European Practices in the Management of Accidental Dural Puncture in Obstetrics

EPiMAP Obstetrics
A European prospective multicentre observational study

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European Society of Anaesthesiology (ESA)
Clinical Trial Network
Rue des Comédiens 24, 1000 Brussels, Belgium
Phone: +32 2 743 3290
E-mail: research@esahq.org

Chief Investigator:
Anil Gupta MD, FRCA, PhD
Associate Professor
Department of Anaesthesiology, Surgical Services and Intensive Care
Karolinska University Hospital, Solna
SE 11716 Stockholm
Sweden
## PROTOCOL SIGNATURE SHEET

### Chief Investigator

<table>
<thead>
<tr>
<th>Name</th>
<th>Signature</th>
<th>Date</th>
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<tr>
<td>Anil Gupta</td>
<td></td>
<td>01 OCT 2015</td>
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<tr>
<td><strong>Chief Investigator:</strong> Karolinska University Hospital</td>
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### Sponsor

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<tr>
<td>Brigitte Leva</td>
<td></td>
<td>01 OCT 2015</td>
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<tr>
<td><strong>Research and Clinical Trial Coordinator – Research Team Leader</strong> European Society of Anaesthesiology</td>
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### Local Principal Investigators (enter local details, as applicable)

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1. General information

1.1 Steering Committee

Anil Gupta, Chief Investigator
Department of Anesthesiology, Surgical Services and Intensive Care
Karolinska University Hospital
11716 Stockholm, Sweden
anil.gupta@karolinska.se
Phone: +46-8 517 703 87
Mobile phone: +46-7 065 616 76

Seppo Alahuhta
Department of Anaesthesiology
Oulu University Hospital
Kajaanintie 50
90220 Oulu, Finland
seppo.alahuhta@oulu.fi
Phone: +358-83152262

Michela Camorcia
Department of Anaesthesia and Intensive care
Città’ di roma hospitalVia maidaclhini 20
00152 Roma, Italy
michelaca.mc@gmail.com
Phone: +39-65847204

Roshan Fernando
Department of Anaesthesia
University College London Hospital
235 Euston Road
NW1 2BU London, United Kingdom
roshangfernando@gmail.com
Phone: +44-7765645640

Alexandra Schyns-van den Berg
Department of Anaesthesiology
Albert Schweitzer Ziekenhuis
Albert Schweitzerplaats 25
3318 AT Dordrecht, Netherlands
xschyns@me.com
Phone: +31-786542461

Marc Van de Velde
Department of Anaesthesiology
UZ Leuven – KULeuven
Herestraat 49
3000 Leuven, Belgium
marc.vandevelde@uzleuven.be
Phone: +32-16344270

Frederic J. Mercier
Department of Anaesthesia
Hôpital A. Béclère - GH Paris Sud – APHP
157 rue de la Porte de Trivaux
92140 Clamart France
frederic.mercier@abc.aphp.fr
Phone: +33-1 45 37 42 73

Christian von Heymann
Vivantes Klinikum im Friedrichshain
Landsberger Allee 49
10249 Berlin, Germany
Christian.Heymann@vivantes.de
Phone: +49-30130231270

Anders Magnuson (statistician)
Örebro University Hospital
Department of Epidemiology and Biostatistics
70185 Örebro, Sweden
anders.magnuson@regionorebrolan.se
Phone: +46-19 6021000
1.2 Sponsorship

**EPiMAP Obstetrics** is entirely sponsored by a grant from the European Society of Anaesthesiology Clinical Trial Network (ESA CTN). The aim of the European Society of Anaesthesiology Clinical Trial Network is to provide an infrastructure for clinical research in the fields of Anaesthesia, Pain, Intensive Care and Emergency Medicine by transnational European collaborative studies.

No other institution or industrial company is or will be involved in financing, planning or conducting the EPiMAP Project.

The Clinical Trial Network of the European Society of Anaesthesiology can be contacted via:

Benoit Plichon and Brigitte Leva  
ESA Research Department  
European Society of Anaesthesiology  
Rue des Comédiens 24  
1000 Brussels, Belgium  
Tel: +32 2 743 32 91 / +32 2 210 94 14  
Fax: +32 2 743 32 98  
E-mail: benoit.plichon@esahq.org; brigitte.leva@esahq.org; research@esahq.org; epimap@esahq.org

1.3 Endorsements

The EPiMAP study has been endorsed by the following societies:

- **HSA**: Hellenic Society of Anaesthesiology - ΕΛΛΗΝΙΚΗ ΑΝΑΙΣΘΗΣΙΟΛΟΓΙΚΗ ΕΤΑΙΡΕΙΑ
- **IASISA**: Israeli Obstetric Anesthesia Society - איגוד הרופאים המרדים בישראל
- **UAIS - SAAI**: Serbian Association of Anesthesiologists and Intensivists - Udruženje anesteziologa i intezivista Srbiike
1.4. Summary

Postdural puncture headache (PDPH) is the most common serious complication of accidental dural puncture (ADP), and feared by every Anaesthesiologist. It is associated with significant peri-partum maternal distress, and poor bonding with the baby, which in turn leads to physical disability for the mother and psychological and social implications for the whole family. We have estimated that about 10,000 parturients in Europe may have ADP each year. Attitudes and practices in the management of ADP are based on small studies, and sometimes driven by experience rather than evidence. Several methods have been described in the literature to treat PDPH and one common method used is an epidural blood patch (EBP). This is believed to be successful in about 60-80% of parturients on the first attempt, but results from most studies are based on a small numbers of patients. The reasons and predisposing factors for success and failure of different management strategies, specifically EBP, therefore needs to be investigated and described. Large observational studies on post-dural puncture headache in the Obstetric population are singularly absent from the literature. Our expectation is that this study will provide important information in understanding the reasons for failure of EBP and subsequently help to better manage parturients affected by this debilitating complication.

*The primary endpoint* is to examine the risk factors for failed epidural blood patch (EBP) following post-dural puncture headache, in the obstetric population. Secondary endpoints include: strategies and success rates for conservative management of PDPH, the management techniques adopted in different European countries, the volume of blood injected during EBP in relation to success or failure, the complications and side effects of the procedure, the timing of the procedure in relation to success, the reasons for a repeat blood patch and its success rate, the length of hospital stay, the long-term outcome after ADP including chronic headache, backache and other disabilities following accidental dural puncture and epidural blood patch.
### List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ADP</td>
<td>Accidental dural puncture</td>
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<tr>
<td>ASA</td>
<td>American Society of Anesthesiologists Physical status classification</td>
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<tr>
<td>CSE</td>
<td>Combined Spinal-Epidural</td>
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<tr>
<td>CSF</td>
<td>Cerebro-spinal fluid</td>
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<tr>
<td>CTN</td>
<td>Clinical Trial Network</td>
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<tr>
<td>EBP</td>
<td>Epidural blood patch</td>
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<tr>
<td>EC</td>
<td>Ethics Committee</td>
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<tr>
<td>EDA</td>
<td>Epidural analgesia</td>
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<td>ESA</td>
<td>European Society of Anaesthesiology</td>
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<tr>
<td>GCP</td>
<td>Good clinical practice</td>
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<td>IRB</td>
<td>Institutional Review Board</td>
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<td>MRI</td>
<td>Magnetic resonance imaging</td>
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<td>NC</td>
<td>National Coordinating Investigator</td>
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<td>NRS</td>
<td>Numeric rating score</td>
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<td>PDPH</td>
<td>Post-dural puncture headache</td>
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<td>SC</td>
<td>Steering Committee</td>
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2. Introduction and Background

2.1. Introduction

In the European Union, including 28 countries, the number of live births has remained fairly constant in the last 3 years, between 5.2 - 5.4 million each year, 2010-2012 (1). Of these, approximately 20-30% of all babies are born by caesarean delivery where spinal or general anaesthesia are the routine in most countries. In the 27 states that a study in USA encompassed, it was estimated that 40 - 70% women (average 61%) received neuraxial block for their first child birth (2). In the Nordic countries with universal health care for all, we estimated that on average, 32% of all mothers (both primi- and multi-para) received epidural analgesia (3). Therefore, and if the trend is similar in the rest of Europe, we have estimated that approximately 1 million parturients will receive epidurals during labour.

One major risk of epidural analgesia (EDA) is accidental dural puncture (ADP). In 52% patients this leads to post-dural puncture headache (4), typically described as postural and aggravated in the sitting position. We have previously found that approximately 1% of mothers receiving an EDA during labour had an accidental dural puncture (3). If translated into a European perspective, this means that an estimated 10,000 parturients (1% of 1 million EDA inserted) each year in Europe have an accidental dural puncture during insertion of an epidural for pain relief during labour. In the Western world, with relatively free access to EDA during labour, the magnitude of this complication affecting otherwise healthy women is therefore extremely large.

Headache after ADP may be severe and often affects the interaction and early bonding between the newborn baby and the mother. The headaches are orthostatic which makes the patient bedridden, and are associated with symptoms such as nausea, vomiting, tinnitus and changes in hearing (5). The symptoms are thought to result from leakage of cerebro-spinal fluid (CSF) following ADP, which in turn leads to reduced CSF volume and intracranial hypotension (6). These volume changes lead to traction of pain-sensitive intracranial structures. There are no studies in the literature that have either confirmed or visualised CSF leakage after ADP during labour, and no objective methods or tools are available to confirm the diagnosis. Thus, the diagnosis of PDPH remains symptom-based and subjective, and Anaesthesiologists today treat patients on the basis of these clinical criteria of PDPH. Several case reports have used magnetic
resonance imaging (MRI) to clearly demonstrate fluid in the epidural space corresponding to the level of the dural puncture (7). However, limitations of time, resources and the financial implications of performing an MRI prevent its routine use for the diagnosis of PDPH in the parturients. Other methods such as optometry, audiometry and CT scanning have also been used for diagnosis but none of these are used commonly or recommended as a routine in the literature.

There are over 50 different treatment options for PDPH. These treatments can be divided into conservative or invasive. Among others, the conservative treatment options include bed rest, caffeine and various pain medications. Several studies have shown the absence of a definite and curative effect of these treatment options (8). The most widely used method for management of PDPH is the epidural blood patch (EBP) (9). EBP was first introduced in the 60's by applying 3 ml of the patients’ own blood epidurally (10). Over the years, this volume has increased to at least 15-20 ml on the basis of case reports and studies with small number of participants and without any clear scientific evidence. Recently, Paech et al. studied 121 patients and found that the optimal volume of blood injected during EBP should be about 20 ml (11). However, EBP should not be applied sooner than 24 hours after the onset of accidental dural puncture, as the risk of failure is higher (12). About 60 - 70% patients have partial relief of symptoms following an EBP and only 25 - 30% have complete relief (11), and require a further 1-2 EBPs to reach an efficacy of > 80% (11,12). Some patients may suffer from long-standing PDPH that is resistant to management. The reason why EBP is ineffective in some patients and leads to chronic disability in others remains unknown and is poorly studied. Additionally, significant complications have been described in some patients after application of EBP, and untreated PDPH can be associated with serious medical complications (13,14). Whether CSF leakage will cease by applying EBP is only a hypothesis based on case reports and not confirmed by any randomised study in the literature. Even patients who need more than one EBP have not been systematically studied in order to better understand the reasons for failure or the underlying pathophysiology of PDPH and the mechanism behind successful EBP.

In a global context, and in view of the disabling symptoms, PDPH has enormous healthcare and economic consequences. Although some risk factors for ADP have been identified, clinical diagnostic criteria established, and management strategies including EBP used commonly, most of the results are based on studies including a small number of patients. Therefore, a large
observational study is urgently needed in order to better understand the epidemiology, diagnosis, and management of this rare complication of epidural analgesia in the Obstetric population, as well as to identify reasons for failure of the epidural blood patch. Interventional studies that can lead to better management strategies for mothers can then be planned in the future.

2.2 Summary of findings from non-clinical studies
Animal and pre-clinical studies are not pertinent or relevant for the present study. The technique for management of ADP using epidural blood patch has been well described and successfully used over several decades in humans. The present study is observational in character to identify risk factors for failure and therefore we do not believe that any preclinical studies are important for the success of this project.

2.3. Compliance with the protocol, GCP and the applicable regulatory requirement(s)
All participating centres in the trial that are represented by their local coordinating investigators will conduct the trial in compliance with the protocol. The protocol complies with the declaration of Helsinki and will be conducted according to rules and guidelines of good clinical practice (GCP). Specific regulatory, Institutional Review Board (IRB) or Ethics Committee (EC) requirements of each country will be followed.

2.4 Study population
All parturients ≥ 18 years old who have had epidural analgesia or combined-spinal/epidural anaesthesia during labour or for a caesarean section, a confirmed/suspected ADP and with post-dural puncture headache (please see definitions at the end) will be included into this observational study.
3. Aims and Design

3.1 Aims

EPiMAP Obstetrics is an observational study to investigate practices in the management of accidental dural puncture (ADP) during Obstetric epidural anaesthesia and analgesia in Europe. This includes patients with documented ADP and PDPH or those presenting with classical symptoms and signs of post-dural puncture headache (PDPH) when ADP was not documented.

EPiMAP Obstetrics is a prospective, multi-centre, European, observational study to investigate the current practices in the management of patients who have had an accidental dural puncture during epidural insertion in parturients in labour or during caesarean delivery, with PDPH and to assess the causes of failure of EBP. No intervention is planned. Apart from standardised data acquisition no specific procedures are performed.

For the purpose of data collection and to study the epidemiology as well as management of ADP, the study is divided into 6 steps detailed below. Steps 1 and 2 are for all patients included. Steps 3, 4 and 5 are only for patients with persistent or recurrent PDPH For step 6, all patients will be followed up for a minimum period of 7 days (+/- 1 day) after confirmation of PDPH and, if possible, 3 months (+/- 2 weeks after PDPH.

3.2 Study steps details:

Step 1: From Epidural (EDA) insertion to confirmed diagnosis of post-dural puncture headache (PDPH) including initial management

Step 2: Management of PDPH after diagnosis and initial management

Step 3: Re-admission or persistent post-dural puncture headache (PDPH) 24 h after EBP

Step 4: Persistent or Recurrent Post-Dural Puncture Headache (PDPH), despite second EBP

Step 5: Persistent or Recurrent Post-Dural Puncture Headache (PDPH), despite third EBP

Step 6: Home discharge - Follow-up at 7 days and follow-up at 3 months after confirmation of PDPH

3.3 Process for Diagnosis of PDPH

Institutional practices vary as to the criteria for diagnosis of PDPH. We have chosen to use the definition used by Amorim et al. (please see definitions at the end). It is ALWAYS the attending
Specialist Anaesthesiologist who makes the final diagnosis of PDPH based on criteria outlined below (Time of diagnosis, t = 0). All patients having post-partum PDPH within < 5 days of EDA, regardless of observed ADP or not, will be included. The process for inclusion of patients will be one of the following:

1. Patient complains of postpartum headache. Obstetrician/midwife/ward nurse contacts the Anaesthesiologist if the patient describes a postpartum headache and who has received an EDA for labour or caesarean section.

2. At the time of insertion of EDA the Anaesthesiologist suspects ADP (see definition at the end) and the patient subsequently develops PDPH.

4. Selection and Withdrawal of Subjects

4.1 Subject inclusion criteria
All women ≥ 18 years old, admitted to the hospital and who have had an epidural inserted (combined spinal epidural, not spinal alone) for pain relief during labour or for caesarean section and have confirmed/suspected ADP and a clinical diagnosis of PDPH. Signed, informed consent will be obtained from each patient prior to inclusion when this is mandatory in the centre.

4.2 Subject exclusion criteria
1. Patients having PDPH following spinal anaesthesia (during labour or for caesarean section) are excluded.

2. When performing a combined spinal-epidural (CSE) anaesthesia/analgesia, if no definite evidence of ADP was observed at epidural insertion (straightforward epidural insertion) and the patient developed PDPH, it is assumed that this was due to spinal anaesthesia and not ADP and the patient is excluded.

3. Language constraints
4. Any disorder which in the opinion of the investigator might jeopardise the subject's safety, or prevent compliance with the protocol.

5. Patients presenting with PDPH ≥ 1 week after epidural analgesia are excluded.
4.3 Subject withdrawal criteria
In case of withdrawal of consent at any point during the study, data collection will be stopped. The subjects will not be replaced and per-protocol analysis will be performed up to the point of data collection. Please see further details under Statistics section.

5. Data Collection and analysis

5.1 Data collection
Data collection will start following approval from all relevant authorisation bodies in different countries and patient consent if necessary, and continue over a period of one year. A principal investigator will represent each participating centre (hereinafter called Local Principal Investigator). Blinded data will be collected through an internet-based program. All patients receiving an EDA or CSE will not be interviewed for symptoms of PDPH. Those patients who had a demonstrated ADP or those who complain to the midwife/ward nurse or attending Obstetrician/AAnaesthesiologist about post-partum headache and have had an EDA inserted during labour or caesarean section will be followed up by an Anaesthesiologist and diagnosis of PDPH will be confirmed. The following data will be collected:

* Age, weight, height, ASA classification of patient
* Size of needle used for epidural insertion
* Technique to determine loss of resistance used during initial epidural insertion
* Time of application of EBP after diagnosis of PDPH
* Type of conservative management used after diagnosis of PDPH
* Volume of blood injected and time to injection while performing an EBP
* Success of first EBP at 24 h (as defined above)
* Success/failure of second/third EBP and diagnostic methods used before repeat EBP
* Length of hospital stay (days after delivery) and re-admission
* Follow-up of complications, readmissions, adverse effects etc. following EBP and after 3 - 6 months

At the end of the study each centre will provide an “end of study reporting form” (see appendix #4) containing the total number of obstetric epidural anaesthesia and analgesia procedures in the hospital over the study period and the total number of screening failure patients.
5.2 Protocol Flowchart: schematic diagram of trial design, procedures and stages
5.3 Data collection for Epidural blood patch

The Epidural blood patch will be performed according to the local practice in each hospital. As it is an observational study, EPiMAP intends to only collect data and subsequently analyse the impact of procedures and techniques on outcomes. The following clinical data will be collected:

- Intensity of PDPH on lying down and on sitting up
- Time of insertion of EBP
- Experience of anaesthesiologist performing the EBP
- Position of patient when performing EBP
- Details of the procedure itself
- Volume of blood injected
- Duration of rest after EBP
- Side effects and complications of EBP
- Time to home discharge
- Re-admission, if this occurs
- PDPH pain intensity after EBP

5.4 Description of the measures taken to minimise/avoid bias

The study is an observational study and therefore no bias is expected. All patients who have had an ADP (suspected/confirmed) and have PDPH at the study centre will be included. Each national data coordinating investigator will support each centre principal investigator on request regarding recruitment of patients, completeness of data, follow up in the ward. Local Principal Investigators will be responsible for recruitment of patients and data integrity at their site. As a consequence of the trial design, randomization and blinding will not be done.

5.5 Expected duration of subject participation

The study is preliminarily planned to start in 2016 after receiving permission from the Ethics Committee in all countries. Data collection will then continue for 1 year or until a total of minimum 1024 patients are recruited (please see “Power analysis” under Statistics section below). Patients will be followed up until discharge from the hospital and at home by telephone for a minimum of 7 days and maximum 3 months. Any readmission due to PDPH/EBP will be recorded until 3 months and then the CRF will be closed.
5.6 “Stopping rules” or “discontinuation criteria”
This study is not an interventional study and therefore we have no plans of stopping the study earlier or discontinuing the study unless the patient withdraws consent.

6. Participating Centres

Any European centre performing epidurals in labour or for caesarean section and with a minimum number of 500 deliveries/year can participate in this project. ESA, with headquarters in Brussels, will coordinate the study and support for participating centres will be through the National Coordinating Investigators who in turn have constant support from the Steering Committee.

Before inclusion of the first patient, each institution will fill in a site pre-study questionnaire regarding the hospital demographics, local standard of care for patients and experience in performing epidural blood patch. The contents of this questionnaire are listed in the Appendix 3. In the one-year anticipated recruitment period, data will be collected from each centre but with no minimal number of cases to be enrolled per centre. It is planned that all centres that would like to participate in the study throughout Europe will be recruited, with no upper limit to the maximum number of centres. Each centre will have a Local Principal Investigator, and a National Coordinating Investigator will be in contact with the participating centres in his/her country to ensure that Ethics committee approval is obtained as well as to clarify doubts arising following patient recruitment.

**National Coordinating Investigators (NC)**

National coordinating investigators are anaesthesiologists appointed by ESA and the Steering Committee to lead the project within individual nations and:

- Identify local participating centres and recruit local principal investigators in participating hospitals
- Assist in the translation of study documents - upon needs
- Ensure necessary country or regional regulatory approvals are in place prior to start of patient inclusion
• Assist and train the Local Principal Investigator and monitor the conduct of the study according to good clinical practice (ICH-GCP guidelines)
• Ensure good communication with ESA headquarter and the participating sites in his/her countries (e.g. At data cleaning NC will cascade the information/requests to the relevant sites and assist when necessary).

Local Principal Investigators are Anaesthesiologists in each participating institution who will have the following responsibilities:

• Provide leadership for the study in their institution
• Ensure all relevant regulatory/ethical approvals are in place for their institution
• Ensure adequate training of all relevant staff prior to data collection
• Supervise daily data collection and assist with problem solving
• Ensure timely completion of eCRF and follow up data; Local Principal Investigator is the main responsible for ensuring integrity of data collection. By signing the data on eCRF Local Principal Investigator confirms the data integrity
• Communicate with ESA headquarter and the relevant National Coordinating Investigator
7. Statistics

7.1 Sample size calculation
There are two known risk factors for success of EBP: time of application of EBP after PDPH (<48 h vs. > 48 h) and volume of blood injected (10 - 15 ml vs. 15 - 20 ml). Since most Anaesthesiologists now wait at least 24 h before application of EBP, it would be difficult to have a sufficient number of patients where EBP was performed within 24 h. Therefore, the sample size calculation was based on the results of a previous study on success rate (including both partial or complete success) for the first EBP, which was found to be 73% when 15 - 20 ml EBP was used and 61% when 10 - 15 ml was used (Paech et al 2011). With these expected success rates, a Fisher's exact test with a 0.050 two-sided significance level will have an 80% power to detect the difference between these groups when the sample size in each group is 256. This gives a total of 512 patients who have an EBP injected. However, about 50% patients with a PDPH today have an EBP. Therefore, we need to recruit approximately 1024 patients with ADP/PDPH in order that approx. 512 patients would receive an EBP. Of the 512 patients it is expected that approximately 33% will not have partial or complete relief of PDPH (incidence: 27 -39%) i.e. failure rate of approximately 33% = 170 patients. These 512 patients and 170 events would be further evaluated with multiple logistic regression to understand the risk factors for failure of EBP. Using a rule of thumb of at least 10 events/risk factor, we should be able to evaluate at least 10 risk factors for EBP failure since the number of patients in each sub-group may not be equally distributed.

7.2 Number of subjects planned to be enrolled
Minimum number of patients with ADP ("wet tap") and suspected/confirmed PDPH: > 1024
Minimum number of patients with PDPH ("wet tap" during EDA): 1024
Minimum number of patients with EBP: 512

7.3 The level of significance to be used
In all calculations, the corrected significance level of p < 0.05 will be used.
7.4 Criteria for the termination of the trial
This is an observational study and therefore there are no plans to terminate the study until all patients have been followed up as defined above. After one year, if there are less than 1024 patients with ADP enrolled, the study period would be extended to reach that goal.

7.5 Procedure for accounting for missing, unused, and spurious data
If the patient withdraws consent during the study, data until that time point will be included in the analyses. Patients will not be completely withdrawn from the study if some data points are missing. Instead, appropriate statistical tests will be used in case of missing data.

7.6 The selection of subjects to be included in the analyses
6 steps of the study have been identified:

**Step 1:** From Epidural (EDA) insertion to confirmed diagnosis of post-dural puncture headache (PDPH) including initial management. All patients having an ADP at the time of EDA insertion (for labour or caesarean section) and consenting to be included in the observational study (EPiMAP) will be included in the analyses. Patients with a "suspected ADP" during EDA insertion but fulfilling diagnostic criteria for PDPH will also be included. Patients with a straightforward epidural insertion during CSE but later developed symptoms consistent with PDPH will be included.

**Step 2:** Management of PDPH after diagnosis and initial management

**Step 2a.** All patients followed up and treated conservatively (no EBP) will be included in the analyses (expected number of patients approx. 512).

**Step 2b.** All patients having an EBP will be included in the data analyses (approx. 512).

**Step 3:** All patients having persistent PDPH will be included in the data analyses

**Step 4:** All patients having persistent PDPH despite a second EBP will be included in the data analyses

**Step 5:** All patients having persistent PDPH despite a third EBP will be included in the data analyses

**Step 6:** Post-home discharge (follow-up phase). All patients will be followed up for a minimum period of 7 days (+/- 1 day) after confirmation of PDPH. Follow up of the patients after 3...
months (+/- 2 weeks) after confirmation of PDPH is encouraged in order to determine long-term success. Adverse events will be included in this phase of the study and statistical analyses performed appropriately.

7.7 Statistical methods
For the primary endpoint, risk factors for failure of EBP, the following factors will be included in a regression model:
1. Volume of blood injected (< 15 vs. > 15 ml)
2. Caesarean section vs. vaginal delivery
3. Primi vs. multigravida
4. Use of vacuum extraction or not
5. Time to onset of PDPH after ADP (< 24 h vs. > 24 h),
6. Air vs. saline for detection of loss of resistance
7. Young vs. old (< 30 years vs. > 30 years)
8. BMI (< 35 vs. > 35)
9. Previous h/o headache vs. no previous h/o headache
10. Experience of Anaesthesiologist performing EBP (< 5 EBP vs. > 5 EBP)

8. Quality Assurance and Quality Control

The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements. The sponsor is also responsible for securing agreement from all involved parties to ensure direct access to all trial related sites, source data/documents and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities. Quality control will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly. Agreements, made by the sponsor with the investigator / institution and any other parties involved with the clinical trial, will be in writing, as part of the protocol or in a separate agreement.

It will be the responsibility of Local Principal Investigators that the data in eCRF is carefully
entered and verified regularly. It will be the responsibility of Local Principal Investigator to ensure that periodic and random checks are done to ensure data quality. It will be the final responsibility of the sponsor to make random assessments of centres in order to confirm that there is no improper and incorrect data entered into eCRF.

9. Ethics Description of Ethical Considerations Relating to the Trial

The proposed study is an observational study. Therefore, no ethical concerns can be foreseen. Written, informed consent will be obtained from each patient prior to inclusion, if necessary. Patients will be allowed to withdraw from the study at any time point after inclusion, and without any explanation. All patients will receive routine care according to the standards laid out in each institution and no research related interventions are anticipated. Institutional approval will be obtained from each participating centre in order to get permission for collecting relevant clinical information. Patient identity will be protected and therefore the name or local patient hospital number will not be used to identify any patient in any database.

In all cases, all participating centres must submit the study to the local Institutional Review Board (IRB) for ethical judgment and obtain document of proof that the trial has been subject to IRB/IEC review and given approval/favourable opinion and/or exemption of patient consent. If informed consent is not required by the local IRB, an explicit, written exemption must be obtained from the Institutional Review Board. This process should take place prior to initiation of the trial and in compliance with the applicable national regulatory requirement(s).

If applicable, informed consent forms and any other written information to be provided to the patients as well as advertisement for subject recruitment (if used) should be subject to IRB/IEC review and given approval/favourable opinion. The consent form will be obtained as follows. The patients will be presented with Patient Information Sheet following PDPH diagnosis and prior to conservative management (≥ 24 h) and individual written consent will be sought prior to anaesthesia.
The study coordinator provides a template of Patient Information Sheet and Participant’s Informed Consent and Authorized Informed Consent in English (see Appendix 1A, 1B, 1C). All translation and Adaptation of the Appendix 1A, 1B, and 1C should be sent to ESA the Sponsor for validation. Guidance published by the Sponsor should be followed in this regard.

10. Data Handling and Record Keeping

Participating hospitals will be provided with a screening inclusion form (appendix 6) that enables standardized screening of a patient.

The hospital will also be provided with a coversheet (appendix 7) that will contain the patient’s name and hospital specific identification number and help sites to link patient with ID number. Paper coversheet of the CRFs will have identifiable patient data in order to allow follow-up of clinical outcomes and quality control.

Data will be then be collected in individual centres on paper case report forms (CRFs) (appendix 2). CRF are identified through a Patient Identification Number and shall not include any names, patient initials or local hospital patient numbers.

Local investigators will then transcribe all collected data from the data acquisition sheet (CRF) onto an internet-based electronic CRF. Data are thus first collected on paper CRF then entered into the electronic Case Report Form (eCRF) by the site staff anonymously using only the specific patient identification number (PIN).

Paper and electronic CRF will be in English for all Nations and centres involved in this trial. Paper CRFs will be stored within a locked cabinet/office in accordance with local and national regulations until the Sponsor has agreed to archive the Study.

Access to the data-entry system is protected by a personalized and confidential username and password.

No names, patient initials or local hospital patient numbers are collected or are kept on the data acquisition forms, nor electronically in the eCRF. Each centre will keep a confidential patient log sheet which matches each CRF/eCRF, through their PIN, to the individual patient. The log sheet will be stored behind a lock, together with the data acquisition forms. Data will be handled confidentially and all data will be stored for the length of the study and for at least 10 years or
longer if locally required, for further publication. Each centre will maintain an Investigator File including: protocol, IRB judgment, EC approval (if applicable), local investigator delegation log, local translation of informed consent form (if applicable), signed informed consent forms (if applicable), etc.

Anonymised data will be analysed at the study statistician’s institution (Anders Magnuson, Department of Biostatistics and Epidemiology, Örebro University, Örebro, Sweden). This institution will keep data until publication of the material. After completed publication, data must be sent for storage to ESA headquarters located in Brussels and destroyed at the statistician’s site. A respective document signed and dated by the the study statistician and the chief investigator will be sent to ESA headquarters. ESA also declares to respect the data protection laws of the participating European countries.

All handling of personal data will comply with the GCP Guidelines. All collected data will remain the property of the Sponsor.

11. Publication Policy

Data collected from this project can be used for publication of one or more studies in a peer-reviewed international journal of high quality. After recruitment of patients, data acquisition, cleaning and analysis of the data obtained, authorship will be considered according to participant involvement. All collaborators will be detailed in the manuscript appendix and can be tracked via PubMed (in accordance with the Journal authorship policy). Local Principal Investigator will be asked to submit names of staff actively involved from their institution in the End of Study Reporting Form (Appendix 4). If the number of recruited patients from a country/centre is too low to justify sufficient active involvement, the steering committee will decide on the legitimacy of authorship. The final decision will be left to the decision of the Chief Investigator in consultation with the ESA and members of the steering committee and in line with journal policy.

Following the initial European publication of data, each country National Coordinating Investigator will be free to discuss with the local coordinating investigators to publish data from their own country. Following permission from the SC, National Coordinating Investigators (in
agreement with local centres) will be allowed to use their own data for publication. Proposals for secondary analyses of collected data must be submitted to the Steering Committee that will approve these analyses and may revise all papers prior to submission. Duplicate data publication is, however, not be permitted. The sponsor of the study (ESA CTN) can use anonymised data for internal analyses and educational purposes.
12. References


13 List of Supplements/appendices

1. Template for Patient Documentation:
   • 1A. Study information sheet for the Patient
   • 1B. Patient Informed Consent
   • 1C. Authorized Informed Consent Form
2. Case Report Form /Data Acquisition sheets
3. Pre-study questionnaire
4. End of study Reporting Form
5. Definitions
6. Screening – Inclusion Form
7. Patient Confidential Identification CRF Coversheet
8. Confidential patient Log Sheet

14 Protocol history of changes

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