Neuraxial Morphine–Induced Hypothermia After Cesarean Delivery Managed With Nalbuphine: A Case Report

Kyra Bernstein, MD, and Ruth Landau, MD

Neuraxial morphine–induced hypothermia has been reported as a relatively rare complication, with the successful use of naloxone and lorazepam to reverse symptoms. We report a case of intrathecal morphine–induced hypothermia with profuse sweating, intractable nausea, and vomiting in a primigravid woman undergoing cesarean delivery in the setting of preeclampsia. All symptoms rapidly resolved after a single dose of intravenous nalbuphine. Because nalbuphine has a long track record of safe use on labor and delivery units, it is an attractive and novel choice for treatment of neuraxial morphine–induced hypothermia. (A&A Practice. 2020;14:e01220.)

GLOSSARY

ERAC = enhanced recovery after cesarean; **HIPAA** = Health Insurance Portability and Accountability Act; **IV** = intravenous; **NM** = nonmeasurable; **OR** = operating room; **PACU** = postanesthetic care unit; **SOAP** = Society for Obstetric Anesthesia and Perinatology

Neuraxial morphine is recommended for opioid-sparing multimodal analgesia at cesarean delivery in the United States and is increasingly used as part of Enhanced Recovery After Cesarean (ERAC) protocols.[1] Common side effects of neuraxial morphine include nausea and vomiting, pruritus, respiratory depression, and sedation.

While hypothermia does occur with neuraxial local anesthetic alone due to vasodilation and radiant heat loss, the addition of neuraxial opioids has been reported to exacerbate this effect.

There have been several reports of a distinct syndrome of intrathecal morphine–induced symptomatic hypothermia with temperatures <35°C, subjective warmth, profuse sweating, nausea, vomiting, and pruritus.[2–8] In these cases, treatment modalities have included naloxone and lorazepam, although the exact mechanism by which a benzodiazepine may be effective is unknown.

We report a case of severe intrathecal morphine–induced hypothermia in the postanesthetic care unit (PACU) following an urgent cesarean delivery in the setting of preeclampsia. Based on potential mechanisms and the desire to avoid full opioid receptor antagonism, we chose a pragmatic approach and used intravenous (IV) nalbuphine 5 mg with excellent effect. To our knowledge, this is the first successful use of nalbuphine to treat intrathecal opioid–induced hypothermia. Health Insurance Portability and Accountability Act (HIPAA) authorization has been obtained from the patient.

CASE DESCRIPTION

A 50-year-old Caucasian primigravida, 70.3-kg, 163-cm tall woman with a pregnancy induced by in vitro fertilization presented to labor and delivery at 38-week gestation with oligohydramnios and preeclampsia without severe features. Urgent cesarean delivery was indicated, and the patient consented for spinal anesthesia. Preoperative vital signs included blood pressure 144/72 mm Hg, heart rate 68 beats per minute, room air oxygen saturation 99%, and temperature 36.8°C (Figure). With standard maternal monitoring, a spinal anesthetic was administered (at 23:08), which included hyperbaric bupivacaine 0.75% 12 mg, preservative-free morphine 150 µg, fentanyl 15 µg, and clonidine 30 µg, as is often the case in our clinical practice. Surgical antibiotic prophylaxis was provided with IV cefazolin 2 g, and baseline maternal blood pressure was supported with a continuous IV phenylephrine infusion (50 µg/mL) started immediately after the spinal injection. As per our institutional practice, an underbody warming blanket (3M Bair Hugger; 3M Medical, St. Paul, MN) was maintained throughout the procedure. A T7 dermatomal level, determined by pin-prick testing, was established 10 minutes after the spinal dose, followed by uneventful skin incision (at 23:22). After delivery of a male infant (at 23:30), weighing 2745 g with Apgar scores of 9 and 9, oxytocin was started at 15 U/h and the phenylephrine was rapidly titrated off (stopped at 23:30). Two doses of ondansetron 4 mg followed by metoclopramide 10 mg were given IV for symptomatic nausea. The procedure was overall uneventful, the anesthesia time lasted 94 minutes, estimated blood loss was 500 mL, and urinary output was 100 mL. Maternal temperature was not measured during the case. The patient received IV ketorolac 30 mg at the end of the surgery. She was comfortable on arrival in the PACU (at 00:27),

From the Department of Anesthesiology, Columbia University Medical Center, New York, New York.

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Address correspondence to Ruth Landau, MD, Department of Anesthesiology, Columbia University Medical Center, 622 W 168th St, New York, NY 10032. Address e-mail to rl262@cumc.columbia.edu.

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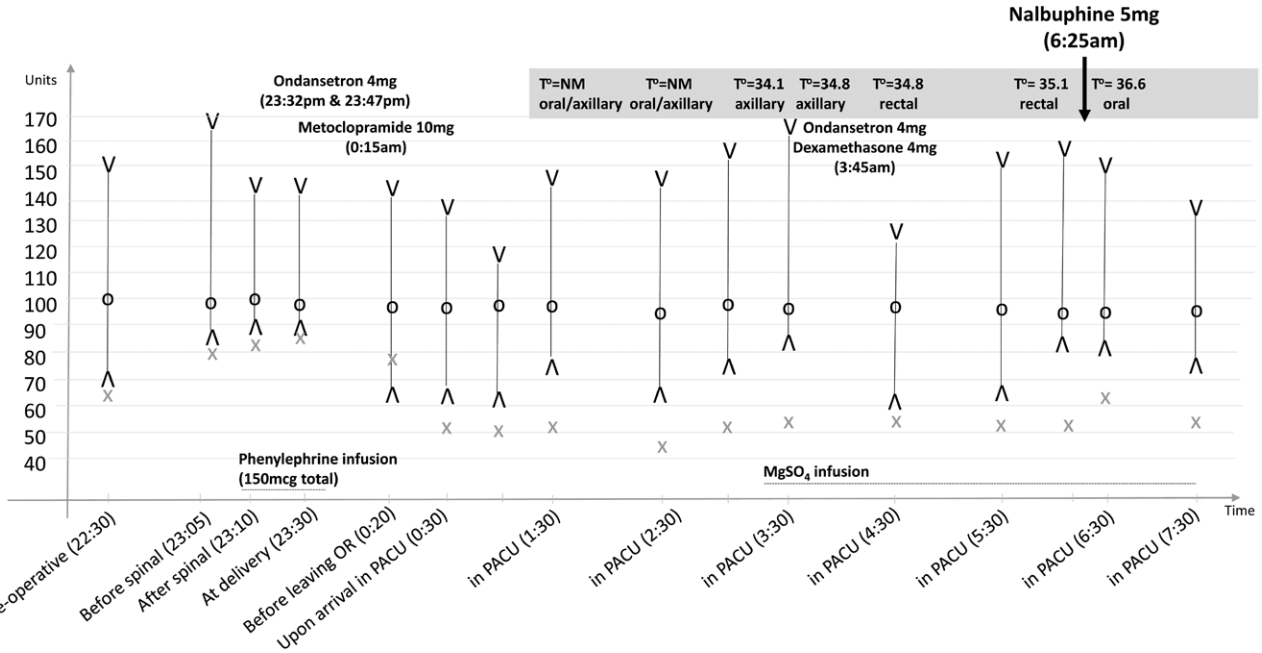

Figure. Perioperative events, including hemodynamic and temperature trends. Blood pressure, oxygen saturation, heart rate, and temperature are presented over time. ˅ = systolic blood pressure (mm Hg); o = oxygen saturation (%) at room air; x = heart rate (bpm); ^ = diastolic blood pressure (mm Hg); T^{o} = temperature in Celsius degrees; measurement is indicated (rectal, oral, axillary, or NM). NM indicates nonmeasurable; OR, operating room; PACU, postanesthetic care unit.

with a blood pressure of 117/76 mm Hg, a heart rate of 53 bpm, and oxygen saturation of 97% on room air. Over the first postoperative hours, the patient exhibited nausea, vomiting, pruritus, profuse sweating, and intense shivering. The nursing team was unable to measure the patient's temperature during the first 2 hours because the thermometer routinely used in the PACU (Welch-Allyn SureTemp PLUS; Welch Allyn Inc, Skaneateles Falls, NY) with an oral or axillary probe was not registering (Figure). The obstetric and anesthesia teams were made aware of the somewhat discrepant symptoms with profuse sweating despite a patient feeling cold to touch, and an over body warming blanket was applied. Sensory-motor block recovery from the spinal anesthetic was noted at 3 AM, and refractory hypothermia persisted beyond expected recovery from the spinal anesthetic. The first measured temperature was 34.1°C (at 3:30). At this time, a magnesium sulfate infusion had also been started for persistent elevated blood pressures (Figure) consistent with the diagnosis of preeclampsia. The patient continued to report nausea, vomiting, and sweating, which were in part also attributed to the initiation of magnesium sulfate, and pruritus. Additional ondansetron (4 mg) and a dose of dexamethasone (4 mg) were administered IV with no effect. A rectal temperature probe registered a value of 35.1°C (at 6:15). At this time, the anesthesiology attending was called to the PACU to assess the patient for refractory hypothermia and nausea. Suspecting intrathecal opioid–induced hypothermia, the attending decided to start with nalbuphine 5 mg IV, which was given at 6:25 AM. This approach was pragmatic, because nalbuphine seemed a simple, practical, and safe initial therapy. All symptoms rapidly improved, and much to her own surprise, the patient reported that nausea, pruritus, shivering, and sweating all resolved within 10 minutes of the nalbuphine administration. The next temperature measurement, taken orally, was 36.6°C (at 7:00). The temperature remained above 36°C, measured orally for the remainder of her hospitalization.

DISCUSSION

When anticipating complications of neuraxial opioids, clinical recommendations and guidelines are geared toward prevention and management of respiratory depression, nausea, vomiting, and pruritus. However, neuraxial opioid–induced hypothermia and persistent sweating can be distressing to patients and stymie providers who are unaware of this relatively rare entity and unaccustomed to managing it. The mechanism by which neuraxial opioids, typically preservative-free morphine, cause severe hypothermia and profuse sweating, with or without shivering, in humans has not been elucidated. In an observational study, the incidence of presumed intrathecal morphine–induced hypothermia in women undergoing a planned cesarean delivery receiving 250 µg of intrathecal morphine was 7% (14 of 193 women) with paradoxical symptoms of hyperthermia (diaphoresis and sensation of feeling hot, with no shivering).[5] No risk factors or particular obstetric or demographic factors were identified, and because symptoms persisted after regression of spinal anesthesia and despite active warming, it was attributed to a central effect of intrathecal morphine on thermoregulation.[5] It is not known whether this phenomenon is dose dependent, although our patient received 150 µg, similar to the dose that was evaluated in a placebo-controlled trial on the hypothermic effect of intrathecal morphine.[9] Others have reported opioid-induced hypothermia in women receiving intrathecal morphine dose of 250,[2,5] 200,[4,8] 100 µg[3,6] or even as low as 50 µg.[7] Labor does not seem to be a contributing

factor, since most cases were planned cesarean deliveries in the absence of uterine contractions. In none of the cases was there excessive bleeding or transfusion of blood products. In our case, the patient was 50 years of age and had a diagnosis of preeclampsia, but to our knowledge, opioid-induced hypothermia in the setting of preeclampsia has not been reported.

Neuraxial opioids have been reported to induce hypothermia by inhibiting shivering, though in the obstetric setting, where shivering is widespread, this seems to be an incomplete answer. In rat models, neuraxially administered selective k-opioid agonists lower body temperature, while μ-opioid agonists raise body temperature, suggesting that endogenous opioid receptors maintain a homeostatic balance to contribute to body temperature regulation.[10] Other models suggest that the hypothermic effect of neuraxial morphine is mediated by dopaminergic or adrenergic receptors.[11] Based on the successful use of lorazepam to treat neuraxial morphine–induced hypothermia, γ-aminobutyric acid activation or anxiety may play a role; however, this has not been directly tested and remains an empirical approach.[5]

The occurrence of hypothermia and shivering remains an issue among women undergoing a planned or unplanned cesarean delivery. The importance of adequate temperature monitoring in patients receiving neuraxial anesthesia for cesarean delivery has been addressed, and although several modalities to prevent intraoperative hypothermia have been tested, the best strategy remains unclear.[12] The Society for Obstetric Anesthesia and Perinatology (SOAP) ERAC statement cites maintenance of normothermia as a goal during cesarean delivery, and designation of a SOAP center of excellence requires active maternal warming during cesarean delivery. We acknowledge our failure to perform intraoperative temperature monitoring, and the inability to obtain temperature readings in the PACU should have prompted an earlier alert to the attending anesthesiologist. This emphasizes the importance of temperature-monitoring protocols, both in the operating room and in the PACU, for early identification and treatment of intrathecal morphine–induced hypothermia. Elucidation of the mechanism and potentially more targeted approaches for management of intrathecal morphine–induced hypothermia are warranted.

Spinal clonidine has been proposed as an adjuvant for cesarean delivery, to prolong sensory-motor block, improve intraoperative pain relief, provide anxiolysis and mild sedation intraoperatively, and reduce shivering.[13] It is commonly used in our institution at doses ranging between 0.5 and 1 μg/kg of maternal weight for women who are anxious, with a history of acute or chronic pain or a poor experience during a prior cesarean delivery, and for anticipated longer surgical duration. To our knowledge, there have been no studies reporting an association between spinal clonidine administration and maternal hypothermia. On the contrary, both clonidine and dexmedetomidine have been proposed to prevent postoperative shivering.

A handful of case reports described the use of naloxone to treat neuraxial morphine–induced hypothermia in obstetric patients, at doses of 80 μg,[8] 200 μg,[2] and up to 400 μg.[4,7] Although, mechanistically, naloxone's pure opioid antagonism makes it a logical choice for reversal of intrathecal opioid–induced side effects, concerns related to the possible reversal of analgesia and its pharmacokinetic profile that may require repeated and/or prolonged IV administration depending on circumstances, made it a second choice in this case. Nalbuphine's long-standing safe use as a partial opioid antagonist for management of opioid-induced pruritus in obstetric patients receiving neuraxial opioid analgesia makes it an attractive alternative. Although there is some evidence to support the use of smaller doses of nalbuphine for pruritus, with some reversal of analgesia being reported with the 4-mg dose compared with doses of 2–3 mg,[14] 5 mg has a long track record of efficacy and safety in obstetric anesthesia practice.[15]

Our successful use of a single dose of IV nalbuphine to treat severe maternal hypothermia 6 hours postcesarean delivery offers a simple and practical new therapeutic approach for this rare but ominous scenario. Future research may better elucidate the mechanism of neuraxial morphine–induced hypothermia, the potential mechanism by which nalbuphine may mediate temperature regulation, as well as the optimal dose of nalbuphine to be used for managing this condition.

DISCLOSURES

Name: Kyra Bernstein, MD.
Contribution: This author helped write and edit the case report.
Name: Ruth Landau, MD.
Contribution: This author helped write and edit the case report.
This manuscript was handled by: BobbieJean Sweitzer, MD, FACP.

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