Northwestern University Feinberg School of Medicine
Department of Anesthesiology
Protocol

Title: Incidence of Post-Dural Puncture Headache following Unintentional Dural Puncture: A Randomized Trial of Intrathecal Morphine versus Saline

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Research Aims:

1. **Research Questions(s):** Does the administration of intrathecal morphine after delivery reduce the risk of post-dural puncture headache (PDPH) following unintentional dural puncture (UDP) with a 17-g Tuohy needle in obstetric patients?

2. **Hypotheses:** Intrathecal morphine decreases the incidence of PDPH as compared to placebo after UDP with a Tuohy needle in obstetric patients.

Background: Unintentional dural puncture is a known risk of neuraxial techniques, occurring in roughly 1% of all epidural catheter placements.[1-3] The incidence of PDPH after unintentional dural puncture is 50-80%.[3-5] The International Headache Society has defined PDPH as a headache that occurs following a dural puncture, worsens within 15 minutes after sitting or standing and improves within 15 minutes after lying, with at least one of the following: neck stiffness, tinnitus, hypacusia, photophobia, or nausea. The headache develops within 5 days after dural puncture and resolves either spontaneously within 1 week or within 48 hours after effective treatment of the spinal fluid leak (usually by epidural blood patch).[6] PDPH can be a significant cause of maternal morbidity in the obstetric patient. In addition to interfering with the mother's ability to care for her newborn, treatment of PDPH can increase health care costs by prolonging the length of hospitalization and number of emergency room visits.[7]
Several strategies exist to treat PDPH, but currently there are no proven interventions for preventing or reducing the likelihood of PDPH following unintentional dural puncture.[8,9] Previously investigated strategies include prophylactic epidural blood patch, the use of intrathecal (IT) catheter with delayed removal, intrathecal saline injection and infusion, and cosyntropin administration.[10-15] Retrospective and observational studies have demonstrated a decrease in PDPH rates following unintentional dural puncture when intrathecal catheters are placed instead of subsequent placement of an epidural catheter.[1,12] Other observational studies have examined the use of intrathecal opioids to reduce the incidence of PDPH.[14,16] Recently, one randomized controlled trial explored the use of epidural morphine for the prevention and treatment of PDPH with positive results. Al-metwalli showed a decrease in the PDPH rate from 48% to 12% after administration of epidural morphine 3 mg at the time of delivery and again at 24 hours postpartum.[17] Administration of epidural morphine following UDP may produce unpredictable central nervous system side effects, however, as a large dural hole may facilitate intrathecal translocation of epidural morphine, increasing the risk of respiratory depression. At our institution, it is common practice for an intrathecal catheter to be placed after UDP instead of an epidural catheter at another spinal level. Given that the administration of epidural morphine after known UDP may have unpredictable effects and that the use of intrathecal catheters following UDP is a common practice, we feel it is necessary to study the use of intrathecal morphine administration following UDP to decrease the incidence of PDPH. In our randomized prospective study, the rates of PDPH following unintentional dural puncture with placement of an intrathecal catheter will be compared in two groups: intrathecal morphine versus intrathecal saline

administration 1-2 hours after delivery followed by immediate catheter removal. We have chosen to administer intrathecal morphine 150 μg as this is the current dose given to parturients receiving morphine via spinal administration for Cesarean delivery and has a predictable side effect profile and history of safety in this population. The dose roughly corresponds to the epidural morphine dose administered by Al-metwalli in his randomized controlled trial.[17]

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4. Choi A, Laurito CE, Cunningham FE. Pharmacologic management of postdural puncture headache. Ann Pharmacother 1996;30:831-9. PMID: 8826568
5. Hartopp R, Hamlyn L, Stocks G. Ten years of experience with accidental dural puncture and post-dural-puncture headache in a tertiary obstetric anaesthesia department. Int J Obstet Anesth 2010;19:118. PMID: 19945855
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9. Sudlow C, Warlow C. Posture and fluids for preventing post-dural puncture headache. Cochrane Database Syst Rev 2002:CD001790. PMID: 12076420
10. Hakim SM. Cosyntropin for prophylaxis against postdural puncture headache after accidental dural puncture. Anesthesiology 2010;113:413-20. PMID: 20613476
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13. Charsley MM, Abram SE. The injection of intrathecal normal saline reduces the severity of postdural puncture headache. Reg Anesth Pain Med 2001;26:301-5. PMID: 11464346
14. Cohen S, Amar D, Pantuck EJ, Singer N, Divon M. Decreased incidence of headache after accidental dural puncture in caesarean delivery patients receiving continuous postoperative intrathecal analgesia. Acta Anaesthesiol Scand 1994;38:716-8. PMID: 7839783
15. Scavone BM, Wong CA, Sullivan JT, Yaghmour E, Sherwani SS, McCarthy RJ. Efficacy of a prophylactic epidural blood patch in preventing post dural puncture headache in parturients after inadvertent dural puncture. Anesthesiology 2004;101:1422-7. PMID: 15564951
16. Eldor J, Guedj P, Cotev S. Epidural morphine injections for the treatment of postspinal headache. Can J Anaesth 1990;37:710-1. PMID: 2278354
17. Al-metwalli RR. Epidural morphine injections for prevention of post dural puncture headache. Anaesthesia 2008;63:847-50. PMID: 18547293
18. Banks S, Paech M, Gurrin L. An audit of epidural blood patch after accidental dural puncture with a Tuohy needle in obstetric patients. Int J Obstet Anesth 2001;10:172-6. PMID: 15321606

Significance: PDPH can lead to significant morbidity. Along with headache, patients may develop cranial nerve palsy during the postpartum period leading to permanent disability. In addition, new mothers are unable to bond with their babies due to headache and associated symptoms including nausea, vomiting and limited mobility secondary to pain. PDPH can negatively impact patient satisfaction with postpartum recovery. Therefore, an effective intervention to decrease the risk of PDPH after UDP would be useful.

Investigational Plan:

Study design: prospective, randomized-controlled, blinded study

Methods:

1. Size of study groups(s):

The incidence of PDPH has been estimated to approximately 50% after unintentional dural puncture.[18] Assuming that a decrease of at least 50% would be necessary to suggest a clinical utility of this treatment, we determined that a sample size of 64 patients in each group would be required to achieve an 80% power to detect this difference between epidural and intrathecal catheter. Group sample sizes of 64 achieve 80% power to detect a difference between the group proportions of 0.25. The proportion in group one (the treatment group) is assumed to be 0.5 under the null hypothesis and 0.25 under the alternative hypothesis. The proportion in group two (the control group) is 0.5. The test statistic used is the two-sided Fisher's exact test. The significance level of the test was targeted at 0.05. The significance level actually achieved by this design is 0.03. Sample size was calculated using PASS 11, version 11.0.01, release date 11/3/2010 (NCSS Inc. Kaysville, UT). To account for protocol exclusions and patients lost to follow-up, 170 patients will be randomized. Recruitment for this project will take roughly 1-2yrs.

2. Patient entry, exclusion and dropout criteria:

Inclusion: Postpartum patients following vaginal delivery with an unintentional dural puncture and functioning intrathecal catheter. Patients must be 18 years of age or older and English speaking.

Exclusion: Previous PDPH, body mass index BMI>40 kg/m^2, obstructive sleep apnea (OSA), morphine allergy and patients who receive Cesarean delivery (as these patients would all receive intrathecal morphine and could therefore not be randomized).

3. Protocol specific methods: Eligible patients will be asked by anesthesia personnel to participate in this study shortly following delivery when the nurse taking care of the patient deems the patient appropriate for discharge. Informed, written consent will be obtained and the pharmacy on the 10th floor Prentice Women's Hospital will determine group allocation by randomization table. The patient will be randomized to one of two groups: intrathecal morphine (treatment) vs. saline (control) which will be administered through the existing intrathecal catheter. Patients randomized to the treatment group (morphine) will receive preservative-free morphine 0.3 mL (150 mcg) intrathecally. Those randomized to the control group will receive normal saline 0.3 mL intrathecally. The drugs will be prepared in syringes by a pharmacist on the 10th floor Prentice Women's Hosptial and labeled as "IT morphine study drug." The anesthesiologist injecting the study drug, the study nurse collecting follow-up data, and the patient will be blinded to group assignment. After thoroughly sanitizing the catheter port with a Chloroprep wipe and allowing adequate time for drying of the Chloroprep, the anesthesiologist will first attach a 3-mL syringe to the catheter port and aspirate to a volume of 1 mL. This syringe will then be removed from the port. The study drug will then be administered through the intrathecal catheter via the tuberculin syringe. The 3-mL syringe containing the aspirate will then be injected via the catheter, effectively flushing the study drug through the catheter. The intrathecal catheter will be removed immediately following the injection. If the anesthesiologist is unable to aspirate from the catheter, the intrathecal drug will be administered and flushed with 1.0 mL of preservative free saline to ensure drug delivery. The inability to aspirate will be noted on the data sheet at the time of administration. Sterile gloves will be used for all morphine or saline administration.

After administration of intrathecal morphine, all patients will have their respirations monitored every hour for a period of 12 hours and then every two hours for a period of 12 hours. This is standard protocol after the administration of neuraxial morphine at NMH. If the patient develops symptoms of nausea, vomiting, urinary retention or pruritus, she will receive standard interventions per the NMH order-set for neuraxial opioids.

On postpartum days 1-5, all patients will be visited daily while inpatient and called by phone after discharge from the hospital. The following information will be also recorded in this study: presence or absence of PDPH (as defined by the International Headache Society), signs and symptoms of cranial nerve injury, the patient's verbal rating score for pain (VRSP, 0-10 scale), current headache treatments including oral analgesics, intravenous caffeine, or epidural blood patch, side effects of intrathecal morphine (respiratory depression, nausea, vomiting, pruritus, urinary retention. Patients who develop a headache will be followed for 3 days after the resolution of their headache. Physician observers will make treatment recommendations according to the following protocol (previously described by Scavone et al, 2004[15]): Mild postural headaches (defined as VRSP <4) will be treated with conservative therapy including oral hydration, increased oral caffeine intake, and oral analgesics as needed. Moderate postural headaches (defined as VRSP 4-6 without limitation of childcare ability) will also receive conservative therapy. Patients with moderate postural headaches limiting childcare abilities, and patients complaining of severe postural headaches (defined as VRSP >6) will be advised to undergo a therapeutic epidural blood patch (EBP). This treatment will consist of the epidural injection of 20 mL of autologous blood over 2 to 3 min through the epidural needle, injected at the level of the presumed UDP or one level below. The patient will be positioned in the sitting position for the procedure and then repositioned supine for a period of 1 hour after the epidural blood injection. The EBP will not be performed for at least 24 hours after dural puncture. If the EBP fails to relieve the headache after 24 hours, or if the headache recurs after successful treatment, the EBP may be repeated. The protocol outlined above follows standard procedure at NMH.

4. Risks/Benefits:
Risks to study patients include: itching, nausea, vomiting, urinary retention, constipation, dizziness, hypotension, depression of cough reflex and slowing of respirations. The rare risk is respiratory depression leading to respiratory arrest.

The presumed risks are similar to that assumed by any parturient who receives spinal morphine for Cesarean delivery, which is common practice. To minimize the risk of apnea, patient will be monitored postpartum in the same manner that patients receiving neuraxial morphine for Cesarean delivery are routinely monitored as described above.

If any patient experiences nausea, vomiting or pruritus, she will be treated with medications based on the clinical scenario as evaluated by the attending anesthesiologist on duty who will not be blinded to treatment group. There is also a risk of loss of confidentiality.

Confidentiality: Access to electronic data is computer password protected. All data will be deleted from the password protected computer 5 years after manuscript preparation. Electronic and paper documents will be destroyed using current technology. The paper documents will be shredded using the current vendor for HIPAA sensitive documents using the current technique.

Data Analysis:

1. Data collection form: Data collection form attached.

2. Data evaluation: The primary outcome is the incidence of PDPH. The intrathecal morphine and saline groups will be compared using the Fisher's exact test. The clinical characteristics of the study groups will be compared between groups using the Mann Whitney test for interval and continuous data and a $\chi 2$ statistic for nominal data. Secondary outcomes include severity of headache, need for epidural blood patch, rate of neuraxial infection, neuraxial complications. $P < 0.05$ will be required to reject the null hypothesis.

3. Interpretation of Anticipated Results: A reduced incidence of PDPH in the intrathecal morphine group without an unacceptable incidence of side effects would support the effectiveness its administration after UDP.

Budget:

1. **Materials:** Preservative free morphine (2-mL) 1000 microgram ampule – cost 80 cents per vial for 64 patients. Preservative free 0.9% saline (10-mL) vial – cost 35 cents per vial for 64 patients. The total cost for study drugs is $74.75, which will be provided by the Department of Anesthesiology.

2. **Labor Requirements:** Obstetric anesthesiology research nurses and obstetric anesthesiology fellows will recruit patients for the study and will perform all data collection.

3. **Presentation Cost:** This project will be presented at a national meeting such as ASA or SOAP.

Consent: *(Provide a consent form in the relevant IRB format. The template for these forms can be found on the Web at: http://www.research.northwestern.edu/oprs/irb/templates/*

Additional information for preparation of an IRB Submission:

NA

DATA COLLECTION FORM

Study Number:_____ **Date:** _____

EGA:_____ Parity:_____

Height (inches):_____ Weight (kilogram):_____

Procedure performed by:_____ If resident/fellow specify level of training **PGY-**_____

Loss of Resistance - air / saline

Dural puncture interspace - _____

Intrathecal Catheter Placement: Date_____ Time_____ Location (skin)____cm

Intrathecal Catheter Removal: Date_____ Time _____ Location (skin)____cm

Total infusion dose: _____mLs

Mode of delivery - Vaginal / Forceps or Vacuum Assisted

Start of pushing - _____ End of pushing - _____

Delivery time - _____ Time of removal of catheter _____

Aspirate of CSF prior to drug administration - yes / no

Patient Study Number _____
Postpartum day # _____
Evaluator:_____
Date:_____ Time:_____Presence of PDPH yes / no
If yes, Headache VPRS score (1-10):0 1 2 3 4 5 6 7 8 9 10

Current Headache therapy (please circle and specify doses when appropriate)

1. Hydration _____
2. Oral analgesics _____
3. IV analgesics _____
4. IV Caffeine _____
5. Epidural blood patch date -_____
   (please fill out EBP data sheet with details)

Headache VPRS score after treatment_____

Cranial nerve involvement - yes / no
If yes, please specify_____

Presence of backache - yes / no
Backache VPRS score0 1 2 3 4 5 6 7 8 9 10

Signs/symptoms of infection

1. Max Fever in last 24hours_____
2. Superficial (i.e., swelling, redness, purulence around site yes / no What? _____
3. CNS (i.e., meningitis, epidural abscess)

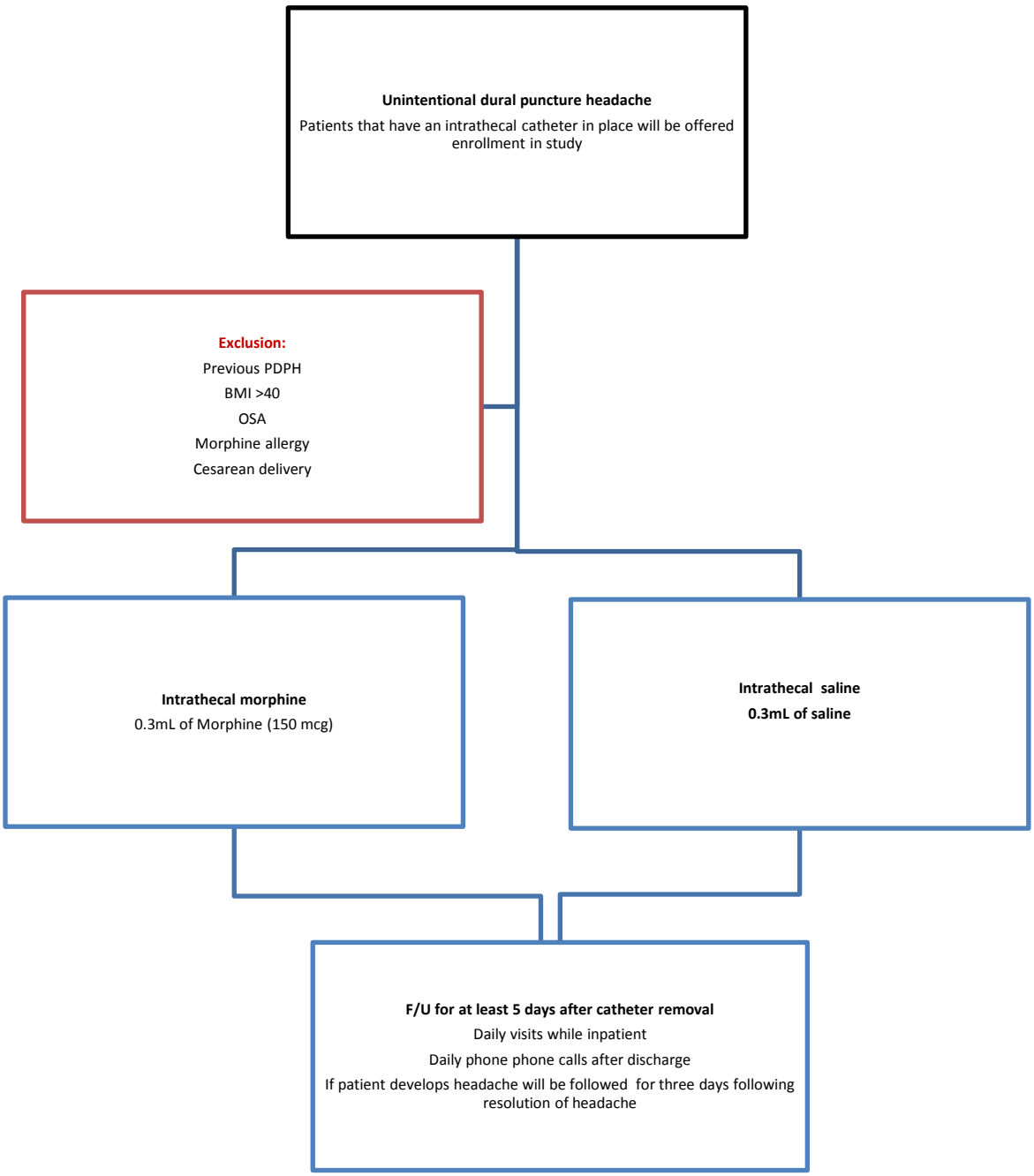
_____

Lower extremity peripheral nerve symptoms

1. Weakness (where) _____
2. Paresthesia (where) _____

Recommended Therapy (please circle all that apply)

1. Hydration
2. Oral analgesics
3. IV analgesics
4. IV Caffeine
5. Epidural blood patch


Unintentional dural puncture headache
Patients that have an intrathecal catheter in place will be offered enrollment in study
Exclusion:
Previous PDPH
BMI >40
OSA
Morphine allergy
Cesarean delivery
Intrathecal morphine
0.3mL of Morphine (150 mcg)
Intrathecal saline
0.3mL of saline
F/U for at least 5 days after catheter removal
Daily visits while inpatient
Daily phone phone calls after discharge
If patient develops headache will be followed for three days following resolution of headache