Evaluation of the effectiveness and tolerance of tetracosactide in the treatment of post-dural puncture headaches (ESYBRECHE): A study protocol for a randomized controlled trial

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Celia Depaulis  celia.depaulis@gmail.com
Hospices Civils de Lyon
Corresponding Author
ORCiD: 0000-0002-4164-0202

Nadia Steer
Hospices Civils de Lyon

Dominique Chassard
Hospices Civils de Lyon

Frederic Aubrun
Hospices Civils de Lyon

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Abstract

Background

Post-dural puncture headache (PDPH) is one of the most common complications of neuraxial anesthesia. It limits patients’ general activity and increases hospital length of stay and use of care. It is particularly disabling during the postpartum period, when mothers have to take care of their child. Epidural blood patch is the standard treatment of PDPH. However, it is an invasive procedure that may result in rare but serious complications. Recent evidence suggests the effectiveness of adrenocorticotropic hormone (ACTH) in the management of PDPH. The aim of this study is to assess the efficacy and safety of tetracosactide (Synacthen®), a synthetic analogue of ACTH, in the treatment of PDPH in patients who received neuraxial anesthesia during labor.

Method

This is a randomized, double-blinded, placebo-controlled, parallel-arm trial, performed in two French university hospitals. Eligible patients are those suffering from postpartum PDPH, who are randomized to receive either 1 mg of tetracosactide intravenously over 20 min, or 0.9% saline (placebo). The primary endpoint of the study is the rate of epidural blood patch within a 15-day follow-up period. Duration of headache, intensity of pain, reduction of general activity, increase of hospital length of stay, adverse events, analgesic use (type and duration), and number of blood patches per patient in each group are recorded.

Discussion

We expect a decrease in the use of epidural blood patch in those who receive tetracosactide, thus indicating a decrease in PDPH symptoms in these patients. This will define the therapeutic success of tetracosactide and the possibility to use this treatment as a noninvasive alternative to blood patch in the treatment of PDPH.
Background

Epidural analgesia is the most effective method used to control pain during labor and is frequently used in France (77% of vaginal deliveries in 2010) (1). Spinal anesthesia is preferred for cesarean section, artificial delivery, or uterine revision because of the risk associated with general anesthesia in pregnant women (such as difficult of airway management(2)). However, neuraxial anesthesia can also lead to adverse effects and in particular post-dural puncture headache (PDPH). The incidence of PDPH among those with dural puncture mainly depends on the type of needle (diameter, bevel) (3-10); for instance it is reported to be between 0.7% and 4% for 24–27 G conical needles used for spinal anesthesia, and 50–85% for large Tuohy needles used for epidural analgesia (3,10,11). However, the incidence of PDPH among patients receiving these types of anesthesia is close, as the incidence of dural puncture during epidural placement is reported to range from 0.04 to 6% (12). In addition, postpartum women are more prone to PDPH than the general population (13-15).

PDPH is a clinical diagnosis. According to the International Headache Society, it is a severe postural, bilateral, disabling, constrictive, occipital or diffuse headache, radiating to the neck that develops within 7 days after the dural puncture. In 66% of cases it occurs during the first 48 hours, and in 90% during the first 3 days (3). PDPH is aggravated by a sitting or standing position and is relieved by lying down. Other symptoms such as neck stiffness, hearing disorders (tinnitus, hypoacusia) (16), dizziness, photophobia, nausea or vomiting, diplopia by injury of the cranial nerve IV (17) may be associated with the headache and patients remain afebrile. Differential diagnoses are migraine, pre-eclampsia, meningitis, intracranial hemorrhage, cerebral thrombosis, pneumocephalus and tension headaches (18,19).

Intracranial hypotension by leakage of cerebrospinal fluid (CSF) appears as the main
cause of PDPH, as described by Vandam and Dripps as early as 1956 (20). CSF is critical to reduce impacts between the brain and the cranium during orthostatism and the loss of this cushioning leads to headaches. Furthermore, the cerebral and meningeal vessels are stressed during the downward displacement of the brain in orthostatism. This caudal traction activates the stretch-sensitive receptors of the trigeminal nerves (frontal headache), glosso-pharyngeal and vagus nerves (occipital headache) (11,21,22) and the first three cervical nerves (arm pain or neck pain) (23). According to the Monro-Kellie theory, headaches may also be related to painful venous and arterial cerebral vasodilation which compensates for decreased CSF volume (3,21). In the inner ear, hypotension of the perilymph also causes an imbalance between endolymph and perilymph itself leading to an impairment of hearing, tinnitus and/or vertigo (16,24).

In most cases, dural puncture closes spontaneously without consequence. PDPH is reported to resolve in more than 50% of patients within 4 days, and in more than 70% within a week (although headache may persist in a limited number of patients) (3,20). However, PDPH limits patients’ activity, increases the duration of hospital stay and the use of care (25), and it is particularly disabling during the postpartum period, when the mother has to take care of her child. It is therefore important to treat this syndrome. Epidural blood patch is currently the gold-standard and most effective treatment for PDPH. However, the moment at which the blood patch must be performed remains uncertain. On the one hand, some studies have suggested a greater risk of failure with early blood patch although no causal link could be established (26–28), however it has been suggested that the severity of CSF leak could explain the diminished effectiveness of early blood-patch (28). On the other hand, a delayed blood patch could increase the duration of bed rest while waiting for this intervention. A delay of 24 to 36 hours between the onset of headaches and the completion of a blood patch seems reasonable and it is recommended
not to delay it by more than 48 hours (29).

Historically the reported rate of success after the first blood patch is around 80% (28,30), yet more recently efficacy has been found to be lower (at most 32%) (27). However, it is an invasive procedure that may result in rare but serious complications such as spinal subdural hematoma (31) or permanent paraparesis and cauda equina syndrome (32), but also it may trigger anxiety and discomfort in patients and can sometimes be painful (back pain, transient bradycardia).

Alternative treatments have been studied recently; these aim to be less invasive or to reduce headache intensity whilst waiting for the blood patch or the disappearance of PDPH. Several lines of evidence have suggested the effectiveness of adrenocorticotropic hormone (ACTH) in the management of PDPH (33-41). Several mechanisms have been proposed to explain the effects of ACTH or its analogues on headaches. First, it has been shown by several teams that fragments of ACTH interact with opioid receptors in vitro and have morphine-like effects in vivo (42-44). Second, ACTH may increase brain β-endorphins that change the perception of pain (35-37). Third, ACTH stimulates the adrenal cortex which releases different hormones such as glucocorticoids, androgens, and mineralocorticoids. Glucocorticoids have an anti-inflammatory effect that may explain in part the analgesia observed after ACTH injection (38). Fourth, mineralocorticoids are responsible for fluid retention that may lead to meningeal edema and overlapping edges of the dural puncture (36).

The trial reported by Hakim found that administration of tetracosactide after accidental dural puncture in 90 parturients was associated with a significant reduction in the incidence of PDPH and requirement for epidural blood patch (39). The efficacy of tetracosactide for the treatment of PDPH in 32 patients has been reported to be 56% (95% CI [33; 79%]) (40), and to be similar to that of epidural blood patch in a study that
included 28 patients (41) although 4 of the 15 in the tetracosactide group also received a blood patch. However, a randomized trial that included 18 patients did not find any efficacy of tetracosactide to treat PDPH, nor to reduce the use of blood patch (45). This study was conducted among a small group of patients, and did not report any data on the interval between PDPH onset and blood patch. Taken together, evidence for the efficacy of ACTH analogues on PDPH remains limited with contradictory results (all obtained in small groups of patients). It is therefore difficult to conclude and establish a protocol for the management of PDPH.

In the proposed study, we have designed a therapeutic trial to evaluate the efficacy of tetracosactide in the treatment of PDPH in 88 postpartum patients.

Methods/design

1.3.1 Aim of the study

The aim of this study is to assess the efficacy and safety of tetracosactide (Synacthen®) in the treatment of post-dural puncture syndrome for patients who received neuraxial anesthesia during childbirth.

Our working hypothesis is that a single intravenous infusion of tetracosactide may avoid the need for epidural blood patch. To challenge this hypothesis we compare two groups: the study group receives an infusion of 1 mg of tetracosactide whereas the control group receives a placebo (0.9% saline). Both groups receive standard analgesic treatment and epidural blood patch if needed (after a minimum 24 h following the injection of the experimental treatment).

1.3.2 Trial Design

The study is a randomized, double-blind, placebo-controlled, parallel-arm, double centers trial. It is conducted in two sites of a French university hospital. Patient enrollment started
in October of 2016 and was expected to be completed within 2 years after the start of the study.

Once participants are enrolled in the study with informed consent, they are randomized into the two study arms. The study group receives 1 mg of tetracosactide intravenously whereas the control group receives 0.9% saline. Outcomes will be measured between 2 and 6 hours, at 1 day, 2 days, 3 days, and between day 13 and 17 post-randomization. Adverse events are collected throughout the study.

1.3.3 Primary endpoint

The primary endpoint of the study is the rate of epidural blood patch within a 15-day follow-up period.

1.3.4 Secondary endpoints

The secondary endpoints include: duration of headache, intensity of headache (11-point numerical rating scale, NRS) (46), the need for analgesic treatments (type, delay after study treatment, and duration), appearance of associated features (neck stiffness, tinnitus, hypoacusia, photophobia, diplopia, dizziness or nausea), activity limitation (qualitatively as described in Figure 1, and quantitatively on a scale from 0 to 100%; both self-assessed), hospital length of stay, the number of epidural blood patches performed per patient, and tolerance. Tolerance is assessed by the collection of all side effects (type, frequency, severity): any abnormality of clinical examination occurring during or after the infusion.

1.3.5 Population

Number of patients needed

The sample size calculation is based on a previous study that investigated tetracosactide in PDPH (39) and, retrospectively, on observational data from our hospital database. The
primary end point is the rate of blood patch in the two groups. We defined the efficacy of tetracosactide as a decrease in blood patch use by 30% in the tetracosactide group, a clinically relevant difference reducing the need for invasive treatment and replacing it with an easily administered treatment that has a known safety profile.

In our center, 90% of patients with PDPH after epidural analgesia receive a blood patch. The study reported by Hakim (39) found a greater than 50% decrease in PDPH incidence and blood patch use after prophylactic treatment with tetracosactide, in a context of epidural analgesia. We therefore need to include 44 subjects in each group, given power of 0.80 and type I error of 0.025 ($\alpha = 2.5\%$ Fisher’s exact test, power of 80%, $p_1 = 0.9$; $p_2 = 0.6$), to reduce blood patch requirement by 30%. Thus a total of 88 patients need to be randomized.

**Eligibility**

Patients eligible for enrolment in this clinical trial are those suffering from PDPH due to epidural analgesia, combined spinal-epidural analgesia, or spinal anesthesia for childbirth.

The headache should be as follows:

within five days after delivery
relieved in the supine position and/or worse while sitting or standing intense (NRS >3/10)
with or without associated with neck stiffness, tinnitus, hypoacusia, photophobia, visual impairment, nausea or vomiting
having eliminated differential diagnosis: pre-eclampsia or eclampsia, cerebral venous thrombosis, migraine.

Patients must be older than 18 years of age and benefit from healthcare insurance. They also have to provide a written informed consent.

**Exclusion criteria**

Exclusion criteria are as follows:

Diplopia (which requires an epidural blood patch without delay)
Contraindication to ACTH: uncontrolled arterial hypertension, uncontrolled diabetes mellitus, acute psychosis, infectious diseases
Contraindication to tetracosactide:
currently receiving a drug associated with an increased risk of Torsades de Pointes: astemizole, bepridil, IV erythromycin, halofantrine, pentamidine, sparfloxacin, sulprofamide, terfenadine, vincamine

Patient who received a live vaccine in the month prior to inclusion

Previous history of hypersensitivity to tetracosactide

Patient who has previously received tetracosactide since childbirth

Contraindication to epidural blood patch: HIV, HVC, leukocytosis, fever

Pre-eclampsia or eclampsia during this pregnancy (may be confounding for the etiology of headache)

Patient who has already received a prophylactic blood patch (at the time of accidental dural puncture diagnosis)

Under 18 years old or adult under guardianship

Mental disorder which does not allow informed consent

Patients who are enrolled in another clinical trial

**Consent**

When PDPH diagnosis is made by the anesthesiologist, screening of patients for inclusion and exclusion criteria is performed. The investigator then presents the study to the patients. Written information is provided to the patients. Final inclusion occurs after a cooling-off period and a written informed consent is signed by the patients.

**1.3.6 Randomization, blinding, and data management**

The anesthesiologist checks patient inclusion criteria and the absence of exclusion criteria. After signing informed consent, patients are randomized online using the ClinSight-Online software program (Ennov society, Paris, France). The randomization is performed by block stratification according to site. Patients are allocated to a treatment number. The study is performed as a double-blinded study. An anesthetic nurse prepares the treatment according to the assigned number to which the rest of the healthcare team is blinded. Patient data are collected on electronic case report forms (eCRFs). The promoter will independently monitor both locations of this multisite trial every ten patients.

**1.3.7 Intervention protocols**

During the post-partum period, patients are usually followed by midwives. In case of headache, whether an accidental dural puncture was diagnosed or not, the
anesthesiologist is warned by midwives. Therefore any symptomatic patient is examined by an anesthesiologist. All the anesthesiologists of the maternity are study’s investigators. Patients are enrolled when diagnosed with PDPH based on the clinical evaluation of the anesthesiologist. They are randomized to receive intravenous tetracosactide or placebo. In the study group, patients receive a single intravenous injection of 1 mg tetracosactide (Synacthen®, Sigma-Tau laboratory, Roma, Italy). Four vials containing 0.25 mg tetracosactide (in 1 ml of solvent) are reconstituted in 100 ml of normal saline. This solution is infused intravenously over 20 min. In the control group, patients receive an equal volume of normal saline (0.9% NaCl): 104 ml over 20 min.

Standard analgesic medication is also initiated in both groups from the beginning of headache as concomitant treatments, as follows:

For mild headache (NRS<3/10): 1 g paracetamol and 400 mg ibuprofen orally every 6 hours
For moderate headache (NRS = 3): nefopam 20 mg and/or a combination of paracetamol 300 mg and opium 10 mg is given in addition every 4 hours
For severe headache (NRS≥4) morphine 10 mg orally every 4 h can be added as required

These treatments are adjusted daily.

The primary and secondary endpoint, including tolerance criteria are evaluated blindly during infusion of study treatment, 2–6 hours later, 1 day, 2 days, 3 days, and between 13 and 17 days post-treatment by the investigator. The latter is conducted by phone. The total duration of the study is therefore 13 to 17 days. Any alternative analgesic interventions required after receiving the study treatment are reported at each time point as noted above. The study timeline is summarized in Figure 2.

Epidural blood patch is performed for patients who reported a persistent moderate to severe headache a minimum of 24 hours after administration of the study treatment and 36 hours after the dural puncture based on the clinical appreciation of the
anesthesiologist. Epidural blood patch can be repeated twice if required (i.e. if headache
does not improve or if it increases again). Epidural blood patch is performed by the
anesthesiologist. Autologous blood is injected into the epidural space using an 18 gauge
Tuohy needle. The injection is stopped when the patient feels pressure in the lower back
or pain.

1.3.8 Statistical analysis

Unblinding occurs at the end of the study and once the database has been frozen.
Statistical analyses will be performed using IBM SPSS statistics for windows (IBM corp.,
Armonk, NY, USA) and R (R Foundation for Statistical Computing, Vienna, Austria). All data
will be checked for normal distribution using the Kolmogorov test. For normally distributed
data, variables will be presented as mean ± standard deviation (SD). Non-normal
distributed data will be presented as the median and interquartile range [IQR]. Categorical
variables will be presented as number and percentage of the total. To compare the two
groups (tetracosactide and placebo), we will use Fisher’s exact test for qualitative data
and the non-parametric Mann-Whitney tests for quantitative variables. A comparison of
the two groups at randomization will identify potential bias due to unequal allocation. A
multivariate logistic regression analysis will be performed to study factors independently
associated with the response to tetracosactide and to control potential confounding
factors.

Intermediate analysis

The hypothesis of a 30% difference between the two groups is conservative compared to
the 50% reduction reported by Hakim (39); a difference of only 30% between the two
groups should already be clinically relevant. An interim analysis is therefore planned after
enrollment of 44 patients. The overall alpha risk will be adjusted according to the
Bonferroni method and will be 2.5% (5% / 2). A p value <0.025 will therefore be
considered statistically significant. If this initial analysis is statistically significant (p <0.025), the independent monitoring committee may decide to stop the study without waiting for the planned recruitment. Otherwise, the study will be continued until the inclusion of 88 patients.

1.3.9 Ethical approval

This trial is conducted in accordance with the protocol and in compliance with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki (1989) and Good Clinical Practice (GCP). It is also conducted in accordance with French legislation (Public Health Code; Act No. 2004-806 of August 9, 2004). It is registered in Clinical Trial Protocol Registration and Results System: NCT02813655 (registration date: June 24, 2016). An ethics committee (comité de protection des personnes sud Est V, CPP) has approved the study for both participating sites on 6 April 2016. The national drugs authority (Agence Nationale de Sécurité du Médicament et des produits de santé, ANSM) authorized this trial (authorization date: April 18, 2016).

1.3.10. Adverse events management

During the study period, adverse events will be reported and recorded in the participants’ CRF. The severity of adverse events will be graded as mild, moderate, severe, life threatening or death, and the potential relationship between the adverse event and the study treatment will be assessed by clinical judgment. If a side effect requiring extension of hospitalization or causing a medically critical situation occurs, the event will be recorded as a severe adverse event. All severe and life threatening adverse events or death will be reported to the investigator and to the promoter within 24 h after the information has been collected. The promoter will report all those events to legal authority (ANSM and CPP). The investigator must follow patients until the adverse events have been
resolved.

1.3.11. Protocol amendment

Because patient enrollment/inclusion was more difficult than expected the protocol was amended (January 2017) to extended inclusion from PDPH due to a dural puncture carried out by large Tuohy needle to all postpartum PDPH, i.e. PDPH related to a large dural puncture and PDPH related to small needle (25–27G) for spinal anesthesia. A second amendment (November 2018) extended the inclusion period until 10/10/2021 to allow the further progress of the study.

Discussion

We propose herein a protocol to investigate the use of tetracosactide, an ACTH analogue, to treat PDPH. Blood-patch is currently the gold standard for PDPH treatment, and tetracosactide could be interesting by reducing the need for the invasive procedure and replacing it with an easily administered treatment that has a known safety profile. However, the currently evidence for the efficacy of ACTH analogues for PDPH remains limited, with contradictory results obtained in small groups of patients.

Initially, the inclusion was limited to PDPH due to a dural puncture carried out by large Tuohy needle. Because patient enrollment/inclusion was more difficult than expected the protocol was amended to extended inclusion to all postpartum PDPH. This widening of the inclusion criteria raises the issue of population heterogeneity, which we hope to limit by the randomization process.

Since the management strategy of PDPH (with blood-patch and non-invasive treatments) is not clearly defined, the rate of blood-patch varies. Rucklidge, for example, described that 50 blood-patches were received by 144 patients treated for PDPH after epidural anesthesia over 20 years in the hospital in which he practiced (47); the blood-patch rate
was therefore 35%. In the study reported by Aya et al. all patients (100%) treated for PDPH after epidural obstetric anesthesia in their unit received a blood-patch (48). Therefore, a potential limitation of the study described herein is that the sample size could be insufficient if the rate of blood patch in the control group is lower than 90%.

**Trial status**

It is the fourth protocol version dated 2018/09/28. The study is ongoing; the first patient was included in October 2016, and in May 2019 a total of 25 patients had been enrolled. Initially we expected to finalize the study in October 2018, but we had to extend the inclusion phase until 2021 to reach a total of 88 inclusions. Due to the ongoing nature of the study and in order to avoid influencing its conduct, the final results are not presented herein. Intermediate analysis will be performed after 44 inclusions, and if there significant difference in the primary outcome is found the study will be discontinued.

**Conclusion**

We expect a decrease in the use of epidural blood patch in those who receive tetracosactide, thus indicating a decrease in PDPH symptoms in these patients. This will define the therapeutic success of tetracosactide and the possibility to use this treatment as a noninvasive alternative to blood patch in the treatment of PDPH.

**List Of Abbreviations**

ACTH Adrenocorticotropic Hormone

ANSM *Agence Nationale de Sécurité du Médicament et des produits de santé*: the national drugs authority

CPP *Comité de Protection des Personnes*: an ethics committee

CSF Cerebrospinal Fluid

eCRFs electronic Case Report Forms
Declarations

Ethics approval and consent to participate

An ethics committee (comité de protection des personnes sud Est V, CPP) has approved the study for both participating sites on 6 April 2016. Patients’ inclusion occurs after a cooling-off period and a written informed consent is signed by the patients.

Consent for publication

Not applicable

Availability of data and materials

Data sharing is not applicable to this article as no datasets were yet generated or analysed during the current study.

Competing interests

The authors have no conflict of interest to declare.

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Funders have no role in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Authors’ contributions
Célia Depaulis was a major contributor in writing the manuscript. Nadia Steer, Dominique Chassard and Frederic Aubrun read and approved the final manuscript.

Bibliography

1. Kpéa L, Bonnet M-P, Le Ray C, Prunet C, Ducloy-Bouthors A-S, Blondel B. Initial Preference for Labor Without Neuraxial Analgesia and Actual Use: Results from a National Survey in France. Anesth Analg. 2015 Sep;121(3):759–66.

2. Yıldırım İ, İnal MT, Memiş D, Turan FN. Determining the Efficiency of Different Preoperative Difficult Intubation Tests on Patients Undergoing Caesarean Section. Balkan Med J. 2017 Sep 29;34(5):436–43.

3. Turnbull DK, Shepherd DB. Post-dural puncture headache: pathogenesis, prevention and treatment. Br J Anaesth. 2003 Nov;91(5):718–29.

4. Matas SL de A. Why should we use atraumatic needles in lumbar puncture? Arquivos de Neuro-Psiquiatria. 2013 Sep;71(9B):681–4.

5. Evans RW, Armon C, Frohman EM, Goodin DS. Assessment: prevention of post-lumbar puncture headaches: report of the therapeutics and technology assessment subcommittee of the american academy of neurology. Neurology. 2000 Oct 10;55(7):909–14.

6. Flaatten H, Felthaus J, Kuwelker M, Wisborg T. Postural post-dural puncture headache. A prospective randomised study and a meta-analysis comparing two different 0.40 mm O. D. (27 g) spinal needles. Acta Anaesthesiol Scand. 2000 Jul;44(6):643–7.

7. Lambert DH, Hurley RJ, Hertwig L, Datta S. Role of needle gauge and tip configuration in the production of lumbar puncture headache. Reg Anesth. 1997 Feb;22(1):66–72.

8. Lavi R, Yarnitsky D, Yernitzky D, Rowe JM, Weissman A, Segal D, et al. Standard vs atraumatic Whitacre needle for diagnostic lumbar puncture: a randomized trial.
9. Halpern S, Preston R. Postdural puncture headache and spinal needle design. Metaanalyses. Anesthesiology. 1994 Dec;81(6):1376-83.

10. 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 Anaesth. 2003 May;50(5):460-9.

11. Diemunsch P, Schlotterbeck H, Pottecher J. Brèches dure-méro-arachnoïdiennes. Conférence d’actualisation 2003 [Internet]. SFAR. 2003; Available from: http://www.sfar.org/acta/dossier/archives/ca03/html/ca03_09/ca03_09.htm

12. Basurto Ona X, Uriona Tuma SM, Martínez García L, Solà I, Bonfill Cosp X. Drug therapy for preventing post-dural puncture headache. Cochrane Database Syst Rev. 2013;2:CD001792.

13. Wu CL, Rowlingson AJ, Cohen SR, Michaels RK, Courpas GE, Joe EM, et al. Gender and post-dural puncture headache. Anesthesiology. 2006 Sep;105(3):613-8.

14. Diaz JH. Epidemiology and outcome of postural headache management in spontaneous intracranial hypotension. Reg Anesth Pain Med. 2001 Dec;26(6):582-7.

15. Bezov D, Lipton RB, Ashina S. Post-Dural Puncture Headache: Part I Diagnosis, Epidemiology, Etiology, and Pathophysiology. Headache: The Journal of Head and Face Pain. 2010 Jun 1;50(7):1144-52.

16. Pogodzinski MS, Shallop JK, Sprung J, Weingarten TN, Wong GY, McDonald TJ. Hearing loss and cerebrospinal fluid pressure: case report and review of the literature. Ear Nose Throat J. 2008 Mar;87(3):144-7.

17. Nishio I, Williams BA, Williams JP. Diplopia: a complication of dural puncture. Anesthesiology. 2004 Jan;100(1):158-64.

18. Goldszmidt E, Kern R, Chaput A, Macarthur A. The incidence and etiology of
postpartum headaches: a prospective cohort study. Can J Anaesth. 2005 Nov;52(9):971–7.

19. Bleeker CP. Postpartum post-dural puncture headache: is your differential diagnosis complete? British Journal of Anaesthesia. 2004 Sep 1;93(3):461–4.

20. Vandam LD, Dripps RD. Long-term follow-up of patients who received 10,098 spinal anesthetics; syndrome of decreased intracranial pressure (headache and ocular and auditory difficulties). J Am Med Assoc. 1956 Jun 16;161(7):586–91.

21. Fournet-Fayard A, Malinovsky J-M. [Post-dural puncture headache and blood-patch: theoretical and practical approach]. Ann Fr Anesth Reanim. 2013 May;32(5):325–38.

22. Candido KD, Stevens RA. Post-dural puncture headache: pathophysiology, prevention and treatment. Best Pract Res Clin Anaesthesiol. 2003 Sep;17(3):451–69.

23. Schabel JE, Wang ED, Glass PS. Arm pain as an unusual presentation of postdural puncture intracranial hypotension. Anesth Analg. 2000 Oct;91(4):910–912, table of contents.

24. Lybecker H, Andersen T, Helbo-Hansen HS. The effect of epidural blood patch on hearing loss in patients with severe postdural puncture headache. J Clin Anesth. 1995 Sep;7(6):457–64.

25. 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 Anaesth. 2005 Apr;52(4):397–402.

26. Loeser EA, Hill GE, Bennett GM, Sederberg JH. Time vs. success rate for epidural blood patch. Anesthesiology. 1978 Aug;49(2):147–8.

27. Paech MJ, Doherty DA, Christmas T, Wong CA, Epidural Blood Patch Trial Group. The volume of blood for epidural blood patch in obstetrics: a randomized, blinded clinical trial. Anesth Analg. 2011 Jul;113(1):126–33.
28. Safa-Tisseront V, Thormann F, Malassiné P, Henry M, Riou B, Coriat P, et al. Effectiveness of epidural blood patch in the management of post-dural puncture headache. Anesthesiology. 2001 Aug;95(2):334-9.

29. Les blocs périmédullaires chez l’adulte. Annales Françaises d’Anesthésie et de Réanimation. 2007 Jul;26(7-8):720-52.

30. van Kooten F, Oedit R, Bakker SLM, Dippel DWJ. Epidural blood patch in post dural puncture headache: a randomised, observer-blind, controlled clinical trial. J Neurol Neurosurg Psychiatr. 2008 May;79(5):553-8.

31. Verduzco LA, Atlas SW, Riley ET. Subdural hematoma after an epidural blood patch. Int J Obstet Anesth. 2012 Apr;21(2):189-92.

32. Diaz JH. Permanent paraparesis and cauda equina syndrome after epidural blood patch for postdural puncture headache. Anesthesiology. 2002 Jun;96(6):1515–7.

33. Foster P. ACTH treatment for post-lumbar puncture headache. Br J Anaesth. 1994 Sep;73(3):429.

34. Kshatri AM, Foster PA. Adrenocorticotropic hormone infusion as a novel treatment for postdural puncture headache. Reg Anesth. 1997 Oct;22(5):432–4.

35. Collier BB. Treatment for post dural puncture headache. Br J Anaesth. 1994 Mar;72(3):366–7.

36. Cánovas L, Barros C, Gómez A, Castro M, Castro A. Use of intravenous tetracosactin in the treatment of postdural puncture headache: our experience in forty cases. Anesth Analg. 2002 May;94(5):1369.

37. Carter BL, Pasupuleti R. Use of intravenous cosyntropin in the treatment of postdural puncture headache. Anesthesiology. 2000 Jan;92(1):272-4.

38. Gupta S, Agrawal A. Postdural puncture headache and ACTH. J Clin Anesth. 1997 May;9(3):258.
39. Hakim SM. Cosyntropin for prophylaxis against postdural puncture headache after accidental dural puncture. Anesthesiology. 2010 Aug;113(2):413–20.

40. Zeger W, Younggren B, Smith L. Comparison of cosyntropin versus caffeine for post-dural puncture headaches: A randomized double-blind trial. World J Emerg Med. 2012;3(3):182–5.

41. Hanling SR, Lagrew JE, Colmenar DH, Quiko AS, Drastol CA. Intravenous Cosyntropin Versus Epidural Blood Patch for Treatment of Postdural Puncture Headache. Pain Med. 2016 Mar 25;

42. Terenius L. Effect of peptides and amino acids on dihydromorphine binding to the opiate receptor. J Pharm Pharmacol. 1975 Jun;27(6):450–2.

43. Terenius L, Gispen WH, De Wied D. ACTH-like peptides and opiate receptors in the rat brain: structure-activity studies. Eur J Pharmacol. 1975 Oct;33(2):395–9.

44. Plomp GJ, Van Ree JM. Adrenocorticotrophic hormone fragments mimic the effect of morphine in vitro. Br J Pharmacol. 1978 Oct;64(2):223–7.

45. Rucklidge MWM, Yentis SM, Paech MJ. Synacthen Depot for the treatment of postdural puncture headache. Anaesthesia. 2004 Feb;59(2):138–41.

46. Hjermstad MJ, Fayers PM, Haugen DF, Caraceni A, Hanks GW, Loge JH, et al. Studies comparing Numerical Rating Scales, Verbal Rating Scales, and Visual Analogue Scales for assessment of pain intensity in adults: a systematic literature review. J Pain Symptom Manage. 2011 Jun;41(6):1073–93.

47. Rucklidge OMWM. All patients with a postdural puncture headache should receive an epidural blood patch. International Journal of Obstetric Anesthesia. 2014 May;23(2):171–4.

48. Aya AG, Mangin R, Nouvellon E, Robert C, Ferrer JM, Eledjam JJ. [Dural puncture in obstetric analgesia. Epidemiologic features and therapeutic management]. Ann Fr
Anesth Reanim. 2001 Nov;20(9):757–62.

Figures

| Only able to lie down | ☐ YES | ☐ NO |
|-----------------------|-------|------|
| Able to walk around   | ☐ YES | ☐ NO |
| Able to get up and to take a shower | ☐ YES | ☐ NO |
| Able to sit for more than thirty minutes (for a meal) | ☐ YES | ☐ NO |
| Able to bathe your child | ☐ YES | ☐ NO |
| Able to feed your child | ☐ YES | ☐ NO |
| Able to change your child | ☐ YES | ☐ NO |

Figure 1

Questionnaire for qualitative assessment of activity limitation. A simple questionnaire corresponding to the needs of a postpartum patient.

| TIMEPOINT | STUDY PERIOD |
|-----------|--------------|
| ENROLMENT:| Enrolment | Allocation | Post-allocation | Close-out |
| Eligibility screening: inclusion/exclusion criteria | Less than -6 hours | to hour 2 to hour 6 | Day 1 | Day 2 | Day 3 | Day 13 to 15 |
| Informed consent | X |
| Randomization | X |
| INTERVENTIONS: | Treatment infusion | X |
| Analgesic treatment | Blood work if needed | | | | |
## Schedule of enrolment, intervention, and assessment.

### Supplementary Files

This is a list of supplementary files associated with the primary manuscript. Click to download.

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