 (38.9)	97 (15.1)	45 (7.0)
4 h after EBP	575	276 (48.0)	207 (36.0)	71 (12.4)	21 (3.6)
24 h after EBP	636	344 (54.1)	167 (26.3)	60 (9.4)	65 (10.2)
48 h after EBP (only readmitted or patients with persistent PDPH measured at 48 h)	199	7 (3.5)	18 (9.1)	54 (27.1)	120 (60.3)
Having a second EBP		19.6% (126 of 643)			
Hours from first to second EBP, median (IQR)	126	49 (44–69)			
Second EBP within 24 h		6.4% (8 of 126)			
Second EBP within 48 h		41.3% (52 of 126)			

EBP (Table 2), and a second EBP was performed in 126/643 women (19.6%; 95% CI: 16.6–22.9%).

In the multinominal adjusted logistic regression model with multiple imputation, the following variables were statistically significantly associated with a greater risk of failure of the EBP (P<0.01): history of migraine compared with no history of migraine, and ADP occurring at a higher level (L1/L3) compared with a lower level (L3/L5) (Table 3). EBP volume was not found to be associated with failure. All variables included in the model are presented in Supplementary Table 1S. Complementary analysis did not show any different association when combining the level of ADP with EBP (Supplementary Table 2S). The adjusted failure risk of an EBP was lowest when ADP had occurred at L4–L5, higher with an ADP at L3–L4, and highest if ADP occurred at L2–L3 or L1–L2 levels (Supplementary Table 3S). A significantly lower risk of failure of the EBP was observed when there was a longer time interval between ADP and EBP: EBP ≥48 to <72 h after ADP and EBP ≥72 h after ADP compared with EBP <48 h (Table 3). Higher levels (L1/L3) were associated with greater risk of partial success compared with lower levels (L3/L5). EBP ≥72 h after ADP was associated with a significant lower risk of partial success (Table 3). The same variables associated with a significant risk of EBP failure were also found in a complete case analysis, not using multiple imputation for missing data.

For all variables associated with significant risk of EBP failure, headache intensities in the upright position before and after application of EBP and the frequency of a second EBP are presented in Supplementary Table 4S. A higher level of ADP (L1/L3) compared with lower (L3/L5) was associated with greater headache intensity in the first 24 h after EBP (P<0.01) but not associated with an increased risk of higher NRS scores at 48 h, or receiving a second EBP, whilst a history of migraine was only significantly associated with a greater risk of receiving a second EBP but not with an increased intensity of headache at any time after EBP. To differentiate migraine from PDPH, the incidence of orthostatic headache before and after application of EBP was compared between patients with or without migraine, but no differences were found (Supplementary Table 5S). Finally, late application of EBP (≥72 h) was significantly associated with lower headache intensity at 4 and 24 h after EBP and with a lower risk of receiving a second EBP.

Table 3 Significant variables from the adjusted multinominal logistic regression with outcome classified as complete success (reference), partial success, or failure. CI, confidence interval; OR, odds ratio. *The unadjusted analysis was adjusted for country, and multiple imputation is used for missing data on variables and outcome; *n*=643. †The adjusted analysis was adjusted for all variables in Supplementary Table 1S, and multiple imputation is used for missing data on variables and outcome; *n*=643.

	Partial success				Failure			
	Unadjusted*		Adjusted†		Unadjusted*		Adjusted†	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
Previous history of migraine headache								
No	Reference		Reference		Reference		Reference	
Yes	1.06 (0.57–1.95)	0.86	1.25 (0.61–2.56)	0.55	2.09 (1.16–3.78)	0.0149	3.16 (1.48–6.78)	0.0032
Level of accidental dural puncture								
L3/L5	Reference		Reference		Reference		Reference	
L1/L3	1.83 (1.12–2.98)	0.0152	2.69 (1.47–4.94)	0.0014	2.11 (1.23–3.60)	0.0065	3.28 (1.64–6.53)	0.0008
Time from accidental dural puncture to epidural blood patch (h)								
<48	Reference		Reference		Reference		Reference	
48 to <72	0.70 (0.38–1.28)	0.24	0.60 (0.30–1.19)	0.14	0.43 (0.23–0.78)	0.0060	0.37 (0.18–0.77)	0.0073
≥72	0.45 (0.25–0.78)	0.0046	0.36 (0.19–0.70)	0.0022	0.10 (0.06–0.19)	<0.0001	0.08 (0.04–0.16)	<0.0001

Of the 643 patients included in this study, 39 (6.1%; 95% CI: 4.3–8.2%) were further investigated using CT/MRI when sympt oms did not resolve or changed in character after EBP. In three patients (0.5%; 95% CI: 0.1–1.4%), intracranial bleeding was found: two subdural and one subarachnoid haematoma. In all three patients, symptoms had resolved at 3 months without surgical intervention.

Discussion

In this prospective, multicentre, international observational study, 28.3% of EBPs failed to relieve PDPH, 38.7% succeeded partially, and in 33.0% of patients EBP led to complete resolution. There was a significantly greater association with failure of EBP in patients with a history of migraine headache, who received a second EBP more frequently. When initial ADP occurred at higher lumbar segmental levels (L1/L3), there was a greater headache intensity in the first 24 h after EBP and an increased association for application of a second EBP. Regarding the EBP procedure itself, we found a higher success rate when the EBP was placed later (≥72 h) after ADP.

Post-dural puncture headache after ADP in parturients often results in severe, commonly orthostatic headache. If treated conservatively, PDPH is self-limiting in most patients, but when symptoms are severe, disabling, or persisting, physicians and patients often prefer treatment with an EBP.[12] Although EBP is an invasive procedure, it is rarely associated with major complications.[7] It usually relieves symptoms initially, but it may sometimes fail later in partially or completely eliminating the headache.[9,13,15] A satisfactory definition of failure or success of EBP has never been established, and failure has often been categorised as complete or partial.[8,9,14,20,21] Using our definition, the frequency of failure and the incidence of second EBP were similar to that reported in previous studies, including one that prospectively randomised patients to different volumes of blood administered for EBP.[9]

We identified several factors associated with EBP failure. Our finding of an association between history of migraine and failure of EBP is interesting. We found no statistically significant difference in the intensity of postural headache at any time after EBP between patients with and without migraine, and yet migraine patients received a second EBP significantly more often (31.6% *vs* 17.4%). A possible explanation for this might be that migraine headache was misdiagnosed as PDPH after EBP, as migraine is known to reappear in the first postpartum week.[22–24] However, this is unlikely for several reasons. In contrast to PDPH, migraine usually presents with unilateral headache, and postural changes have never been described.[25] Additionally, the incidence of orthostatic headache before and up to 24 h after EBP was similar between patients with and without migraine. However, this does not explain why, despite similar NRS scores after EBP, patients with migraine received a second EBP more frequently. Stress, anxiety, and pain around childbirth affect patients with a chronic pain syndrome, such as migraine, more often, resulting in differences in pain perception and pain catastrophising, which might explain a more frequent use of a second EBP,[26–28] which needs to be further investigated.

We also found a significantly increased incidence of failed EBP when the initial ADP occurred at a higher lumbar level (L1/L3) compared with lower levels (L3/L5). Although anaesthesiologists are unreliable in estimating the correct intervertebral space, this finding is interesting and not reported previously.[29] Misclassification of the level of ADP (higher *vs* lower lumbar levels) by anaesthesiologists can occur, but no association with failure of EBP should be expected, as no underlying mechanisms are known that can explain an association between lumbar level of the initial ADP and subsequent therapy failure. Anatomical and physiological differences in meningeal neural innervation are known to exist between higher and lower spinal levels but are not likely to explain our findings.[30,31] The greater failure rate of an EBP when ADP occurs at L1/L3 compared with L3/L5 levels might depend on the level of the subsequent EBP. It is believed that blood injected during EBP migrates predominantly cephalad, and therefore, an EBP would be more successful if inserted at the same or lower lumbar level than where the ADP occurred.[7,32,33] However, we did not find that the level at which EBP was performed changed the association with failure at any lumbar level of ADP, nor was EBP level alone statistically significantly associated with failure. Therefore, the greater failure rate is more likely because of the higher level of initial ADP and not the level of subsequent EBP. Future research on PDPH and EBP should include the use of ultrasound to identify the lumbar level of neuraxial procedures to confirm these interesting findings.

Regarding timing of EBP application, we found that early application of EBP increased the association with failure, which confirmed findings of several smaller observational studies.[9,13,34] An overwhelming majority of patients had no or only mild headache immediately after inserting the EBP (77.9%) or 4 h later (84.0%). Nevertheless, headache intensity increased after 4 h, and almost one in five patients required a second EBP. It is possible that when EBP is applied early after PDPH, the blood injected mixes freely with a large volume of CSF, leaking into the epidural space leading to poor clot formation, which might prevent sealing of the dural puncture, and subsequent failure of the EBP, as was shown in an *in vitro* study using thromboelastography.[30,35] These findings imply that increasing blood volume when EBP is applied early might improve success rates, but this has never been shown in clinical studies and needs to be investigated in future studies.[9,35]

We did not find an association between the volume of blood injected and EBP failure. However, most patients received ≈20 ml of blood, which was a common practice at the time this study was performed.[9] Although early application of EBP was associated with increased incidence of failure, it may nevertheless be desirable to perform early EBP because of severe intensity of the headache, or to avoid a potential risk of intracranial bleeding if applied late.[16,36] The latter was found in a recent retrospective observational cohort study using hospital readmission data.[16]

Study limitations

As this is an observational study, no causation, only associations, could be determined for failure of EBP, and randomised studies are needed to confirm our findings for modifiable factors. The number of patients was limited compared to the number of variables included in the regression model. Low statistical power is a limitation, as several associations showed OR with low precision and wide 95% CI. We did not study all risk factors that might be associated with EBP failure, such as total analgesic consumption and fluid management before EBP. Most variables were identified *pre hoc* from observational

studies, but some were included later, after a consensus within the Steering Committee.

As in previous studies, classification of EBP failure is not standardised, and distinguishing PDPH from migraine and other postpartum headaches can sometimes be difficult. Therefore, standardised definitions for failure should be developed. The study population did not include consecutive cases and was dependent on identification of PDPH by the midwife or attending physician in the maternity ward, and some cases may have been misdiagnosed or missed. However, our study comprises the largest number of patients with PDPH receiving an EBP collected prospectively in the obstetric population.

Another limitation of our study is that application of EBP (both first and second) and the timing of application were decisions made without objective criteria by the attending anaesthesiologist together with the patient, and may have been arbitrary in some cases or dependent on local guidelines and traditions. Finally, body weight was registered differently by collaborators; some used pre-pregnancy weight and others weight immediately before delivery.

Conclusions

In this international, prospective, observational cohort study, we found that failure of epidural blood patch was seen in 28.3% of patients with post-dural puncture headache, with the rest either partially or completely successful. A history of migraine and a higher lumbar level of the accidental dural puncture were associated with a greater risk of failure of epidural blood patch. A lower incidence of epidural blood patch failure was seen when the epidural blood patch was performed $\geq$48 h after accidental dural puncture.

Authors' contributions

Study design: all authors
Patient recruitment: AG, CvH, AMJVS-vdB
Data collection: AG, SA, EG
Data analysis: AG, AM, FJM, AMJVS-vdB
Data interpretation: AG, MVdV, AM, CvH, FJM, AMJVS-vdB
Writing of article: all authors

Declarations of interest

MVdV is editor-in-chief of *Best Practice & Research: Clinical Anaesthesiology*, associate editor of the *European Journal of Anaesthesiology*, executive editor of Regional Anesthesia & Pain Medicine, chair of the European Society of Regional Anaesthesia & Pain Therapy (ESRA) Procedure Specific Postoperative Pain Management Working Group, chair of the ESRA Education, and Obstetric Anaesthetists' Association Committee member. FJM is associate editor of *Anaesthesia, Critical Care & Pain Medicine* and BARA (Belgien Association of Regional Anesthesia) board member. The other authors declare that they have no conflicts of interest.

Funding

European Society of Anaesthesiology and Intensive Care (clinical trial network grant 2015 to AG)

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2022.06.040.

References

1. Choi PT, Galinski SE, Takeuchi L, Lucas S, Tamayo C, Jadad AR. PDPH is a common complication of neuraxial blockade in parturients: a meta-analysis of obstetrical studies. *Can J Anesth* 2003; **50**: 460–9
2. van de Velde M, Schepers R, Berends N, Vandermeersch E, de Buck F. Ten years of experience with accidental dural puncture and post-dural puncture headache in a tertiary obstetric anaesthesia department. *Int J Obstet Anesth* 2009; **17**: 329–35
3. Loures V, Savoldelli G, Kern K, Haller G. Atypical headache following dural puncture in obstetrics. *Int J Obstet Anesth* 2014; **23**: 246–52
4. Angle P, Tang SLT, Thompson D, Szalai JP. Expectant management of postdural puncture headache increases hospital length of stay and emergency room visits. *Can J Anesth* 2005; **52**: 397–402
5. Orbach-Zinger S, Eidelman LA, Livne MY, et al. Long-term psychological and physical outcomes of women after postdural puncture headache: a retrospective, cohort study. *Eur J Anaesthesiol* 2021; **38**: 130–7
6. Russell R, Laxton C, Lucas DN, Niewiarowski J, Scrutton M, Stocks G. Treatment of obstetric post-dural puncture headache. Part 1: conservative and pharmacological management. *Int J Obstet Anesth* 2019; **38**: 93–103
7. Russell R, Laxton C, Lucas DN, Niewiarowski J, Scrutton M, Stocks G. Treatment of obstetric post-dural puncture headache. Part 2: epidural blood patch. *Int J Obstet Anesth* 2019; **38**: 104–18
8. Booth JL, Pan PH, Thomas JA, Harris LC, D'Angelo R. A retrospective review of an epidural blood patch database: the incidence of epidural blood patch associated with obstetric neuraxial anesthetic techniques and the effect of blood volume on efficacy. *Int J Obstet Anesth* 2017; **29**: 10–7
9. Paech MJ, Doherty DA, Christmas T, Wong CA. The volume of blood for epidural blood patch in obstetrics: a randomized, blinded clinical trial. *Anesth Analg* 2011; **113**: 126–33
10. Sachs A, Smiley R. Post-dural puncture headache: the worst common complication in obstetric anesthesia. *Semin Perinatol* 2014; **38**: 386–94
11. Paech M. Epidural blood patch—myths and legends. *Can J Anesth* 2005; **52**: 1–5
12. Gupta A, von Heymann C, Magnuson A, et al. Management practices for postdural puncture headache in obstetrics: a prospective, international, cohort study. *Br J Anaesth* 2020; **125**: 1045–55
13. Kokki M, Sjövall S, Keinänen M, Kokki H. The influence of timing on the effectiveness of epidural blood patches in parturients. *Int J Obstet Anesth* 2013; **22**: 303–9
14. Safa-Tisseront V, Thormann F, Malassiné P, et al. Effectiveness of epidural blood patch in the management of post-dural puncture headache. *Anesthesiology* 2001; **95**: 334–9

15. Taivainen T, Pitkänen M, Tuominen M, Rosenberg PH. Efficacy of epidural blood patch for postdural puncture headache. *Acta Anaesthesiol Scand* 1993; **37**: 702–5
16. Moore AR, Wieczorek PM, Carvalho JCA. Association between post-dural puncture headache after neuraxial anesthesia in childbirth and intracranial subdural hematoma. *JAMA Neurol* 2020; **77**: 65–72
17. Headache Classification Subcommittee of the International Headache Society. The international classification of headache disorders. *Cephalalgia* 2004; **24**: 9–160. 2nd edition
18. World Health Organization. *Physical status: the use and interpretation of anthropometry*. Geneva: Report of a WHO expert committee; 1995
19. Rubin DB. Inference and missing data. *Biometrika* 1976; **63**: 581–92
20. Xavier J, Pinho S, Silva J, et al. Postdural puncture headache in the obstetric population: a new approach? *Reg Anesth Pain Med* 2020; **45**: 373–6
21. Stein MH, Cohen S, Mohiuddin MA, Dombrovskiy V, Lowenwirt I. Prophylactic vs therapeutic blood patch for obstetric patients with accidental dural puncture—a randomised controlled trial. *Anaesthesia* 2014; **69**: 320–6
22. Lim SY, Evangelou N, Jürgens S. Postpartum headache: diagnostic considerations. *Pract Neurol* 2014; **14**: 92–9
23. Kvisvik EV, Stovner LJ, Helde G, Bovim G, Linde M. Headache and migraine during pregnancy and puerperium: the MIGRA-study. *J Headache Pain* 2011; **12**: 443–51
24. Sances G, Granella F, Nappi RE, et al. Course of migraine during pregnancy and postpartum: a prospective study. *Cephalalgia* 2003; **23**: 197–205
25. Charles A. The pathophysiology of migraine: implications for clinical management. *Lancet Neurol* 2018; **17**: 174–82
26. López-Martínez AE, Ramírez-Maestre C, Serrano-Ibáñez ER, Ruiz-Párraga GT, Esteve R. Intolerance of uncertainty moderates the relationship between catastrophizing, anxiety, and perceived pain in people with chronic nononcological pain. *Pain Med* 2022. https://doi.org/10.1093/pm/pnac030
27. Ziegler DK, Paolo AM. Profile of headache-prone individuals. *Arch Neurol* 1995; **52**: 602–6
28. Ashina S, Bendtsen L, Buse DC, Lyngberg AC, Lipton RB, Jensen R. Neuroticism, depression and pain perception in migraine and tension-type headache. *Acta Neurol Scand* 2017; **136**: 470–6
29. Schlotterbeck H, Schaeffer R, Dow WA, Touret Y, Bailey S, Diemunsch P. Ultrasonographic control of the puncture level for lumbar neuraxial block in obstetric anaesthesia. *Br J Anaesth* 2008; **100**: 230–4
30. Groen GJ, Baljet B, Drukker J. The innervation of the spinal dura mater: anatomy and clinical implications. *Acta Neurochir (Wien)* 1988; **92**: 39–46
31. Sakka L, Gabrillargues J, Coll G. Anatomy of the spinal meninges. *Oper Neurosurg (Hagerstown)* 2016; **12**: 168–88
32. Beards SC, Jackson A, Griffiths AG, Horsman EL. Magnetic resonance imaging of extradural blood patches: appearances from 30 min to 18 h. *Br J Anaesth* 1993; **71**: 182–8
33. Vakharia SB, Thomas PS, Rosenbaum AE, Wasenko JJ, Fellows DG. Magnetic resonance imaging of cerebrospinal fluid leak and tamponade effect of blood patch in postdural puncture headache. *Anesth Analg* 1997; **84**: 585–90
34. Loeser EA, Hill GE, Bennett GM, Sederberg JH. Time vs. success rate for epidural blood patch. *Anesthesiology* 1978; **49**: 147–8
35. Armstrong S, Fernando R, Tamilselvan P, Stewart A, Columb M. The effect of serial in vitro haemodilution with maternal cerebrospinal fluid and crystalloid on thromboelastographic (TEG®) blood coagulation parameters, and the implications for epidural blood patching. *Anaesthesia* 2015; **70**: 135–41
36. Zeidan A, Farhat O, Maaliki H, Baraka A. Does postdural puncture headache left untreated lead to subdural hematoma? Case report and review of the literature. *Middle East J Anesthesiol* 2010; **20**: 483–92

Handling editor: Hugh C Hemmings Jr