**Thoracic Epidural and Regional Analgesia in the Patient on a Novel Anticoagulant or Antiplatelet Agent: Is It Worth the Risk?**

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**Stem Case and Key Questions Content**

A 52-year-old male presents for open resection for colon cancer. He has had multiple prior abdominal surgeries and the planned approach is a supraumbilical midline incision that will cover the T6-T10 dermatomes. The patient is obese and has a history of COPD.

Vitals: HR 70, BP 126/68, O2 sat 95% on RA, Ht 6'0", Wt 285 lbs

1) What surgical features and patient factors make this patient a good candidate for a thoracic epidural?

2) What level should this block be placed at? Should it be placed paramedian or midline? What should be infused?

3) Does it matter if the epidural is activated before surgery (pre-emptive analgesia) or after? What are the pros and cons of early dosing?

The patient also has chronic abdominal pain treated with methadone 10 mg three times daily and oxycodone 5-10 mg four times daily. He is very concerned about difficulty with extubation, postoperative pain, and ileus.

Medications: Methadone 10 mg tid, oxycodone 5-10 mg q 6 hrs prn, albuterol inhaler prn, fluticasone/salmeterol inhaler bid, metoprolol XL 50 mg daily

ECG: irregularly irregular @ 70 bpm, QTc 440 ms

4) What patient characteristics suggest the need for postoperative pain control? Will thoracic epidural analgesia decrease ileus? Will it shorten duration of postoperative mechanical ventilation?

5) Does thoracic epidural analgesia affect long-term outcomes such as mortality or chronic postoperative pain?
6) Should his methadone be continued perioperatively if he has a neuraxial block for pain control?
Upon reviewing the ECG and questioning the patient further, he reports a recent diagnosis of atrial fibrillation for which he takes dabigatran 150 mg bid for stroke prevention. His last dose was 7 days prior and he received bridging therapy with lovenox, and though he does not recall the dose, he does note that he received injections twice daily with the last injection 24 hours ago.
Labs: Pltts 168, INR 1.1, Cr 1.0

7) Should this patient receive a neuraxial block given his coagulation profile and medications?

8) What are alternatives to thoracic epidural placement? Why might these be chosen? How are they performed?
It is now four days postoperative and the patient has had his nasogastric tube removed and is tolerating clear liquid diet but still with some nausea. He is hesitant about discontinuing the epidural.

9) How long should the epidural remain? What are the risks? What are appropriate endpoints?
You decide to discontinue the epidural but when you check labs, his INR is now 1.4 and trending down, likely the result of dilution from significant perioperative transfusion and fluid shifts. He is receiving heparin 5000 mg SC bid.

10) How would you approach removing the epidural catheter in this situation?

Model Discussion Content
- Thoracic epidural analgesia is most commonly advocated for open thoracic surgery and abdominal surgery above the umbilicus. It is unclear that it provides significant benefit for laparoscopic or video-assisted procedures. Advantages of epidural analgesia include relief of splinting, decreased opioid use, decreased postoperative ileus, decreased sympathetic tone and increased peristalsis, and retained ability to ambulate versus lumbar epidural with high volume infusion (1). In addition, epidural analgesia may provide particular benefit for patients with pre-existing chronic pain and opioid use who may otherwise prove challenging to manage. Incidence of complications from epidural placement is quite low and includes hematoma, abscess, dural puncture (0.4-1.2%, more common at lower levels), radicular pain, and pneumothorax. The most common documented complication (6.1%) is unsuccessful placement (1).

- Epidural placement in the setting of anticoagulant or antiplatelet agents primarily raises the concern of neuraxial hematoma, which carries an estimated frequency of 1 in 20,000 in the absence of coagulopathy. However in certain populations with risk factors such as old age, female gender, renal insufficiency, and difficult placement, that number can be as frequent as 1 in 3,000 (2). Importantly, should hematoma occur it is likely to happen several days after intervention, not immediately. A low
threshold for suspicion is important as emergent decompression within 8 hours of symptom onset correlates strongly with good neurological recovery. Several consensus guidelines are available to guide practice, including the commonly referenced 2010 American Society of Regional Anesthesia 3rd edition guidelines (3). These provide strong recommendations based on accumulated data for placement and removal of neuraxial catheters and deep plexus blocks in patients on heparin, low molecular weight heparins, and antiplatelet agents (thienopyridines and glycoprotein IIb/IIIa inhibitors). However, increasingly patients are presenting for surgery on newer anticoagulant and antiplatelet agents for which consensus guidelines and data are more limited. At the end of 2014, ASRA released a draft of recommendations for several of the more frequently used new antithrombotic/thrombolytic medications and will publish full 4th edition guidelines in 2016. In cases where there is not much available evidence, five half-lives will be recommended as the interval between dosing and neuraxial block placement/manipulation. Additionally, rational monitoring and testing based on mechanism of action will be proposed to ensure normal coagulation status. Thus use of neuraxial anesthesia in patients receiving these newer medications will be dependent on an understanding of the mechanism and duration of action of these agents, their monitoring and reversibility, and available evidence for safety.

-Dabigatran (Pradaxa) is an oral direct thrombin inhibitor with a long half life of 12-17 hours. It is indicated for stroke prevention in patients with atrial fibrillation. Clearance is renal. ASRA’s pending recommendation will be discontinuation 5 days prior to neuraxial block. PTT and thrombin time, but not INR, can be used to monitor adequate coagulation status (2, 4).

-Rivaroxaban (Xarelto) is an oral non-AT-III dependent factor Xa inhibitor indicated for prevention of stroke and venous thromboembolism. It has a half life of 9-13 hours depending on hepatic and renal clearance. Based on European guidelines, it should be held 22-26 hours prior to intervention and should be resumed no earlier than 4-6 hours after (2, 4). ASRA’s draft guidelines suggest 3 days. In emergency situations, anti-factor Xa assay can be used to assess effect and rivaroxaban can be reversed with prothrombin complex concentrate but this carries a risk for thrombotic/embolic events.

-Apixaban (Eliquis) is a factor Xa inhibitor indicated for treatment and prevention of VTE and thrombotic events in patients with atrial fibrillation. It has a half-life of 9-14 hours. Based on a safety study published in the New England Journal of Medicine, recommendations for interval between dosing and invasive procedures are 2 days for CrCl>60, 3 days for CrCl 50-59, and 5 days for CrCl<49. ASRA’s recommendation is 3 days.

-Dabigatran, rivaroxaban, and apixaban can be re-started 6 hours following neuraxial puncture or catheter removal. Indwelling catheters are not recommended with continued use.

-Fondaparinux (Arixtra) is an injectable (SC) AT-III mediated factor Xa inhibitor used for prevention of venous thromboembolism after orthopedic surgery. It has a 20 hour half life. Initial dose range studies
included a spinal hematoma, leading to further inclusion in subsequent clinical trials only if needle passage was atraumatic, accomplished on the first pass, and catheters were removed 2 hours prior to initiating therapy. If these conditions cannot be assured, neuraxial block in conjunction with its use should be reconsidered. A more recent case series demonstrated safe catheter use so long as any manipulation was 36 hours after last dosing and subsequent dosing held 12 hours (2, 4). ASRA will likely recommend 3-4 days, though this recommendation has not been published as yet. Anti-Xa levels can measure activity and emergency reversal may be possible with recombinant factor VIIa along with tranexamic acid.

- Prasugrel (Effient) is a newer thienopyridine similar to clopidogrel (Plavix) but with significantly faster and stronger, irreversible platelet inhibition - 50% only 2 hours after a single dose and 90% after 7 days. It is indicated for acute coronary syndrome in patients awaiting percutaneous coronary intervention. Though it has a short half-life, 2-15 hours, it should be discontinued 7-10 days in advance of neuraxial intervention per ASRA as its effect on platelets is irreversible (2, 4).

- Ticagrelor (Brilinta) is also a platelet inhibitor, reversible, indicated for prevention of thrombotic events in pts with ACS. Like prasugrel, it produces 90% platelet inhibition compared with 50-60% with clopidogrel. It is liver metabolized with a half-life of 7-9 hours and has an active metabolite. ASRA will recommend 5-7 days and the manufacturer package insert currently states 7 days discontinuation prior to invasive procedures.

- For both prasugrel and ticagrelor, a P2Y12 assay or thromboelastrogram can be used to ensure normal platelet function, with < 20% inhibition considered safe. Emergently, platelet transfusions can be administered. Either can be re-started 6 hours after neuraxial puncture or catheter manipulation and indwelling catheters with ongoing dosing are not recommended.

- Often newer anticoagulant or antiplatelet agents are appropriately held in advance of a surgical procedure and “bridged” with low molecular weight heparin, usually enoxaparin. Note that this bridging dose is often therapeutic (1 mg/kg bid or 1.5 mg/kg daily) and not prophylactic (40 mg/daily) and thus needle placement should occur 24 hours after last dosing. If an indwelling catheter is to remain, dosing may only be resumed if prophylactic and begun > 4 hours after placement (an increase from 2 hours in prior ASRA guidelines) based on an FDA advisory after reviewing manufacturer surveillance data (3).

- In addition to intended anticoagulation, attention should be paid to other medications the patient is taking which may have effects on bleeding time, most commonly by platelet inhibition. These include NSAIDs, SSRIs, SNRIs, TCAs, and various herbal medications. It is unlikely that on their own any of these agents would result in a clinically significant alteration in coagulation status; however, in combination they may pose a concern and in fact, cessation prior to certain high and intermediate risk
pain procedures has been advocated in recent 2015 guidelines endorsed by several regional anesthesia and pain societies, including ASRA and ESRA (5). It should be noted, however, that these guidelines are intended to be applied to outpatient, elective pain procedures, some of which are significantly more invasive than placement of a thoracic epidural catheter. Nonetheless, the recommendations can be helpful as some procedures performed in the in- and out-patient settings do overlap.

- When placing a thoracic epidural, an anatomical review of surface landmarks is helpful: T3 scapular spine, T4 nipple line, T7 inferior scapula, T10 umbilicus. In general, a thoracic epidural is best placed at the interspace that serves the middle of the proposed surgical incision. Placement can be paramedian or midline. Paramedian approach is most frequently used as it avoids sharply angulated spinous processes, allows for loss of resistance at shallower depth, and can be easier to redirect the Tuohy owing to less tissue travel. Midline approach can be used as an alternative approach and can be more familiar for practitioners accustomed to lumbar epidural placement as it does not require triangulation; however, the caudad angle of overlapping spinous processes can make access difficult or impossible at commonly accessed sites between T4-T10 (6). For large incisions, such as esophagectomy or thoraco-abdominal aortic aneurysm, some practitioners advocate placement of two catheters, one in the upper thoracic region and another in the lower, to allow for more reliable coverage of a large incision with a lower overall infusion than attempting spread through one catheter.

- Local anesthetic only or local and opioid are the most commonly used infusions and offer the best evidence for improved analgesia and decreased overall opioid requirements. Opioid only infusions may be used if the patient cannot tolerate local anesthetic due to hypotension, however there is no demonstrable benefit versus parenteral infusion and systemic opioid levels are similar after several hours (7). Opioid choice can be lipophilic vs. hydrophilic, resulting in greater systemic vs. CSF spread. Addition of epinephrine to the infusate decreases systemic absorption. Local anesthetic choice is most commonly bupivicaine vs. levobupivicaine or ropivicaine, which offer better cardiotoxicity profiles. The dose administered epidurally is well below toxic levels regardless, generally 0.1-0.125% at a rate of 4-15 cc/hr. Patient controlled epidural analgesia allows for patients to titrate the block to effect.

- Alternatives to thoracic epidural analgesia include transversus abdominis plane block, intercostal nerve block, paravertebral block, and intrathecal morphine. These blocks have the advantage of being performed as single shot if there is anticipated coagulopathy or if the patient presents for ambulatory surgery. Also, some can be performed unilaterally to minimize systemic hypotension or to limit local anesthetic dose (8). Finally, there is some evidence that complications related to blocks in the anticoagulated patient are primarily related to bleeding and not direct nerve injury, and therefore so long as the structure is compressible the incidence of significant adverse event can be minimized (2). There remains debate as to which approach is superior, but the evidence in general favors epidural >
paravertebral > TAP = intrathecal opioid > PCA, though this may be due in part to greater published literature on epidurals as the technique has been used longer.

- With regards to when to activate a thoracic epidural, the decision is largely based on surgery and patient co-morbidities. If major blood loss or hypotension is not anticipated, then pre-emptive and intra-operative epidural analgesia is often utilized. More commonly, epidural analgesia is instituted at the end of a case once surgical hemostasis has been achieved. In review of current studies, pre-emptive use of thoracic epidural versus post-operative use demonstrates decreased PACU opioid use and pain scores but no evidence of longer term benefit. Discontinuing the epidural is often performed when the patient is tolerating oral intake, nasogastric tube has been removed, chest tubes are out, return of bowel function is documented, or if there is evidence of systemic infection. Infection risk for indwelling catheters are low but increase after the 2nd day and substantially increase after the 4th day, though the overall incidence remains 1 in 10,000. Often coagulation parameters will be perturbed following surgery but so long as coagulation factors remain at 40% of normal, hemostasis is adequate. This level is assured at INR ≤ 1.4 (2, 3).

- In summary, thoracic epidural analgesia can be of significant benefit for thoracic and upper abdominal surgeries. A recent meta-analysis of 2200 patients receiving thoracic epidural analgesia vs. PCA for > 24 hours after surgery requiring general anesthesia demonstrated decreased mortality, 3.1% vs. 4.9%, OR 0.6 (9). Other documented positive outcomes include decreased incidence of pneumonia and duration of mechanical ventilation, decreased postoperative ileus in abdominal surgery (opioid sparing effects) decreased mortality for rib fractures (particularly if >5 ribs), decreased incidence of atrial fibrillation (sympathectomy), decreased incidence of DVT (increased mobility), and increased patient satisfaction (10). It does bear noting that no effect on development of chronic pain has yet been demonstrated. The benefit appears greatest in the sickest pts and though there is a high NNT for mortality benefit, this is balanced by an exceedingly low complication rate for most patients. In the setting of new anticoagulant and antiplatelet agents with long duration of action and limited pharmacologic reversibility, however, the risk can be substantially higher than the usual quoted figures. Careful and individual attention to the risk/benefit is warranted.

References