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EDITORIAL

Don't throw the baby out with the bathwater: spinal-epidural hematoma in the setting of obstetric thromboprophylaxis and neuraxial anesthesia

Venous thromboembolism (VTE) remains a leading cause of maternal death worldwide,[1] responsible for approximately 9% of maternal deaths in the United States.[2,3] Decreased maternal mortality from VTE has been associated with the use of thromboprophylaxis,[4] although statistically significant differences in outcomes are difficult to demonstrate, in part due to the wide variation in practice.[5,6] Even for obstetric patients undergoing cesarean delivery, the mode of prophylaxis (mechanical devices versus pharmacologic agents) and the timing and dose of heparins (once versus twice daily; low, intermediate or high dose; pre- and/or postoperative dosing) varies for patients with the same risk profile.[7,8] A recent population-based study demonstrated that thromboprophylaxis after cesarean delivery varied from fewer than 20% of patients to greater than 80% of patients, depending on the hospital.[9]

Despite these uncertainties, all major obstetric professional organizations recommend VTE thromboprophylaxis[10–14] given the five- to six-fold increase in VTE in obstetric patients that is magnified post partum or with cesarean delivery.[15,16] However, bleeding risks associated with thromboprophylaxis with heparins which were initially noted in surgical patients in the 1990s have been documented in the obstetric population: these include injection site hematomas and the need for surgical re-exploration.[6,17–19] One of the most catastrophic complications is spinal-epidural hematoma (SEH) following a neuraxial procedure, because a relatively small amount of blood can result in permanent neurological disability.

In a recent volume of this journal, Pujic et al. reported a case of an "Epidural hematoma following low molecular weight heparin prophylaxis and spinal anesthesia for cesarean delivery".[20] In general, SEH in obstetric patients has historically been extremely rare and estimated to occur in 1 in 200–250 000 neuraxial procedures,[19,21] compared to 1 in 3600 in elderly women undergoing knee arthroplasty.[19] The lower frequency in pregnant women has been attributed to hypercoagulability, larger spinal canal dimensions (which could accommodate a greater volume of blood before cord and root ischemia occurs) and less use of pharmacologic thromboprophylaxis. However, the relevant large epidemiologic series were performed prior to the more aggressive protocols developed for obstetric VTE thromboprophylaxis. A recent systematic review of SEH in the setting of obstetric thromboprophylaxis and neuraxial anesthesia, commissioned by the Society for Obstetric Anesthesia and Perinatology (SOAP) interdisciplinary consensus statement taskforce, revealed no specific cases, although the denominator of cases was unknown.[22] There were, however, two cases in which heparin thromboprophylaxis was given to obstetric patients who had received neuraxial anesthesia and ultimately developed a SEH. Both cases were confounded by additional important elements. In one, the patient complained of severe back pain (consistent with SEH) before receiving her first dose of heparin.[23] In the second, the patient did not manifest signs or symptoms of SEH until after being therapeutically anticoagulated for a pulmonary embolus on the fourth postpartum day (Table 1).[24]

The patient described in the report by Pujic et al.[20] met criteria for thromboprophylaxis in the setting of a planned cesarean delivery, based on her body mass index (BMI) greater than 40 kg/m^2. Mechanical compression devices were not available, so she received pre-operative as well as postoperative anticoagulant dosing with nadroparin. The spinal procedure was performed by an experienced provider, without evidence of undue bleeding, and a small gauge needle was used, although it was not of the recommended pencil-point type. These characteristics are generally thought to be favorable in reducing the odds of SEH. Nadroparin, the low molecular weight heparin (LMWH) she received, is less commonly described in the literature for obstetric thromboprophylaxis than is enoxaparin. However, the pharmacokinetic and pharmacodynamic properties appear to be comparable[25] except for the longer anti-Xa effect (18 h for nadroparin and 12 h for enoxaparin).

Pujic et al.[20] state that their VTE protocol "conformed with both the American Society of Regional Anesthesia (ASRA) and SOAP guidelines"; but this is not the case. There are at least three factors that may have impacted the outcome in this case:

Table 1 Three complex case reports of spinal-epidural hematoma in obstetric patients receiving heparin in the peripartum period after a neuraxial procedure.

Case	Patient demographics and medical history	Heparin before delivery	Neuraxial procedure	Heparin after delivery	Symptoms and Imaging	Management	Impression
Walters IJOA 2012[23]	Healthy 28-year-old, BMI 28 kg/m^2 G2P1, 39 weeks. Planned repeat cesarean delivery	None	**CSE** 18-guage Tuohy 27- gauge pencil-point needle (hyperbaric bupivacaine 7.5 mg and sufentanil 2.5 μg) **Post-op:** **PCEA bolus (4 mL)** (levobupivacaine 0.125% and sufentanil 2.5 μg/mL) 23 h (52 mL)	"that evening" **enoxaparin prophylactic dose 40 mg SC OD**	*A few hours post-op* New back pain radiating to legs *24 h post-op* Complete motor block from sacral dermatomes to T12 *20 h later* **MRI: intrathecal hematoma at L3-4 with cauda equina compression**	Decompressive laminectomy Wheelchair bound with some sensation and weak extension and flexion of only her feet	Possible delayed diagnosis as initial symptoms attributed to PCEA bolus. Onset of symptoms preceded administration of LMWH
Chiaghana RAPM 2016[24]	Congenital cardiac defect (Fontan physiology), 30-year-old Superficial phlebitis during pregnancy, BMI 42 kg/m^2 (107 kg) Planned cesarean delivery and tubal ligation 36 weeks Metoprolol Aspirin 81 mg Furosemide Normal coagulation profile	**Unfractionated heparin prophylaxis 7500 iu SC BID** Held for >24 h prior to neuraxial procedure	**Continuous spinal anesthetic (unknown type of needle/catheter)** Catheter removed at the end of the surgery	*>12 h after catheter removal* **enoxaparin prophylactic dose 1 mg/kg OD** Day three postop Diagnosed as pulmonary embolus. **Enoxaparin therapeutic dose 1 mg/kg BID**	*Day four postop* Back pain, lower extremity weakness, perineal paresthesia. **MRI showed neuraxial hematoma from T6 to sacrum**	Decompressive laminectomy and hematoma evacuation. *3 months* Functional recovery of lower extremity strength, incomplete recovery of sensation and bladder control *18 months* Full recovery	Initial prophylactic dose high (1 mg/kg SC OD) Aspirin 82 mg daily was maintained ASRA guidelines followed but case confounded by use of high-dose LMWH for treatment of the pulmonary embolus 72 h after neuraxial procedure (spinal catheter)

Pujic IJOA 2019[20]	Morbidly obese, 31-year-old , BMI 42 kg/m^2 (110 kg) G2P1, 39 weeks. Planned cesarean delivery. Normal coagulation profile	*14 h prior to delivery* **Nadroparin prophylactic dose 0.3 mL** (2850 anti-factor Xa IU)	**Spinal anesthesia** 26-gauge Quincke needle (hyperbaric bupivacaine 11 mg and fentanyl 25 μg)	*9 h after end of case* **Nadroparin 0.3 mL BID daily* for 7 days** *considered more than prophylactic dosing	*Day 3 postop* Fever and small anterior abdominal wall hematoma, back and thigh pain. LMWH continued to day 7 postop *Day 10 postop* Severe back pain **MRI showed epidural hematoma causing moderate dural compression at L4: L3-4 disc herniation without compression**	Conservative therapy. *Day 17 postop* EMG showed radicular lesions L3-L4 and L5-S2 (chronic) *Day 34 postop* Discharged with resolution of pain and ability to sit and ambulate without issue	Shorter time interval than SOAP or ASRA recommendation for restart of LMWH post-operatively for BID dosing Higher dose of LMWH (BID) continued after day 3 postop despite back pain. Disc herniation may have contributed to the back pain.

ASRA: American Society of Regional Anesthesia and Pain Medicine. BID: twice daily. BMI: body mass index. CSE: combined spinal-epidural. EMG: electromyography. LMWH: low molecular weight heparin. MRI: magnetic resonance imaging. OD: once daily. PCEA: patient-controlled epidural analgesia. SC: subcutaneous. SEH: spinal-epidural hematoma. SOAP: Society for Obstetric Anesthesia and Perinatology. UFH: unfractionated heparin.

1. The time interval between the initial (low) LMWH dose and the neuraxial procedure was $\geq$12 h but the nadroparin was restarted nine hours after the end of surgery, and was administered twice daily. In the current ASRA guidelines, for postoperative twice-daily dosing of a LMWH, the first dose is to be given the following day and no sooner than 12 h after needle/catheter placement.[26] The 2010 ASRA recommendation cited by the authors actually stated a 24-h delay between needle placement and the first dose of twice-daily LMWH, regardless of the technique.[27]

2. The nadroparin dose was 0.3 mL twice daily (0.3 mL = 2850 antifactor Xa IU). The product monograph does not recommend twice daily dosing for thromboprophylaxis; instead a single 0.4 mL daily dose of nadroparin is to be administered in the first three days postpartum/postoperatively, followed by 0.6 mL daily dose for a total of 10 days. However, due to her BMI a larger and twice daily dose was advised by hematologists. Importantly, both early postoperative and twice-daily dosing of LMWH have been repeatedly identified as risk factors for SEH.[18,19,26]

3. Finally, post cesarean delivery analgesia is often provided with non-steroidal anti-inflammatory drugs (NSAIDs). If the patient received NSAIDS in combination with the higher dose of nadroparin, the effect on hemostasis could have been additive and might have increased the risk and severity of bleeding.

In addition, the evaluation and diagnosis of the SEH was delayed. The patient reported "pain in the back and both thighs" on the third postoperative day, although SEH was not investigated and recognized until 10 days postpartum. In the meantime, thromboprophylaxis was continued for the intended seven-day' course, despite the back pain and a visible bleeding complication of a (small) abdominal hematoma. On day 10, when she returned with back pain and fever, a magnetic resonance image (MRI) revealed an epidural hematoma situated dorsolateral to the right side of the dura, causing moderate dural compression at the L4 level. In addition, there was partial herniation of the L3-4 intervertebral disc, contacting both L4 nerve roots at the lateral recesses, without compression. Diclofenac was administered twice to this patient when re-admitted even though SEH was suspected and eventually confirmed.

Several important elements remain unclear based on the presentation and imaging, including: 1. When did this epidural hematoma develop (could she have bled twice?), and 2. Was the back pain related to the hematoma, to the chronic lumbar disc disease or to some combination of the two? The chronic L3-S1 radiculopathies that were subsequently diagnosed by electromyography may have made these roots more susceptible to the compressive effects of the

hematoma. Whatever the etiology of the severe back pain, it is vitally important that it triggered imaging of her back. Like the two previous cases of SEH with anticoagulants in obstetric patients, this was not straightforward low dose thromboprophylaxis as the title of the case report suggests. The heparin dosing in this case was higher than the often recommended thromboprophylactic doses and the time interval was shorter than recommended for restarting the medication. In addition, NSAIDs and compressive disc disease may have increased her risk of a symptomatic SEH.

It is, of course, very concerning when a young woman develops a SEH after a spinal anesthetic for cesarean delivery. Although overarching conclusions are not justified from a single case, provocative questions can be raised. First, should we continue to provide neuraxial anesthesia in the setting of heparin thromboprophylaxis? We assert that it is vital not "to throw the baby out with the bathwater!" There are compelling reasons to continue the widespread use of neuraxial anesthesia in obstetric patients. Compared to general anesthesia for cesarean delivery, neuraxial anesthesia continues to result in fewer serious airway complications, surgical infections, thromboembolic events and improved opioid-sparing postoperative pain management, maternal-fetal bonding and breastfeeding.[21,28–33] Similarly, neuraxial techniques provide the most effective labor pain analgesia.[34] In the absence of direct tools to measure the risk of SEH in obstetric patients, SOAP, working with ASRA and other key stakeholders, recently published an interdisciplinary consensus statement, based on the best-available evidence, to help guide the anesthetic care of obstetric patients on thromboprophylaxis and higher-dose anticoagulants.[35] We maintain that proceeding with neuraxial anesthesia, if guided by iterative recommendations and clinical judgement, may well be safer than withholding these techniques for fear of complications.

Should we continue to promote obstetric thromboprophylaxis? Here the answer is likely "yes"; with some qualifiers. Again: "don't throw the baby out with the bathwater! " Certainly, we want to administer the heparins when necessary, delaying the first dose as long as is clinically indicated and using the lowest efficacious dose. However, more aggressive thromboprophylaxis may result in an increased risk, as was noted following the initial introduction of LMWH prophylaxis for non-obstetric patients undergoing joint replacement.[36]

The research gaps involving VTE prophylaxis in the obstetric population are substantial. To date, there have been no high-quality studies comparing the impact of mechanical compression devices in obstetric patients with or without heparins after cesarean delivery.[6] In addition, we do not currently have evidence guiding which doses of specific LMWHs, at what time periods, are indicated. A better understanding of the kinetics of all heparins in pregnancy and the immediate postpartum period is needed. One of the few relevant studies showed statistically significant increased bleeding complications in women who received a higher dose of nadroparin (5700 IU immediately pre cesarean and postoperatively) than the same dosing schedule of 5000 IU dalteparin, or alternatively than a lower dose of nadroparin (2850 IU) not earlier than 6–12 h postoperatively.[17] Notably, the mode of anesthesia was not discussed and no SEH was reported.

If we are to learn anything meaningful, and aggregate results of randomized controlled studies, then standardization of obstetric VTE protocols needs to occur first. In their comprehensive review in 2019, Eubanks et al. found 10 different sets of guidelines, even after eliminating reviews, expert opinions and other speculation.[7] Second, a comprehensive capture of all cases of SEH through a national (via the American Society of Anesthesiology or other centralized mechanism) or ideally an international registry must occur so that recurrent patterns and relevant risk factors may be gleaned. Only with a robust and systematic approach will we be able to accrue useful case law that will allow evidence-based obstetric and anesthetic care for women.

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