Two Dose Neuraxial Morphine for Prevention of Postdural Puncture Headache

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RESEARCH AIMS & ABSTRACTS

Research Question(s)/Hypothesis(es): This study aims to determine the efficacy of neuraxial (either epidural or intrathecal) preservative-free morphine to prevent headache after accidental dural puncture in parturients.

Our hypothesis is that 2 doses of neuraxial morphine (epidural or intrathecal) will be superior to placebo in reducing the incidence of postdural puncture headache.

Scientific Abstract: Neuraxial analgesia (most commonly continuous epidural or combined spinal epidural) is the most effective modality available for pain relief during labor. Accidental dural puncture (ADP) with a large bore epidural needle and the resulting post-dural puncture headache (PDPH) is one of the most significant sources of anesthesia-related morbidity in parturients. The incidence of ADP in this population is between 0.04 and 6% (most common cited is ~ 1%), and PDPH occurs in up to 80% of patients with an ADP. For many patients, the headache is debilitating, interfering with the ability to care for a new infant, and may be associated with other unpleasant symptoms, including diplopia, tinnitus, hypoacusis, photophobia, nausea, and dizziness. In the most severe cases, subdural hematoma can occur. Epidural blood patch is the gold standard for treatment of PDPH, and although almost always effective, can result in another ADP, as well as low back pain and lower extremity pain. For this reason, effective measures to prevent PDPH when ADP occurs would be highly valuable. One small study by Al-metwalli, et al. in which 50 women were randomly allocated to receive 2 epidural injections of morphine or saline, demonstrated a beneficial effect of epidural morphine in decreasing the incidence of PDPH. This study aims to determine the efficacy of 2 doses of neuraxial (either epidural or intrathecal) preservative-free morphine (PFM) to prevent headache after ADP in parturients.

Lay Abstract: Epidural or combined spinal epidural analgesia (pain relief) is the most effective modality available for the treatment of pain during labor. The most frequent, bothersome complication of performing these procedures is accidental dural puncture (ADP) with the epidural needle, commonly called a “wet tap.” The dura mater is the membrane that surrounds the fluid that cushions and bathes the brain and spinal cord. If the dura mater is

punctured by the epidural needle, some of the fluid may leak out through the puncture. When ADP occurs, the anesthesiologist, at his/her discretion, may either withdraw the needle and place an epidural catheter at the same or slightly different level in the lower back, or the anesthesiologist may decide to place the epidural catheter through the dural puncture directly into the spinal fluid (known as an intrathecal catheter). Following ADP/wet tap, up to 80% of patients get a headache, known as a post-dural puncture headache (PDPH). The headache usually begins 24 – 72 hours after ADP/wet tap occurs. For many patients, the headache is very painful and interferes with care of their newborn. The headache may also be associated with other unpleasant symptoms, including blurry vision, ringing in the ears, muffled hearing, sensitivity to light, nausea, and dizziness. In the most severe and rare cases, bleeding in the brain can occur. Epidural blood patch is the gold standard for treatment of PDPH, and although almost always effective, can result in another ADP, as well as low back pain and lower extremity pain. For this reason, effective measures to prevent PDPH when ADP occurs would be very useful. One recent study in which 50 women were randomly allocated to receive 2 epidural injections of morphine or saline, demonstrated a beneficial effect of epidural morphine in decreasing the incidence of PDPH. This study aims to determine whether administration of 2 doses of morphine, via either the epidural or intrathecal catheter in place, will prevent headache in women who experienced ADP in during labor.

BACKGROUND

Study Purpose and Rationale: Neuraxial (epidural or combined spinal epidural) analgesia is the most effective modality available for pain relief during labor. For obstetric patients who choose to undergo neuraxial analgesia, accidental dural puncture (ADP) with a large bore epidural needle and the resulting post-dural puncture headache (PDPH) is the most significant source of morbidity. The incidence of ADP in this population is between 0.04 and 6%, with most estimates between 1-2% (1), and PDPH occurs in up to 80% of patients with an ADP (2). For many patients, the headache is debilitating, interfering with their ability to care for a new infant, and it may also be associated with other unpleasant symptoms, including diplopia, tinnitus, hypoacusis, photophobia, nausea, and dizziness. In the most severe cases, subdural hematoma can occur. When ADP occurs during the provision of neuraxial labor analgesia,

management includes placement of an intrathecal catheter or placement of an epidural catheter at the same or different intervertebral level. The data that exists is conflicting regarding what techniques or factors may reduce the risk for PDPH. A meta-analysis, which reviewed data from nine studies, found that insertion of an intrathecal catheter produced a significant reduction in the need for epidural blood patch (EBP), although the incidence of PDPH was not significantly different (3). Epidural blood patch (EBP) is the gold standard for treatment of PDPH, and although almost always effective, it is not without the potential for complications. EBP can result in another accidental dural puncture, as well as low back pain and lower extremity pain. For this reason, effective measures to prevent PDPH when ADP occurs would be useful. At the present time, the efficacy of measures such as continuous intrathecal analgesia, intrathecal saline injection, and prophylactic EBP, to prevent PDPH remain unclear.

One small study by Al-metwalli, et al. (4) in which 50 women were randomly allocated to receive epidural injections of morphine or saline, demonstrated a beneficial effect of epidural morphine in decreasing the incidence of PDPH. Interestingly, epidural morphine is often administered for post-operative analgesia after cesarean delivery, and in patients who experience ADP, cesarean delivery is associated with a lower incidence of PDPH than vaginal delivery (5). This study aims to determine the efficacy of neuraxial (either epidural or intrathecal) preservative-free morphine (PFM) to prevent headache after ADP in parturients.

Study Design: This will be a prospective, randomized, double blind clinical trial. Subjects will be postpartum ASA I and II women aged 18 years and older, who are known to have had ADP with an epidural needle during placement of neuraxial labor analgesia, and have either an intrathecal catheter or epidural catheter. Patients will be randomized to either receive PFM or placebo (sterile normal saline). For patients with an epidural catheter, the group “EPID PFM” will receive 3 mg (6 mL) of PFM, followed by 3 mL of sterile normal saline (NS) to be administered through the epidural catheter. The placebo group, “EPID NS”, will receive 6 mL of NS, followed by another 3mL of NS via the epidural catheter. For patients with an epidural catheter, the group “EPID PFM” will receive 3 mg (6 mL) of PFM, followed by 3 mL of sterile normal saline (NS) to be administered through the epidural catheter. The placebo group, “EPID NS”, will receive 6 mL of NS, followed by another 3mL of NS via the epidural catheter. For patients with an intrathecal catheter, the group, “IT PFM” will receive 200 micrograms (mcg)

(0.4 mL) of preservative-free morphine, followed by a flush of the catheter with 2 mL of NS. The placebo group, IT SAL will receive 0.4 mL and then 2 mL of NS through the intrathecal catheter. 16 to 24 hours after receiving the first study drug, patients in all groups will be visited by an investigator, and then daily thereafter during the hospital admission. They will be evaluated for the presence of headache, analgesia requirements, need for EBP and the severity of opioid side effects. As long as the patient is afebrile, has not been experiencing severe opioid side effects and the catheter is in place and intact, the patient will then receive the identical study drug (for a total of two doses). The epidural/intrathecal catheter will be removed immediately after the second administration of the study drug. After discharge, the patient will be followed up once daily by telephone for up to a minimum of 5 days after receiving the last dose of the study drug if they remain headache free, and for a minimum of 3 days after resolution of PDPH.

Statistical Procedures: This will be a prospective randomized double blind clinical trial. The primary outcome of the trial will be the incidence of PDPH at 48 hours after ADP. A study by Al-Metwalli et al. 2008 (4), utilizing 2 doses of epidural morphine, reported a PDPH headache rate of 12 % in the treatment arm and 48% in the saline arm. Estimates of PDPH rate after ADP range from 50 - 85%. Our internal QA data indicates our PDPH headache rate after an ADP with an epidural needle over the past several years is ~66%. We will consider a difference in incidence of PDPH between the placebo and treatment groups of 25% to be significant, based on the findings of Al Metwalli et al. (4) and the meta-analysis by Heesen et al. (3). For calculation of our sample size, we determined that an absolute 25% decrease in PDPH would be clinically significant (i.e., 66% - 40%). For a power of 90% and an alpha of 0.05%, this requires 83 subjects per group (2 epidural groups compared to each other, 2 spinal groups compared to each other). We are not specifically powering this for comparison of the spinal to the epidural groups, although we will likely be able to do so. We therefore aim to recruit 100 subjects per group (for a total of 400 across all centers) assuming 10- 15% of subjects may be lost because of inadvertent withdrawal of the catheter, subject withdrawal or loss to follow up after discharge. This is intended to be a multicenter study involving 5 or more academic tertiary-care hospitals, having >2,000 vaginal deliveries per year. Since the rate of accidental dural puncture is between 1 and 2%, we estimate we should be able to recruit 100 patients per year. Categorical data (presence of absence of PDPH, need for EBP) will be analyzed using Chi-square analysis. The

two main campuses of NYP will be included (CUMC (including Allen) and Weill-Cornell); additional centers will be enrolled.

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