Case Report

The Potential Contributing Effect of Ketorolac and Fluoxetine to a Spinal Epidural Hematoma following a Cervical Interlaminar Epidural Steroid Injection: A Case Report and Narrative Review

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Cervical interlaminar epidural steroid injections (ESIs) are commonly performed as one part of a multi-modal analgesic regimen in the management of upper extremity radicular pain. Spinal epidural hematoma (SEH) is a rare complication with a reported incidence ranging from 1.38 in 10,000 to 1 in 190,000 epidurals. Current American Society of Regional Anesthesia (ASRA), American Society of Interventional Pain Physicians (ASIPP), and the International Spine Intervention Society (ISIS) recommendations are that non-steroidal anti-inflammatory drugs (NSAIDs) do not need to be withheld prior to epidural anesthesia. We report a case wherein intramuscular ketorolac and oral fluoxetine contributed to a SEH and tetraplegia following a cervical interlaminar (ESI).

A 66 year-old woman with chronic renal insufficiency and neck pain radiating into her right upper extremity presented for evaluation and was deemed an appropriate CESI candidate. Cervical magnetic resonance imaging (MRI) revealed multi-level neuroforaminal stenosis and degenerative intervertebral discs. Utilizing a loss of resistance to saline technique, an 18-gauge Tuohy-type needle entered the epidural space at C6-7. After negative aspiration, 4 mL of saline with 80 mg of methyl-prednisolone was injected. Immediately thereafter, the patient reported significant spasmodic-type localized neck pain with no neurologic status changes.

A decision was made to administer 30 mg intramuscular ketorolac as treatment for the spasmodic-type pain. En route home, she developed a sudden onset of acute tetraplegia. She was brought to the emergency department for evaluation including platelet and coagulation studies which were normal. MRI demonstrated an epidural hematoma extending from C5 to T7. She underwent a bilateral C5-T6 laminectomy with epidural hematoma evacuation and was discharged to an acute inpatient rehabilitation hospital. Chronic renal insufficiency, spinal stenosis, female gender, and increasing age have been identified as risk factors for SEH following epidural anesthesia. In the present case, it is postulated that after the spinal vascular system was penetrated, hemostasis was compromised by the combined antiplatelet effects of ketorolac, fluoxetine, fish oil, and vitamin E.

Although generally well tolerated, the role of ketorolac, a potent anti-platelet medication used for pain relief in the peri-neuraxial intervention period, should be seriously scrutinized when other analgesic options are readily available. Although the increased risk of bleeding for the alternative medications are minimal, they are nevertheless well documented. Additionally, their additive impairment on hemostasis has not been well characterized. Withholding NSAIDs, fluoxetine, fish oil, and vitamin E in the peri-procedural period is relatively low risk and should be considered for all patients with multiple risk factors for SEH.

Key words: Spontaneous epidural hematoma, ketorolac, cervical interlaminar epidural steroid injection, fluoxetine, anti-platelet, neuraxial injection, perioperative pain

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The use of epidural steroid injections (ESIs) for the management of chronic spinal pain has increased significantly in the past 15 years. Presently, there are more than 2 million ESIs performed annually in the Medicare population alone; approximately 250,000 of those in the cervical and thoracic spine (1). Although catastrophic complications following ESI are rare, a parallel increase in adverse events has been reported with the growing prevalence of these procedures. The consequences of these complications have included permanent paraplegia, tetraplegia, and death. Spinal epidural hematoma (SEH) is a rare complication with published rates between 1.38 in 10,000 to 1 in 250,000 epidural procedures (2,3). We describe a case of epidural hematoma and tetraplegia following a cervical interlaminar ESI wherein the current major interventional guidelines regarding anticoagulation use were adhered to.

Case Description

A 66-year-old woman with chronic low back and neck pain radiating down her right arm presented to an ambulatory surgical center for an elective cervical ESI. Her symptoms began at the age of 26 following a motor vehicle accident. Her co-morbidities included chronic renal insufficiency (GFR = 50), fibromyalgia, seizure disorder, nephrolithiasis, hypertension, glaucoma, hypothyroidism, sleep apnea, and chronic obstructive pulmonary disease. She had no history of coagulopathy, liver disease, use of anti-platelet medication, or recent anticoagulation use. Her past surgical history included cholecystectomy, hysterectomy, cystoscopy with ureteral stent placement, left knee arthroplasty, and right ankle fixation after fracture. Her home medications included levothyroxine, atorvastatin, seroquel, carvedilol, ferrous sulfate, gabapentin, docusate, fentanyl patch, carisoprodol, fluoxetine, and omeprazole. She also supplemented daily with a multivitamin (50 IU of vitamin E), and one gram of fish oil. She had no history of tobacco, drug, or alcohol abuse.

Cervical and lumbar magnetic resonance imaging (MRI) revealed multi-level cervical and lumbar neuroforaminal stenosis and central spinal canal stenosis. A recent worsening of the radiculitis into her right arm and bilateral lower extremities prompted an evaluation by an interventional pain physician. She had over the course of 3 years, 5 interlaminar (ESIs) for cervical and lumbar radicular pain with satisfactory results. Previous cervical injections were performed at the C7-T1 interspace using fluoroscopic guidance.

On the day of the sixth injection, the patient underwent an uneventful interlaminar ESI at the L4-L5 level, with injection of 4 mL of preservative-free normal saline with 80 mg of methylprednisolone acetate. Due to the patient's limited access to transportation and increased symptomatology, a decision was made to address both her cervical and lumbar pain at the same setting. Thus, she also received an interlaminar ESI in the midline at the C6-C7 interspace. After performing a sterile preparation and local skin infiltration of 1% lidocaine, the epidural space was entered with an 18-gauge Tuohy-type epidural needle using the loss of resistance to saline technique. Biplanar fluoroscopy with non-iodinated contrast was utilized to localize the level and assure entry into the epidural space. There was no reported blood, paresthesias, or cerebrospinal fluid noted during needle advancement. After negative aspiration, 4 mL of preservative-free normal saline with 80 mg of methylprednisolone acetate was injected into the epidural space, after which the needle was flushed with one mL of normal saline before being withdrawn.

Following the procedure, the patient reported significant pain and muscle spasms at the cervical injection site, and 30 mg of intramuscular ketorolac was administered for pain relief. Her symptoms apparently resolved and she was able to stand and walk without difficulty or complaints. Following a 15-minute observation period, she was discharged home.

While en route home, the patient began to experience numbness and weakness in her lower extremities. She was taken to the emergency department where physical exam revealed abrupt-onset tetraplegia and a sensory loss below the xiphoid process. She did not withdraw to painful stimuli in any extremity and rectal tone was absent. Laboratory values revealed a normal chemistry panel, normal prothrombin and activated partial thromboplastin time, and a normal bleeding time. Cervicothoracic MRI demonstrated an epidural hematoma extending from the C5 to T7 posterior cord level with the most severe compression being noted at the T2 level (Figs. 1 and 2).

Surgical decompression was performed 12 hours after the onset of symptoms, including bilateral C5-T6 laminectomies with evacuation of the epidural hematoma and decompression of the thecal sac. Postoperatively, the patient was noted to have return of some bilateral upper extremity movement. Once medically stabilized, she was discharged to participate in an intensive acute inpatient rehabilitation (AIR) program, and by discharge from the AIR she had regained nearly

full proximal and 1²/₅ distal upper extremity strength, but remained paralyzed in her lower extremities and incontinent of bowel and bladder function.

Discussion

Incidence

The incidence of spinal-epidural hematoma (SEH) has been estimated to be 1:220,000 after a spinal block and 1:150,000 after an epidural block (4). Wulf reported the incidence of SEH to be 1:190,000 after epidural anesthesia (5). Scott and Hibbard reported an incidence of 1:250,000 in the obstetrical population in the United Kingdom (3). Certainly other studies have demonstrated a much more prevalent rate of SEH. A 2013 publication by Ehrenfeldet et al retrospectively reviewed 43,200 patient charts spanning a 9 year period, and reported a SEH incidence of 1.38 in 10,000 epidural catheterizations (2).

However, the incidence of SEH specifically as a complication of ESI has not being defined. Large case series of serial cervical ESIs ranging from 141 to 790 patients have reported no associated serious neurologic complications, including SEH (6,7). In a meta-analysis performed by Xu et al (8) encompassing all relevant literature in PubMed and MedWatch, 8 cases of neuraxial hematoma following epidural injection were identified.

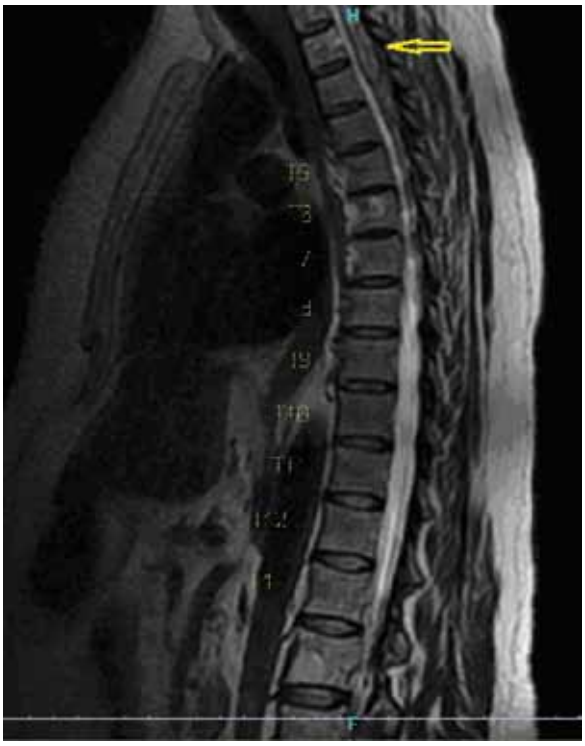

Fig. 1. *Sagittal T2-weighted MRI of posterior epidural hematoma. Arrow points to greatest point of cord compression due to anterior-posterior hematoma collection at approximately T2.*

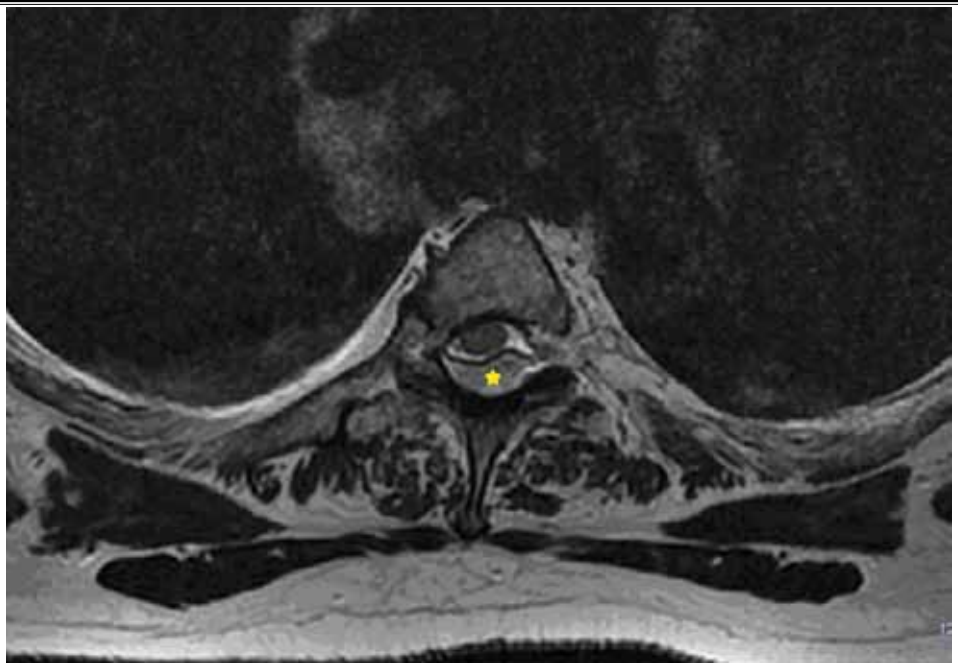

Fig. 2. *Axial T2 weighted MRI showing large epidural hematoma (marked by a star).*

Four cases involved the cervical spine, 4 cases involved the thoracic or lumbar spine, and one case did not describe the level of the hematoma. However, physicians have a tendency to avoid reporting poor outcomes due to health privacy issues and fear of litigation (9). Furthermore, the complications may be reported to different databases making the general analysis even more difficult (10). Review of data from the American Society of Anesthesiologists (ASA) Closed Claims Projects shows that between 1970 and 2000, there were 6 claims for paraplegia or quadriplegia due to epidural hematoma resulting from an interventional pain management procedure (11). In reviewing this database between 2005 and 2008, Rathmell et al (9) reported 3 cases of compressive epidural hematoma due to cervical injections. The ASA Closed Claims database, however, does not provide a reasonably reliable estimate of the numerator (number of these types of complications) or denominator (number of total cases performed) for any given population of patients in any given geographical area. Additionally, like physicians, patients also underreport complications, and thus, these data also likely represent an underestimation of the prevalence of complications due to ESI.

Etiology

Various mechanisms have been suggested to account for SEH (12-15) (Table 1) including unrestrained epidural venous and arterial bleeding, as well as bleeding from arterio-venous malformations. Groen and Ponssen (16) proposed the posterior internal vertebral venous plexus as the most likely source of bleeding. Beatty and Winston (17) argued that venous pressure is less than intrathecal pressure, and thus venous bleeding should not be capable of causing acute spinal cord compression. They subsequently suggested an arterial origin of SEH. In support of this theory, U and Wilson (18) reported 3 cases of SEH with bleeding arising from arteries in the posterior longitudinal ligament following anterior discectomy.

Table 1. Reported causes of epidural hematoma.

Reported Causes of Epidural Hematoma
Spinal surgery
Spinal/epidural injection/anesthesia
Trauma
Spontaneous
Arterial venous malformation
Lumbar puncture
Myelography
Spinal manipulation

Risk Factors

Several risk factors have been reported for SEH: anticoagulation medication use, anatomic abnormalities of the spinal cord and vertebral column, difficult or repeated spinal puncture, larger needle size, older age, the use of indwelling epidural catheters as opposed to "single shot" injections, intrinsic thrombocytopenia or platelet dysfunction related to idiopathic thrombocytopenic purpura, and renal failure, respectively, as well as coagulopathy related to hemophilia A (19-22). In a review of 613 cases published between 1826 and 1993, Kreppel et al (15) reported SEH to be idiopathic or spontaneous in 30% of cases, related to anticoagulation in 17%, and related to spinal or epidural anesthesia in 10% of cases. In cases associated with epidural anesthesia, traumatic procedures and anticoagulation status represented the greatest risk factor for SEH. Vandermeulen et al (23) reported 61 cases of SEH after epidural or subarachnoid block. Eighty-seven percent of these patients had pre-existing coagulopathies or traumatic needle insertions (23). Wulf (5) reviewed the medical literature between 1966 and 1995, and reported 51 confirmed cases of spinal hematoma associated with epidural anesthesia. Factors associated with SEH in this group included: difficult or traumatic catheter insertion (n = 21), intravenous heparin therapy (n = 18), coagulopathy (n = 14), thrombocytopenia (n = 5), aspirin or other non-steroidal anti-inflammatory drug (NSAID) use (n = 3), low molecular weight heparin use (LMWH) (n = 2), and fibrinolytic therapy (n = 2) (5). Stafford-Smith reported an 11-fold increased risk in patients who were not anticoagulated and a 35-fold increased risk in patients who were anticoagulated (24).

Risk factors for SEH due specifically to ESIs have not been clearly described, but are likely similar to those reported for epidural anesthesia. Cervical ESI may be associated with a higher relative incidence of SEH compared to thoracic or lumbosacral ESI. From an anatomic standpoint, the spinal cord is most vulnerable to compression in the cervical region given the relatively smaller diameter of the spinal canal including a smaller diameter peridural space in this area compared to thoracic and lumbar levels (25). A study of 10 cadaver specimens suggested that cervical ESIs may also pose a relatively higher risk of hemorrhagic complication due to an observed high frequency of anatomical variation of arteries within the spinal canal in this area compared with the thoracic and lumbar regions (26). The fact that half of the reported cases of SEH (4 of the 8 cases) associated with ESI occurred following injection in the cervi-

cal region, despite the relative infrequency of cervical compared to lumbosacral ESI, supports these 2 findings.

In 2010 Green and Machin (27) described the management of anticoagulation in patients during neuraxial anesthesia. They recommended that the decisions regarding anticoagulation and neuraxial interventions must take into account the risk of bleeding versus venous/arterial thrombosis if anticoagulation therapies were to be stopped, and recommended taking into account case-by-case risk factors. In their review, they identified multiple patient-related risk factors associated with SEH such as advanced age, female gender, acquired coagulopathy, thrombocytopenia, spinal abnormalities such as spina bifida, spinal stenosis, ankylosing spondylitis, and osteoporosis. They also described procedure-related risk factors including a traumatic procedure with multiple attempts, presence of blood in the needle or the catheter, and use of an indwelling epidural catheter (27).

Patient Factors

Our patient had multiple identified risk factors for the development of SEH after epidural anesthesia, including advanced age, chronic renal insufficiency, female gender, and spinal stenosis. Spinal stenosis, as found in our patient also increases the risk for a deleterious outcome in any case of epidural hematoma. Elevated blood levels of uric acid as found in renal disease can also impair hemostasis. Unfortunately, a uric acid level was not obtained on our patient.

Needle Selection for Epidural Injection

The type of needle used for epidural injection is a consideration in attempting to minimize the risk of epidural hematoma formation. The ideal needle type remains undetermined. Most practitioners prefer using a standard 18 gauge Tuohy-type needle for epidural injections. Some interventionalists advocate for the use of short-beveled, blunt-type, or smaller diameter needles (less than 22-gauge) to reduce the risk of vessel trauma (28,29). In a prospective study conducted on 1,088 patients, that included 2,145 lumbar transforaminal ESIs using a Quincke-type spinal needle, the incidence of vascular penetration with intravascular injection was found to be 6.1% during lumbar transforaminal ESI (30). However, Smuck et al (31) found that short-bevel needles compared to long-bevel needles did not reduce the risk of unintentional vascular penetration in lumbosacral transforaminal epidural injections. Similarly, in a prospective study of 2,376 interlaminar cervical ESIs, Manchikanti et al found no significant hemorrhagic complications including SEH, regardless of needle type (32).

Entry Level of Cervical Epidural Injection

The level of entry in accessing the epidural space during injection may influence the rate of epidural hematoma formation. Practitioners commonly choose to inject into the epidural space at the C6-C7 or the C7-T1 levels. Anatomical characteristics of the epidural space at the C7-T1 level indicate that it may be the safest level to inject. Some fat (1 – 2 mm) may be found at the C7-T1 level but not above (33). This epidural fat creates a larger potential space for injection. Evidence from cadaver studies has shown that the ligamentum flavum, the landmark for the loss-of-resistance technique, frequently fails to fuse in the midline over the cervical interspaces. In dissections, midline gaps were observed in more than 50% of specimens (34). Thus, for cervical injections, the epidural space may be easiest to locate at the C7-T1 level and selecting this level may decrease the risk of hemorrhagic complications, though this has not been formally studied.

Imaging

Imaging with fluoroscopy or computed tomography (CT) scanning has become the standard of care for most interventional neuraxial procedures (35). Epidural injections by trained practitioners without image guidance results in misplacement of the needle tip in up to 40% of cases, whereas fluoroscopy improves the accuracy of needle placement for interlaminar cervical ESI, with ventral epidural spread noted 28% – 93% of the time (36-39). Contrast dye in conjunction with continuous, or "live" fluoroscopy, as well as digital subtraction angiography (DSA) techniques have been shown to identify intravascular injection (40-42). However, these visual aides are not foolproof (43), and remain unlikely to identify vascular compromise or a compressive hematoma, which typically occur immediately post-procedure. Traditional fluoroscopy by itself cannot identify hematoma development.

Medication-Related Risk Factors

Major pharmacologic classes investigated as possible risk factors for the development of SEH in the face of neuraxial procedures have included anti-thrombotic agents including warfarin, heparin, low molecular weight heparin, as well as anti-platelet agents including aspirin and NSAIDs. Guidelines and recommendations have been put forth by many organizations in-

cluding the American Society of Regional Anesthesia (ASRA), American Society of Interventional Pain Physicians (ASIPP), European Society of Anesthesia (ESA), the International Spine Intervention Society (ISIS), and the Nordic Guidelines from the Scandinavian Society of Anaesthesiology and Intensive Care Medicine (44-48).

Anti-platelet Agents

Conflicting evidence exists as to whether NSAIDs increase the risk of epidural hematoma formation. In a prospective study, Horlocker et al (49) found no hemorrhagic complications in 1,035 patients who underwent ESI despite the fact that 384 (32%) were taking aspirin or other NSAIDs. One hundred thirty-five had taken ibuprofen, 134 had taken aspirin, 59 had taken naproxen, 10 had taken diclofenac, one had taken indomethacin, and none had taken clopidogrel or ticlopidine. The authors concluded that ESIs are safe in patients receiving aspirin-like antiplatelet medications (49). Chin et al (50) report a prospective study of 44 patients who received a single 30 mg dose of ketorolac after microdiscectomy surgery and who experienced no hemorrhagic complications. Consistent with the findings of these studies, the ASRA guidelines state that there is grade 1-A evidence (strong evidence) that NSAIDs alone add no significant risk for the development of spinal hematoma in patients undergoing neuraxial blocks (44).

Guidelines from the Scandinavian Society of Anesthesiology and Intensive Care Medicine were published in 2010. They recommended that NSAIDs be discontinued before central neuraxial blockade, with a drug-free interval no less than 24 hours following indomethacin, ketorolac, and lornoxicam use. Additionally, they recommended that a non-selective NSAID be replaced by another analgesic in the immediate perioperative period (48).

According to a 2013 comprehensive review published by the ASIPP, NSAIDs and low dose aspirin when given in isolation, do not increase the risk of SEH and are not a contraindication for interventional techniques. This review does support that the simultaneous use of multiple agents that possess anticoagulant properties (e.g. NSAIDs or aspirin along with SSRIs, fish oil, etc.) increase the risk of morbidity and/or mortality and that consideration for discontinuation should be based on clinical assessment of an individual's risk and benefits (45).

According to the ESA 2010 guidelines, holding a dose the evening prior to a procedure is sufficient "to avoid any negative effect of non-aspirin NSAIDS on platelet function and neuraxial block" (46). Given the low incidence of SEH, it is possible that most studies to date have been too small to demonstrate this complication in association with NSAID use. Additionally, few subjects had been taking anti-platelet agents other than aspirin or ibuprofen. Notably, in the 4 reported cases of SEH after cervical ESI, all were associated with NSAID usage (8). Cases of SEH after ESI or epidural anesthesia have been described in patients who had received aspirin, indomethacin, and IV ketorolac (23,51,52). With regards to stronger anti-platelet agents, the ASRA guidelines recommend that clopidogrel be held for a minimum of 7 days and ticlopidine for 14 days prior to neuraxial blockade (44). Formal guidelines specific to ESI have not been created.

According to the ISIS book of best practices there is no need to cease NSAIDs before spinal diagnostic or treatment procedures (47).

Ketorolac

Ketorolac is one of the few parenteral NSAID available for use in the United States (53). Like many other NSAIDs, it is a reversible non-selective cyclooxygenase enzyme (COX) inhibitor, with a potent anti-platelet effect (54) and associated with an increased risk for bleeding. The increased bleeding risk for ketorolac is multi-modal. Both biosynthesis of thromboxane A2 (TXA2) and collagen-induced platelet aggregation are impaired (55). Ketorolac has been shown to be more active than aspirin in inhibiting arachidonic acid-induced platelet aggregation (56). In a double-blind placebo controlled trial, Conrad et al (56) randomized 26 healthy volunteers to ketorolac 30 mg intramuscular (IM) 4 times a day to 8 healthy volunteers given two 325mg capsules of oral aspirin. Aspirin at a mean serum concentration of 84 mcg/mL did not affect prothrombin time (PT), partial thromboplastin time (PTT), platelet count, or bleeding time. Ketorolac produced prolongation of the bleeding time, from 4.9 ± 1.1 minutes (mean ± SD) to 7.8 ± 4.0 minutes ($P < 0.005$). Ketorolac did not affect the PT or PTT (56). This study is supported by Singer et al (53), who gave a single IM dose of 60 mg of ketorolac to 20 healthy volunteers. Median baseline bleeding time was 3 minutes 34 seconds (+/- 1 min 20 sec). Mean 4-hour post-injection bleeding time increased to 5 minutes 20 seconds (+/- 3 min 8 sec). The mean prolongation of bleeding time was 1 minute 46 seconds, representing a 50% increase (53).

The IM form of ketorolac is rapidly and completely absorbed. Peak plasma concentrations occur on aver-

age 50 minutes after a single 30 mg dose. The terminal plasma half-life is in the range of 5 – 6 hours (57). In the elderly the mean terminal plasma half-life increases from 5 to 7 hours, whereas in renally-impaired patients, the mean half-life is between 6 and 19 hours, dependent on the extent of the impairment. There is a poor correlation between creatinine clearance and total ketorolac clearance in the elderly with renal impairment. Ketorolac is contraindicated in patients with moderate or severe renal impairment (serum creatinine > 180 micromole/L) (58).

Platelet function inhibition by ketorolac resolves within 24 to 48 hours after the medicine is discontinued. Postoperative wound hemorrhage has been reported in association with the immediate perioperative use of IM ketorolac. The manufacturer packet insert cautions use where strict hemostasis is critical (58).

Selective Serotonin Reuptake Inhibitors

Serotonin is an integral component in the hemostatic cascade. It is released from dense intracellular granules and acts as a platelet agonist, causing the activation and recruitment of additional platelets. This anti-platelet effect may explain why bleeding and bruising (59) and possibly even treatment of acute coronary syndrome have been reported for patients taking selective serotonin reuptake inhibitors (SSRIs) (60,61).

SSRIs have been shown to have a significant effect on platelet aggregation and thus primary hemostasis (60-63). SSRIs deplete serotonin in platelets, decreasing platelet-binding affinity, and platelet secretion (64,65). Paroxetine has been shown to decrease intra-platelet serotonin concentrations by -83% ($P < .01$), and inhibit platelet plug formation as reflected by a 31% prolongation of closure time (66).

A multi-center retrospective study by Auerbach et al (67) was recently conducted to examine the perioperative use of SSRIs. These authors analyzed more than 500,000 patients and found that patients receiving SSRIs had increased risk for adverse events, including higher odds of bleeding (1.09 [1.04 – 1.15]) (67). Although the ASRA guidelines do not mention SSRIs in their discussion, current ESA guidelines do not currently consider SSRIs alone a contraindication to neuraxial blockade (46).

Dietary Supplements

Dietary supplements such has fish oil, vitamin E, gingko biloba, garlic, ginseng, and magnesium have been shown to alter coagulation at various points in the cascade (68-73).

Fish oils have been demonstrated to impair hemostasis. These effects are attributed to the bioactive ingredients docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). The hemostatic properties reported include a hypocoagulant effect (74), reduction in vitro-platelet aggregation (75), and prolongation of bleeding time in humans (76). These effects are augmented for fish oil in combination with antiplatelet/antithrombotic agents (74-76). Even so, these effects have not been demonstrated to have any clinically significant impact on bleeding, even in patients being treated with antiplatelet or antithrombotic agents (77).

Vitamin E refers to a group of fat-soluble compounds that are found naturally in 8 chemical forms: alpha-, beta-, gamma-, and delta-tocopherol and alpha-, beta-, gamma-, and delta-tocotrienol. The daily recommended dietary allowance of vitamin E in adults is 22.4 IU (15 mg) per day, and the tolerable upper intake level is 1,500 IU (1000 mg) per day (78,79). Vitamin E has been demonstrated to reduce platelet adhesion to endothelial cells (73), increase bleeding time (80), and inhibit platelet aggregation (81). In a randomized, double-blind study volunteers that took 265 mg/day of vitamin E with 325 mg aspirin for 2 years demonstrated a significant decrease in platelet adhesion compared with volunteers that took 325 mg of aspirin alone (81). Vitamin E has been shown to possess dose-dependent inhibition of platelet aggregation by altering arachidonic acid production (82-84).

Discussion

SEH is a rare complication following interventional neuraxial procedures. However, unrecognized SEH can lead to permanent neurologic sequelae. The interventionalist should be wary of evolving signs and symptoms such as excessive pain or progressive extremity weakness and should refer these patients for emergent imaging. Early decompression, within 8 hours of onset of symptoms, increases the likelihood of favorable outcomes (10,44). In the present case, it is postulated that after the dense venous plexus in the dorsal epidural space was penetrated, hemostasis was compromised by the combined potent anti-platelet effects of ketorolac and fluoxetine. Fish oil and vitamin E may have contributed to impaired hemostasis in our patient, but their precise increase in risk is difficult to quantify. The use of a blunt needle theoretically may decrease the incidence of traumatizing the rich venous plexus in the dorsal spinal space. Utilizing a higher gauge (and hence smaller) needle may also play a role, but this is difficult to dis-

cern. Repeated attempts have been suggested as a risk factor for SEH, but it is impossible to determine an upper limit of attempts that is still safe.

While fluoroscopy itself is unable to reliably detect vascular compromise and an epidural hematoma, it nevertheless represents the state-of-the-art imaging modality used in contemporary interventional practice, and should likely be used in every case of ESI procedures (cervical, thoracic, lumbar, caudal) except in exceedingly rare circumstances (such as ESI performed in the pregnant patient when the benefits are determined to outweigh the risks of proceeding).

Most data on the risks of anti-platelet medication and bleeding have been reported on aspirin and clopidogrel. The effects of non-aspirin NSAIDs are much less studied. Comparative anti-platelet pharmacokinetics does not exist for many of the non-aspirin NSAIDs. Even so, data suggest that ketorolac is a more potent agent than azapropazone, dipyrone, and aspirin (56,85,86).

In our case, the reported coagulation panel, including bleeding time, was normal. Bleeding time is an antiquated, yet still occasionally useful, test for assessing platelet function in patients with hemorrhagic disorders and has been used to assess patients for clinically significant bleeding tendencies before invasive procedures. Even so, the test is subject to reliability and reproducibility issues, with a number of studies showing that it is neither a specific nor a sensitive indicator of bleeding risk associated with invasive procedures (87). Thus, a normal bleeding time does not exclude the possibility of excessive hemorrhage with invasive procedures, nor can it be used to reliably identify patients who may have recently ingested aspirin or other NSAIDs, or those who have a platelet defect attributable to these drugs (88,89).

Both ketorolac, acting on thromboxane A2 (TXA2), and fluoxetine, depleting intracellular serotonin, act on the same pathway in primary hemostasis, that being platelet aggregation. As previously discussed, vitamin E and fish oils also impair platelet function. It is possible that a synergistic mechanism of platelet aggregation inhibition led to a far greater impaired hemostasis and the evolution of SEH in this patient than what may have occurred if each agent had been used exclusively. Furthermore, standard coagulation studies may not identify any increased risk of bleeding with these agents. Future investigation into the additive anti-platelet effect of non-aspirin NSAIDs, SSRIs, and common dietary supplements is necessary.

Current guidelines specific to ESIs have not been created and perhaps need to stratify risk when patients have multiple risk factors such as renal disease, advanced age, spinal stenosis, and consumption of multiple agents that impair hemostasis. Investigation to stratify bleeding risk based on these factors may decrease incidence of SEH. The dilemma with holding of anticoagulation or antiplatelet medication is most critical in patients who are receiving them for thromboprophylaxis against severe causes of morbidity and mortality such as cerebrovascular and cardiovascular thromboembolic events. In the setting where NSAID use is not for prevention of these catastrophes, an alternate analgesic medication or modality could represent a more prudent option. The interventional pain physician should consider temporarily withholding, in part or completely, NSAIDs, SSRIs, fish oil, and vitamin E in a patient with multiple risk factors for SEH, as long as withholding them has low potential for morbidity.

Although the multiple societal guidelines discussed do not preclude the use of NSAIDs for neuraxial procedures, the practice patterns of clinicians reveal a much more conservative stance. In 2012, the results of a survey of 325 members of ASIPP were published. Within this cohort of physicians, 60% discontinued aspirin 350 mg, 39% aspirin 81 mg, and 39% discontinued other NSAIDs, ranging from 3 to 10 days prior to performing interventional pain management techniques (90). Additionally, among 55 reported cases of epidural hematoma, in 26 of them antiplatelet therapy was not withheld.

Conclusion

The role of analgesics with anti-platelet activity in the peri-neuraxial intervention stage should be reconsidered when other options are readily available. Careful monitoring of neurologic status prior to discharge home should be observed, especially in cases where pain or other symptoms may portend an evolving complication.

This case report should stimulate future preparations and updates of society-sponsored guidelines to consider analysis of individual NSAIDs based on unique anti-platelet pharmacokinetics and the study of additive effects of multiple pro-coagulant agents.

References

1. Manchikanti L, Pampati V, Falco FJ, Hirsch JA. Assessment of the growth of epidural injections in the medicare population from 2000 to 2011. *Pain Physician* 2013; 16:E349-E364.
2. Ehrenfeld JM, Agarwal AK, Henneman JP, Sandberg WS. Estimating the incidence of suspected epidural hematoma and the hidden imaging cost of epidural catheterization: A retrospective review of 43,200 cases. *Reg Anesth Pain Med* 2013; 38:409-414.
3. Scott DB, Hibbard BM. Serious non-fatal complications associated with extradural block in obstetric practice. *Brit J Anaesth* 1990; 64:537-541.
4. Ehrenfeld JM, STryba M, Wedel DJ. Central neuraxial block and low molecular weight heparin (enoxaparine): Lessons to be learned from different dosage regimens in two continents. *Acta Anaesthesiol Scand* 1997; 111:100-104.
5. Wulf H. Epidural anesthesia and spinal haematoma. *Can J Anaesth* 1996; 42:1260-1273.
6. Waldman SD. Complication of cervical epidural nerve blocks: A prospective study of 790 consecutive blocks. *RegAnaesth* 1989; 14:149-151.
7. Catchlove RFH, Braha R. The use of cervical epidural nerve blocks in the management of chronic head and neck pain. *Can AnaesthSoc J* 1984; 31:188-191.
8. Xu R, Bydon M, Gokaslan ZL, Wolinsky JP, Witham TF, Bydon A. Epidural steroid injection resulting in epidural hematoma in a patient despite strict adherence to anticoagulation guidelines. *J Neurosurg Spine* 2009; 11:358-364
9. Rathmell JP, Michna E, Fitzgibbon DR, Stephens LS, Posner KL, Domino KB. Injury and liability associated with cervical procedures for chronic pain. *Anesthesiology* 2011; 114:918-926.
10. Araujo M, More-O'Ferrall D, Richeimer, S. Complications of interventional pain management procedures. *Advances in Anesthesia* 2008; 26:1-30.
11. Fitzgibbon DR. Chronic pain management: ASA closed claims project. *Anesthesiology* 2004; 100:98-105.
12. Chan L, Bailin MT. Spinal epidural hematoma following central neuraxial blockade and subcutaneous enoxaparin: A case report. *J Clin Anesth* 2004; 16:382-385.
13. Cullen DJ, Bodganov E, Htut N. Spinal epidural hematoma occurrence in the absence of known risk factors: A case series. *J Clin Anesth* 2004; 16:376-381.
14. Cywinski JB, Parker BM, Lozada LJ. Spontaneous spinal epidural hematoma in a pregnant patient. *J Clin Anesth* 2004; 16:371-375.
15. Kreppel D, Antoniadis G, Seeling W. Spinal hematoma: A literature survey with meta-analysis of 613 patients. *Neuorsurg Rev* 2003; 26:1-49.
16. Groen RJ, Ponssen H. The spontaneous spinal epidural hematoma. A study of the etiology. *J Neurol Sci* 1990; 98:121-138.
17. Beatty RM, Winston KR. Spontaneous cervical epidural hematoma. A consideration of etiology. *J Neurosurg* 1984; 61:143-148.
18. U HS, Wilson CB. Postoperative epidural hematoma as a complication of anterior cervical discectomy. Report of three cases. *J Neurosurg* 1978; 49:288-291.
19. Horlocker TT, Wedel DJ. Neuraxial block and low-molecular weight-heparin: Balancing perioperative analgesia and thromboprophylaxis. *Reg Anesth Pain Med* 1998; 23:164-177.
20. Yoo HS, Park SW, Han JH, Chung JY, Yi JW, Kang JM, Lee BJ, Kim DO. Paraplegia caused by an epidural hematoma in a patient with unrecognized chronic idiopathic thrombocytopenic purpura following an epidural steroid injection. *Spine* 2009; 34:E376-E379.
21. Takahashi K, Koewa F, Tayama H, Satomi A, Akizawa T, Ideura T. A case of acute spontaneous epidural haematoma in a chronic renal failure paitent undergoing haemodialysis: successful outcomes with surgical management. *Nephrol Dial Transplant* 1999; 14:2499-2501.
22. Yokota S, Hirabayashi Y, Wakata M, Maruyama Y, Mukoyama A, Nomura M, Hamada S, Ijichi N, Matsumoto T, Shima M. Mild hemophilia A diagnosed at the onset of acute epidural hematoma after lumbar epidural block. *Rinsho Ketsueki* 2011; 52:78-83.
23. Vandermeulen EP, Van Aken H, Vermylen J. Anticoagulants and spinal-epidural anesthesia. *Anesth Analg* 1994; 79:1165-1177.
24. Stafford-Smith M. Impaired haemostasis and regional anaesthesia. *Can J Anaesth* 1996; 43:R129-R141.
25. Stoll A, Sanchez M. Epidural hematoma after epidural block: Implications for its use in pain management. *Surg Neurol* 2002; 57:235-240.
26. Huntoon MA. Anatomy of the cervical intervertebral foramina: Vulnerable arteries and ischemic neurologic injuries after transforaminal epidural injections. *Pain* 2005; 117:104-111.
27. Green L, Machin SJ. Managing anticoagulated patients during neuraxial anaesthesia. *Br J Haematol* 2010; 149:195-208.
28. Tiso RL, Cutler T, Catania JA, Whalen K. Adverse central nervous system sequelae after selective transforaminal block: The role of corticosteroids. *Spine J* 2004; 4:468-474.
29. Quintero N, Laffont I, Bouhmidi L, Rech C, Schneider AE, Gavardin T, Dizien O. Transforaminal epidural steroid injection and paraplegia: Case report and bibliographic review [in French]. *Ann Readapt Med Phys* 2006; 49:242-247.
30. Nahm FS, Lee CJ, Lee SH, Kim TH, Sim WS, Cho HS, Park SY, Kim YC, Lee SC. Risk of intravascular injection in transforaminal epidural injections. *Anaesthesia* 2010; 65:917-921.
31. Smuck M, Yu AJ, Tang CT, Zemper E. Influence of needle type on the incidence of intravascular injection during transforaminal epidural injections: A comparison of short-bevel and long-bevel needles *Spine J* 2010; 10:367-371.
32. Manchikanti L, Malla Y, Wargo BW, Cash KA, Pampati V, Fellows B. A prospective evaluation of complications of 10,000 fluoroscopically directed epidural injections. *Pain Physician* 2012; 15:131-140.
33. Reina MA, Franco CD, López A, Dé Andrés JA, van Zundert A. Clinical implications of epidural fat in the spinal canal. A scanning electron microscopic study. *Acta Anaesthesiol Belg* 2009; 60:7-17.
34. Lirk P, Kolbitsch C, Putz G, Colvin J, Colvin HP, Lorenz I, Keller C, Kirchmair L, Rieder J, Moriggl B. Cervical and high thoracic ligamentumflavum frequently fails to fuse in the midline. *Anesthesiology* 2003; 99:1387-1390.
35. Renfrew DL, Moore TE, Kathol MH, el-Khoury GY, Lemke JH, Walker CW. Correct placement of epidural steroid injections: Fluoroscopic guidance and contrast administration. *AJNR Am J Neuroradiol* 1991; 12:1003-1007.
36. Manchikanti L, Bakhit CE, Pakanati RR, Fellows B. Fluoroscopy is medically necessary for the performance of epidural steroids. *Anesth Analg* 1999; 89:1330-1331.

37. Johnson BA, Schellhas KP, Pollei SR. Epidurography and therapeuticepidural injections: Technical considerations and experience with 5334 cases. *AJNR Am J Neuroradiol* 1999; 20:697-705.
38. White AH, Derby R, Wynne G. Epidural injections for the diagnosis and treatment of low-back pain. *Spine* 1980; 5:78-86.
39. Mehta M, Salmon N. Extradural block. Confirmation of the injection site by X-ray monitoring. *Anaesthesia* 1985; 40:1009-1012.
40. Rathmell JP, Aprill C, Bogduk N. Cervical transforaminal injection of steroids. *Anesthesiology* 2004; 100:1595-1600.
41. Lee MH, Yang KS, Kim YH, Jung HD, Lim SJ, Moon DE. Accuracy of live fluoroscopy to detect intravascular injection during lumbar transforaminal epidural injections. *Korean J Pain* 2010; 23:18-23.
42. McLean JP, Sigler JD, Plastaras CT, Garvan CW, Rittenberg JD. The rate of detection of intravascular injection in cervical transforaminal epidural steroid injections with and without digital subtraction angiography. *PM R* 2009; 1:636-642.
43. Chang Chien GC, Candido KD, Knezevic NN. Digital subtraction angiography does not reliably prevent paraplegia associated with lumbar transforaminal epidural steroid injection. *Pain Physician* 2012; 15:515-523.
44. Horlocker TT, Wedel DJ, Rowlingson JC, Enneking FK, Kopp SL, Benzon HT, Brown DL, Heit JA, Mulroy MF, Rosenquist RW, Tryba M, Yuan CS. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine Evidence-Based Guidelines (Third Edition). *Reg Anesth Pain Med* 2010; 35:64-101.
45. Manchikanti L, Falco FJ, Benyamin RM, Caraway DL, Kaye AD, Helm S 2nd, Wargo BW, Hansen H, Parr AT, Singh V, Swicegood JR, Smith HS, Schultz DM, Malla Y, Hirsch JA. Assessment of bleeding risk of interventional techniques: A best evidence synthesis of practice patterns and perioperative management of anticoagulant and antithrombotic therapy. *Pain Physician* 2013; 16:SE261-SE318.
46. Gogarten W, Vandermeulen E, Van Aken H, Kozek S, Llau JV, Samama CM; European Society of Anaesthesiology. Regional anaesthesia and antithrombotic agents: Recommendations of the European Society of Anaesthesiology. *Eur J Anaesthesiol* 2010; 27:999-1015.
47. Bogduk N. *ISIS Practice Guidelines for Spinal Diagnostic and Treatment Procedures 2nd edition*. International Spine International Society. 2013
48. Breivik H, Bang U, Jalonen J, Vigfusson G, Alahuhta S, Lagerkranser M. Nordic guidelines for neuraxial blocks in disturbed haemostasis from the Scandinavian Society of Anaesthesiology and Intensive Care Medicine. *Acta Anaesthesiol Scand* 2010; 54:16-41.
49. Horlocker TT, Bajwa ZH, Ashraf Z, Khan S, Wilson JL, Sami N, Peeters-Asdourian C, Powers CA, Schroeder DR, Decker PA, Warfield CA. Risk assessment of hemorrhagic complications associated with nonsteroidal antiinflammatory medications in ambulatory pain clinic patients undergoing epidural steroid injection. *Anesth Analg* 2002; 95:1691-1697.
50. Chin KR, Sundram H, Marcotte P. Bleeding risk with ketorolac after lumbar microdiscectomy. *J Spinal Disord Tech* 2007; 20:123-126.
51. Gilbert A, Owens B, Mulroy M. Epidural hematoma after outpatient epidural anesthesia. *Anesth Analg* 2002; 94:77-78.
52. Williams KN, Jackowski A, Evans PJD. Epidural hematoma requiring surgical decompression following repeated cervical epidural steroid injections for chronic pain. *Pain* 1990; 42:197-199.
53. Singer AJ, Mynster CJ, McMahon BJ. The effect of IM ketorolac tromethamine on bleeding time: A prospective, interventional, controlled study. *Am J Emerg Med* 2003; 21:441-443.
54. Greer IA. Effects of ketorolac tromethamine on hemostasis. *Pharmacotherapy* 1990; 10:71S-76S.
55. Geisslinger G, Peskar BA, Pallapies D, Sittl R, Levy M, Brune K. The effects on platelet aggregation and prostanoid biosynthesis of two parenteral analgesics: Ketorolac tromethamine and dipyrone. *Thromb Haemost* 1996; 76:592-597.
56. Conrad KA, Fagan TC, Mackie MJ, Mayshar PV. Effects of ketorolac tromethamine on hemostasis in volunteers. *Clin Pharmacol Ther* 1988; 43:542-546.
57. Sinha VR, Kumar RV, Singh G. Ketorolac tromethamine formulations: An overview. *Expert Opin Drug Deliv* 2009; 6:961-975.
58. Roche Pharmaceuticals. www.roche-australia.com/fmfiles/re7229005/downloads/anti-inflammatory/toradol-pi.pdf
59. Castro VM, Gallagher PJ, Clements CC, Murphy SN, Gainer VS, Fava M, Weilburg JB, Churchill SE, Kohane IS, Iosifescu DV, Smoller JW, Perlis RH. Incidentusercohortstudyof risk for gastrointestinalbleed and stroke in individuals with major depressive disorder treated with antidepressants. *BMJ Open* 2012; 2:e000544.
60. Schlienger RG, Meier CR. Effect of selective serotonin reuptake inhibitors on platelet activation: Can they prevent acute myocardial infarction? *Am J Cardiovasc Drugs* 2003; 3:149-162.
61. Maurer-Spurej E. Serotoninreuptakeinhibitors and cardiovascular diseases: A platelet connection. *Cell Mol Life Sci* 2005; 62:159-170.
62. Li N, Wallén NH, Ladjevardi M, Hjemdahl P. Effects of serotonin on platelet activation in whole blood. *Blood Coagul Fibrinolysis* 1997; 8:517-523.
63. De Abajo FJ. Effects of selective serotonin reuptake inhibitors on platelet function: Mechanisms, clinical outcomes and implications for use in elderly patients. *Drugs Aging* 2011; 28:345-367.
64. Sewnath ME, van Hillegersberg R, Koopman MM, Levi MM, Gouma DJ. Increased perioperative blood loss during treatment with paroxetine. *Ned Tijdschr Geneeskd* 2002; 146:1800-1802.
65. Turner MS, May DB, Arthur RR, Xiong GL. Clinical impact of selective serotonin reuptake inhibitors therapy with bleeding risks. *J Intern Med* 2007; 261:205-213.
66. Hergovich N, Aigner M, Eichler HG, Entlicher J, Drucker C, Jilma B. Paroxetine decreases platelet serotonin storage and platelet function in human beings. *Clin Pharmacol Ther* 2000; 68:435-442.
67. Auerbach AD, Vittinghoff E, Maselli J, Pekow PS, Young JQ, Lindenauer PK. Perioperative use of selective serotonin reuptake inhibitors and risks for adverse outcomes of surgery. *JAMA Intern Med* 2013; 173:1075-1081.
68. Koch E. Inhibition of platelet activating factor (PAF)-induced aggregation of human thrombocytes by ginkgolides: Considerations on possible bleeding complications after oral intake of Ginkgo biloba extracts. *Phytomedicine* 2005; 12:10-16.
69. Teng CM, Kuo SC, Ko FN, Lee JC, Lee LG, Chen SC, Huang TF. Antiplatelet actions of panaxynol and ginsenosides isolated from ginseng. *Biochim Biophys Acta* 1989; 990:315-320.
70. Agren JJ, Väisänen S, Hänninen O, Muller AD, Hornstra G. Hemostatic factors and platelet aggregation after a fish-enriched diet or fish oil or docosa-

hexaenoic acid supplementation. *Prostaglandins Leukot Essent Fatty Acids* 1997; 57:419-421.

71. Cobiac L, Clifton PM, Abbey M, Belling GB, Nestel PJ. Lipid, lipoprotein, and hemostatic effects of fish vs fish-oil n-3 fatty acids in mildly hyperlipidemic males. *Am J Clin Nutr* 1991; 53:1210-1216.
72. Gawaz M, Ott I, Reininger AJ, Neumann FJ. Effects of magnesium onplatelet aggregation and adhesion. Magnesium modulates surface expression of glycoproteins on platelets in vitro andex vivo. *Thromb Haemost* 1994; 72:912-918.
73. Steiner M. Influence of vitamin E on platelet function in humans. *J Am Coll Nutr* 1991; 10:466-473.
74. Harris WS, Silveira S, Dujovne CA. The combined effects of N-3 fatty acids and aspirin on hemostatic parameters in man. *Thromb Res* 1990; 57:517-526.
75. Svaneborg N. Kristensen SD, Hansen LM, Büllow I, Husted SE, Schmidt EB. The acute and short-time effect of supplementation with the combination of n-3 fatty acids and acetylsalicylic acid on platelet function and plasma lipids. *Thromb Res* 2002; 105:311-316.
76. Harker LA, Kelly AB, Hanson SR, Krupski W, Bass A, Osterud B, FitzGerald GA, Goodnight SH, Connor WE. Interruption of vascular thrombus formation and vascular lesion formation by dietary n-3 fatty acids in fish oil in nonhuman primates. *Circulation* 1993; 87:1017-1029.
77. Bays HE. Safety considerations with omega-3 fatty acid therapy. *Am J Cardiol* 2007; 99:35C-43C.
78. Institute of Medicine. Dietary Reference Intakes: Vitamin C, Vitamin E, Selenium, and Carotenoids. National Academies Press, Washington, DC, 2000, pp 186-263.
79. Stampfer MJ, Jakubowski JA, Faigel D, Vaillancourt R, Deykin D. Vitamin E supplementation effect on human platelet function, arachidonic acid metabolism, and plasma prostacyclin levels. *Am J Clin Nutr* 1988; 47:700-706.
80. Szuwart T, Brzoska T, Luger TA, Filler T, Peuker E, Dierichs R. Vitamin E reduces platelet adhesion to human endothelial cells in vitro. *Am J Hematol* 2000; 65:1-4.
81. Freedman JE, Farhat JH, Loscalzo J, Keaney JF Jr. a-Tocopherol inhibits aggregation of human platelets by a protein kinase c-dependent mechanism. *Circulation* 1996; 94:2434-2440.
82. Mabile L, Bruckdorfer KR, Rice-Evans C. Moderate supplementation with natural alpha-tocopherol decreases platelet aggregation and low-density lipoprotein oxidation. *Atherosclerosis* 1999; 147:177-185.
83. Bakaltcheva I, Gyimah D, Reid T. Effects of alpha-tocopherol on platelets and the coagulation system. *Platelets* 2001; 12:389-394.
84. Marsh SA, Coombes JS. Vitamin E and alpha-lipoic acid supplementation increase bleeding tendency via an intrinsic coagulation pathway. *Clin Appl Thromb Hemost* 2006; 12:169-173.
85. Pallapies D, Peskar BA, Brune K, Geisslinger G. Effects on platelet functions and pharmacokinetics of azapropazone and ketorolac tromethamine given as single parenteral doses. *Br J Clin Pharmacol* 1994; 37:335-339.
86. Geisslinger G, Peskar BA, Pallapies D, Sittl R, Levy M, Brune K. The effects on platelet aggregation and prostanoid biosynthesis of two parenteral analgesics: Ketorolac tromethamine and dipyrone. *Thromb Haemost* 1996; 76:592-597.
87. Lind SE. The bleeding time does not predict surgical bleeding. *Blood* 1991; 77:2547-2552.
88. Rodgers RP, Levin J. A critical reappraisal of the bleeding time. *Semin Thromb Hemost* 1990; 16:1-20.
89. Stuart MJ, Miller ML, Davey FR, Wolk JA.Top of FormBottom of Form The post-aspirin bleeding time: A screening test for evaluating haemostatic disorders. *Br J Haematol* 1979; 43:649-659.
90. Manchikanti L, Benyamin RM, Swicegood JR, Falco FJ, Datta S, Pampati V, Fellows B, Hirsch JA. Assessment of practice patterns of perioperative management of antiplatelet and anticoagulant therapy in interventional pain management. *Pain Physician* 2012; 15:E955-968.