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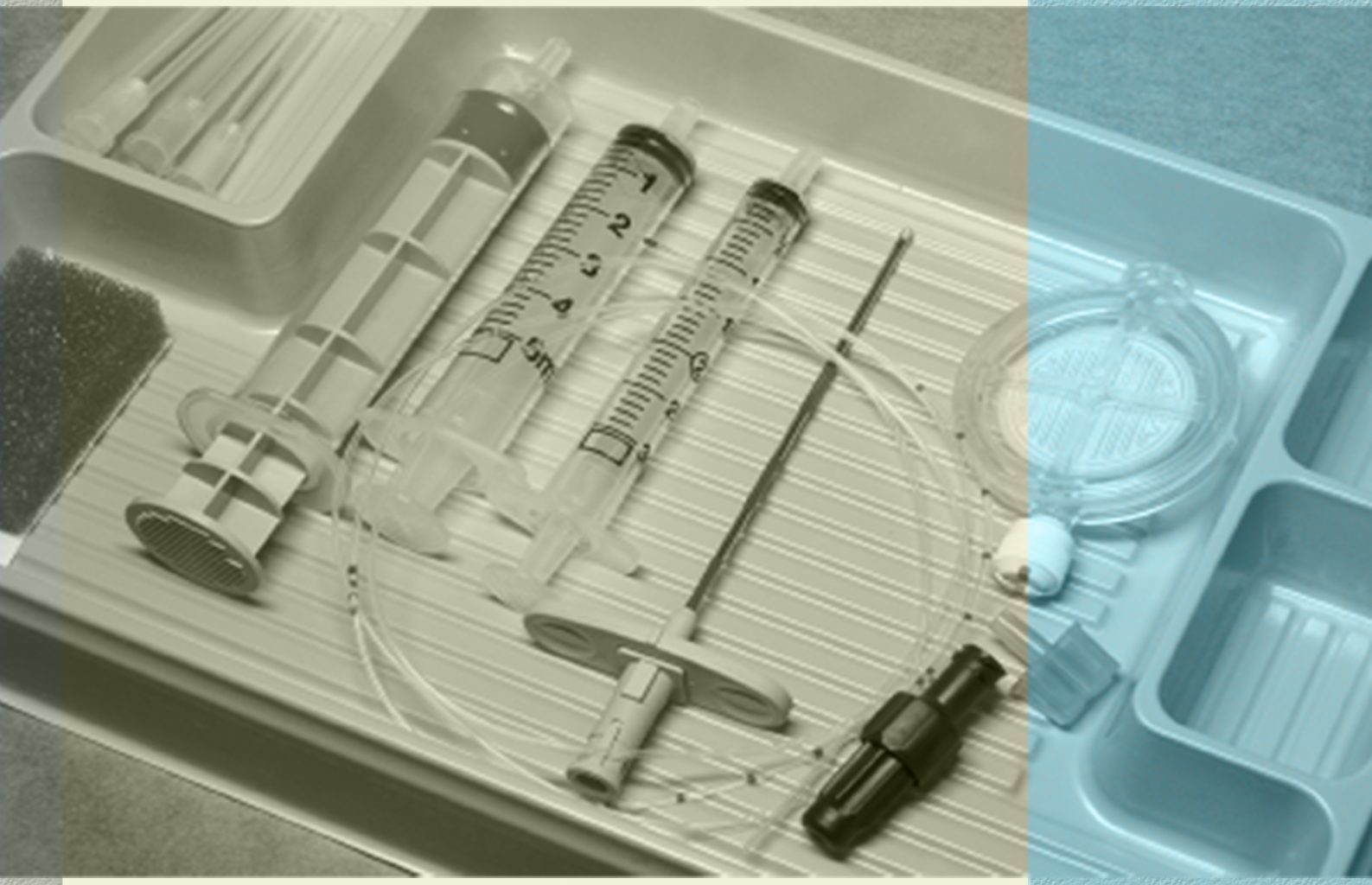

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Editorial

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Hemostasis Management during Adult Extracorporeal Membrane Oxygenation: A Shot in the Dark?

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KEYWORDS: Bleeding; Coagulation; Extracorporeal membrane oxygenation (ECMO).

Extracorporeal membrane oxygenation (ECMO) has been used increasingly in adult patients with cardiopulmonary failure.[1] According to the Extracorporeal Life Support Organization's (ELSO's) 2012 report over 51,000 patients have received ECMO. Most cases are for neonates; however, an increasing proportion is for adults.[2] ECMO is a unique life saving therapy, but many patients experience complications including: hemolysis, systemic thromboembolism, neurologic complications, and bleeding.[3] We previously reported that up to 56% of patients experience at least one significant bleeding event during ECMO and the rate of serious bleeding events is approximately 10 per 100 ECMO days.[4] Our data also suggest that bleeding events and the amount of transfusion on ECMO are associated with decreased survival.

Why do ECMO patients bleed and what hemostatic therapies are most effective for treatment? Unfortunately, there are limited data to help answer these questions. To our knowledge there are no studies comparing bleeding rates with different anticoagulation regiments. Our own work showed that over-anticoagulation with unfractionated heparin contributes to bleeding complications during ECMO, as patients with bleeding were more often above their target activated Partial Thromboplastin Time (aPTT).[4] Data from one small observational study suggest that low dose unfractionated heparin with a target Activated Clotting Time ACT of 180-220 seconds is associated with significantly less bleeding than high dose heparin with a target ACT of 180-220 seconds.[5] In this study low dose heparin was not associated with a higher rate of thrombosis or oxygenator changes.

In addition to these anticoagulation issues, ECMO patients experience a complex coagulopathy. Although, no evidence-based treatments can be recommended at the present time, various pathophysiologic mechanisms have been suggested. Similar to ventricular assist devices, ECMO appears to increase cleavage of large von Willebrand factor multimers by the A disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) enzyme.[6,7] Qualitative platelet dysfunction also develops within 90 minutes of ECMO initiation and enhanced fibrinolysis occurs presumably due to contact pathway activation which facilitates conversion of plasminogen to plasmin.[8,9]

Monitoring patients who are at risk for bleeding during ECMO also remains a significant challenge. Viscoelastic Coagulation Tests (VCT) such as Thromboelastography (TEG) and Rotational thromboelastometry (ROTEM), which have proven useful in other settings have not been shown to predict bleeding events in ECMO patients.[10,11] Our own experience is that patients who are on ECMO typically have elevated fibrinogen levels and have a normal Maximum Amplitude (MA) on heparinase TEG or normal Maximal Clot Formation (MCF) on ROTEM EXTEM or FIBTEM. This is presumably related to elevated fibrinogen levels during ECMO. These tests are also not sensitive for detecting fibrinolysis, unless it is a systemic phenomenon.[12] Likewise, standard plasma based coagulation tests such as the International

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Normalized Ratio (INR) cannot rule out fibrinolysis or qualitative platelet dysfunction and are also unlikely to be sensitive tests for identifying ECMO patients with high bleeding risk. Taken together, the ECMO care team is often left with difficult decisions to ascertain the adequacy of their anticoagulation, and select optimal hemostatic interventions when patients bleed.

Few studies have examined hemostatic therapies in adult ECMO patients with severe refractory bleeding. One small observational study of 15 patients suggested that treatment with activated recombinant Factor VII is safe and effective for treating intractable bleeding during ECMO.[13] However, there is also a case report of a fatal thrombosis in an ECMO patient who received activated recombinant factor VII and activated prothrombin complex.[14]

In summary, bleeding during ECMO remains a serious problem, which impacts patient survival. Clinical trials comparing alternative anticoagulation regiments are badly needed as are mechanistic studies and studies of hemostatic therapies in patients who experience significant bleeding. Unfortunately, until such evidence is available the ECMO care team is left with few evidence-based interventions to prevent and treat serious bleeding.

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Letter to the Editor

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Lost in Translation

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As anesthesiologists, in whatever part of the world we live in, it is very common to be exposed to different cultures and languages. In some hospitals it happens on a daily basis, in others seldom, but the challenge of dealing with the "other" remains. In many institutions, like the one where the Author works, it is mandatory to use a professional medical translator, at least for the consent. However, even when such resource is utilized, there are aspects of communication that transcend language. Translation may address the meaning of word, but it may not get to the very goal of communication, which is, to understand each other. We are confronted with different cultures, where individuals perceive the same "words" in very different ways, and, more importantly, attribute to them a very different affective value. The challenge, then, consists in making the art of communication work. However, this is something that, as anyone of us has learned, it is often independent of the language used. We may run into a great deal of troubles with miscommunication even when we speak the same language... This bring us to talk about empathy, which I think is a necessary element when approaching our patients. It is our responsibility making sure that our message is conveyed to our patients, that they understand the pros and cons of anesthetics and procedures we are going to perform, along with the possible complications. In doing so, we must put all the necessary effort in trying to envision what our patients are seeing and feeling, trying to understand the cultural differences as well as the socioeconomic status. And..... let's not get lost in translation!

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Letter to the Editor

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Pediatric Emergence Agitation

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Emergence Agitation (EA) is still remaining as a major problem during the early stage of recovery from general anesthesia in children. EA was first reported in 1960's and it has been considered as a mental disturbance during recovery from general anesthesia which consists of hallucinations, delusions and confusion manifested by moaning, restlessness, involuntary physical activity and thrashing about in the bed.[1] The incidence of EA is variable and can reach to 80%.[2]

Pre-school aged children, preoperative anxiety, inadequate pain control, type of the surgery (especially ophthalmological and otorhinolaryngological), anesthesia method are defined as the risk factors for EA in children.[3-7] Sevoflurane and desflurane are the preferred inhalational anesthetic agents for the induction of anesthesia in children. However, these agents have been reported to increase the ratio of EA because of their low blood/gas partition coefficients.[8] Although emerge times from propofol and sevoflurane are similar, EA is frequently observed in sevoflurane based anesthesia. In recent studies elevation of intraserebral glucose and lacticasid concentrations were observed with Magnetic Resonance Spectroscopy (MRS) with the use of sevoflurane.[9] Also epileptogenic activity of sevoflurane has been reported.[10] However the exact mechanism of EA has not been understood yet.

Different anesthetic agents such as opioids, midazolam, ketamine, alpha-2 agonist sedatives and nonsteroidal anti- inflammatory drugs have been used to prevent EA. Low dose ketamine added to propofol was found effective in the prevention of EA in children with a history of EA with propofol Total intravenous anaesthesia (TIVA).[11] Hadi et al Found that ketodex (lowdoseketamine 0,15 mg/kg followed by dexmedetomidine 0,3 µ/kg IV) reduced the incidence and severity of EA in children undergoing adenotonsillectomy following sevoflurane based anesthesia and provided smooth extubation.[12] µ-opioid agonists were found effective in decreasing the incidence of EA under sevoflurane anesthesia but postoperativenausea and vomiting were increased.[13] In a study by Fang et al, the efficacy of midazolam, dexmedetomidine, ketamine, fentanyl, and propofol were compared for the prevention of sevoflurane- related EA in children with placebo. They found that all of these agents have decreased the incidence of EA but dexmedetomidine was considered the most effective agent in their study.[14] In a study by Rosen et al, 42% of the anesthesiologists declared that EA was a significant problem at their institution and propofol was found the most common anesthetic agent used to prevent and to treat EA compared with the other medications.[15]

EA is a major problem in the postoperative period that may cause physical harm to the patient and can be disturbing to the parents and nursing staff in there covery room. There is not defined spesific treatment and optimal anesthetic technique in current practice. For this reason further studies are needed to understand the mechanism of EA and improve the treatment.

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Review

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Physiologic Advantages of Peripheral Nerve Blockade Translate to Decreased Length of Stay and Improved Patient Satisfaction

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ABSTRACT

Peripheral nerve blockade is an effective modality involved in controlling perioperative pain. When compared with patient controlled analgesia, neuraxial analgesia, and other anesthetic methods such as periarticular infiltration, peripheral nerve blocks yield superior pain control and reduce length of hospitalization. Not only do these techniques help with patient satisfaction and health care costs, they also have physiologic advantages. In murine models, peripheral nerve blockade reduces expression of different inflammatory markers such as IL-1, IL-6, TNFα and cortisol. Such advantages make this an attractive modality for pain control.

INTRODUCTION

Tissue damage resulting from traumatic injury or surgical procedures activates signaling cascades that lead to the transmission of pain signals. Avoidance of pain-related morbidities is necessary for recovery and rehabilitation after surgery or traumatic insult. Aside from unnecessary patient suffering, inadequate pain control results in unchecked sympathetic outflow, which has detrimental multi-systemic physiologic sequelae. In the cardiovascular system, poorly managed pain results in hypertension and tachycardia, increasing myocardial oxygen demand and placing the patient at risk for cardiac ischemia or myocardial infarction.[1,2] Elsewhere, vasoconstriction decreases flow to the surgical site, increasing risk of surgical site infection. In the limbs, vasoconstriction leads to venous stasis, increasing the risk for thromboembolic events.[1,2] The sympathetic response can also lead to urinary retention, respiratory compromise, catabolic stress, inflammation, immunosuppression, sleep disturbance, and postoperative ileus. These comorbidities can prolong hospital stay and increase health care expenditures.

Adequate pain control helps facilitate recovery. Preventing pain related comorbidities allows for early ambulation, faster return to bowel motility, and increased patient satisfaction.[2] Pain control regimens can have adverse effects of their own.[3] Opioid therapy, the historical mainstay of pain management, can result in respiratory depression, nausea, constipation, postoperative ileus, and pruritus. While opioids are effective analgesics, their use as a sole analgesic may lead to adverse events, further complicating recovery and prolonging length of hospital stay. Other analgesics are not without their own intrinsic risks. NSAIDs can result in renal compromise, surgical bleeding, decreased bone healing, GI bleeding, and cardiovascular events.[3] Gabapentin use can result in heavy sedation and dizziness.[3] Local anesthetics can cause toxicity, seizures, and cardiovascular compromise. Therefore a balanced approach to pain management is necessary for patient safety and satisfaction.

Multimodal therapy for pain management includes an array of techniques and treatments, not limited to neuraxial analgesia with single shot or continuous epidural, single shot

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or continuous Peripheral Nerve Blocks (PNB), opioids, acetaminophen, anti-inflammatory agents, anticonvulsants, NMDA inhibitors, antidepressants, and anxiolytics.[4] Multimodal therapy targets many different pathways of pain transmission.[4] As seen in Figure 1, opioids are able to modulate pain in one pathway of the central nervous system at the level of hypothalamic pituitary functions. However, pain is transmitted *via* multiple pathways in different parts of the body, both centrally and peripherally. Multimodal therapy will prevent pain transmission in several pathways in order to reduce inflammation, catabolic stress, and recovery time for patients.

An increasingly utilized addition to a balanced multimodal perioperative pain management strategy is the use of regional anesthetic techniques.[5] While epidurals and intrathecal injections with local anesthetics and adjuvants have been shown to dampen the surgical stress response, the evidence for peripheral nerve blockade is still being gathered. With the advances in the placement of Peripheral Nerve Catheters (PNC) using ultrasound guidance, PNCs are becoming more widely utilized.[6] This review will focus on the benefits of PNCs in terms of decreased opioid consumption and decreased physiologic response to pain. It will also discuss how this translates to shortened hospital stay and patient satisfaction.

PERIPHERAL NERVE BLOCKADE (PNB)

The utilization of peripheral nerve blocks (PNBs) for postoperative analgesia has increased with advances in block placement techniques. In the past, peripheral nerve blockade was achieved with needle placement by anatomic landmarks and nerve localization was accomplished with elicitation of paresthesia. After the emergence of electrical stimulation, nerves could be localized without the elicitation of painful stimuli; however nerve block success was inconsistent, limiting widespread implementation of nerve blockade in postoperative pain management.[6]

The advent of ultrasound guided regional anesthesia allowed for the visualization target nerves with the placement of local anesthetics and catheters in close proximity to these target nerves.[6] As techniques using ultrasound for placement have evolved, both single shot and continuous PNBs have become more widely utilized. With continuous PNBs patients are able to receive a continuous infusion of local anesthetic around the nerve or plexus. Accordingly, continuous PNBs compared to single PNBs were associated with decreased pain ratings on postoperative days 0,1, and 2; decreased overall opioid use; decreased nausea; and higher patient satisfaction scores compared to single- and multiple-injection techniques (Figure 2).[7,8] Continuous PNBs give physicians the flexibility to adapt to the differing pain thresholds of patients by dropping the volume or concentration of local anesthetic on initial dosing, which decreases the risk of systemic toxicity. Furthermore, by reducing the large initial doses, one is reducing the likelihood of motor and sensory blocks that have been associated with falls and positional injuries.[9-10]

OPIOID PATIENT CONTROLLED ANALGESIA (PCA)

Opioids are able to modulate pain in the central nervous system by blocking pain transmission (Figure 1). A variety of adverse side effects are associated with opioid analgesia, including respiratory depression, postoperative ileus, constipation, emesis,

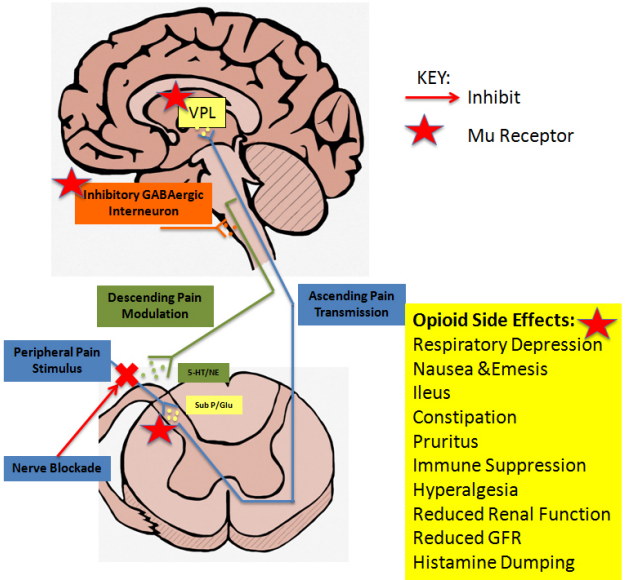

Figure 1: Modulatory effect of morphine on pain. Morphine is able to cross the blood brain barrier and enter the CNS. Once in the CNS morphine binds to μ receptors to inhibit pain transmission. This occurs in the dorsal horn of the spinal cord stopping glutamate and substance P release, in the VPL of the thalamus and in the descending pathway on GABAergic interneurons, which allows the descending pathway to inhibit pain sensation.

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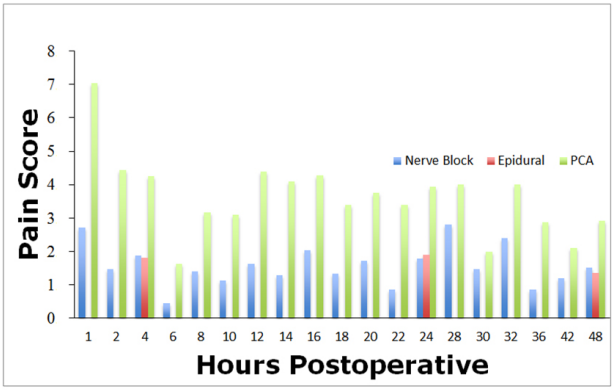

Figure 2: Compilation of data from published reports showing the difference in pain scores postoperatively of nerve blocks, epidurals, and PCA analgesia. PCA has much higher pain scores on average when compared with nerve blocks and epidural analgesia.

inhibition of cough reflex, drowsiness, reduced glomerular filtration rate, reduced renal function, tolerance, opioid hyperalgesia, immune suppression, and non-allergic histamine dumping from mast cells.[11] Although PCA has been shown to be an effective method of inducing analgesia, research in pain management and analgesic techniques suggests that, as a sole modality, PCA is less efficacious than other analgesic techniques. Although use of PCA is widespread, analgesic strategies are shifting away from a single modality approach toward a multimodal pain management approach.

PERIPHERAL NERVE BLOCKADE AND NARCOTIC CONSUMPTION

Side-effects associated with opioid pain relief contribute significantly to the cost of postoperative care. This section will focus on the decrease in narcotic consumption that occurs when PNBs are used to provide postoperative analgesia.

Narcotic consumption is decreased when other analgesic modalities are added to a postoperative regimen. A review of narcotic consumption in patients who received single shot PNBs compared with Continuous Peripheral Nerve Blocks (CPNBs) revealed that CPNBs were associated with decreased maximum pain scores on postoperative days 0, 1, and 2 (Figure 2).[7] There was also an overall decrease in narcotic consumption in patients with CPNBs compared to patients receiving a single shot PNB. The opioid sparing in the CPNB group lead to decreased incidence of nausea and other opioid-related side-effects.[3]

Similarly, Edwards et al[12] showed that CPNBs could decrease opioid consumption on postoperative days 0, 1, and 2 compared to single shot PNBs in patients who underwent Total Knee Arthroplasty (TKA). Indeed, PNBs protect against opioid-induced cardiovascular, respiratory, and gastrointestinal side effects.[8,12,13] Although continuous PNBs have been shown to be more efficacious in treating postoperative pain[9,12-28] and decreasing opioid use, single injection PNBs have been demonstrated to provide superior pain control and decreased side-effects compared to opioid monotherapy.[8,13]

Altering the concentration of the local anesthetic used in the block can also modify narcotic consumption. Aguirre et al[9] increased the concentration of ropivacaine in interscalene blocks for rotator cuff repairs and found significant reductions in morphine consumption. Likewise, they saw decreased nausea, constipation, improved sleep patterns, and increased patient satisfaction.[9] A meta-analysis study in 2006 concluded that CPNBs provide superior pain control compared with opioids.[8] The study revealed significantly lower pain scores at multiple time points in patients with CPNBs.[8] The authors concluded that CPNBs can decrease health care expenses by reducing narcotic-related side-effects.[8]

Edkin et al[14] performed a prospective study on femoral nerve blocks as an substitute to parenteral narcotics for analgesia after anterior cruciate ligament reconstruction. The Winnie 3-in-1 femoral nerve block technique was used for analgesia. The results showed that of the 24 patients who received the nerve block, 92% did not take any parenteral narcotic.[14] The study showed significant reductions in the patients' narcotic requirements and an equally significant extension of the time between incision and the patients' initial narcotic dose.

In another prospective study, Borgeat et al[23] investigated the difference between patients receiving Patient-Controlled Interscalene Anesthesia (PCIA) *via* continuous infusion of 0.2% ropivacaine and opioid Patient-Controlled Anesthesia (PCA) *via* infusion of IV nicomorphine. The patients receiving PCIA had significantly better pain scores in the 12-48 hour period after the procedure.[23] They also noted that nausea and pruritus occurred significantly more in the PCA group.[23] Although this study did not evaluate how PNBs decrease the use of narcotics in the healthcare system, it did show that PNBs are an efficacious form of analgesia that can lead to decreased side-effects and remove the potential for narcotics dependence.

Two studies done by Chelly et al[16] and Singelyn et al[29]

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compared postoperative opioid consumption in patients undergoing TKA with either PNBs, PCA, or epidural analgesia. Chelly et al[16] found that using PNBs reduced the morphine requirement postoperatively by 74% compared to PCA and by 35% when compared with epidural anesthesia. It was also reported that PNBs provided better recovery and decreased side-effects as compared to epidurals and PCAs.[16] Patients receiving PNBs were also found to report less severe maximal pain scores.[16] Singelyn et al.[29] found that the use of morphine postoperatively did not differ between the PNB and Epidural group. There was a significant difference between the PCA and PNB/Epidural use of morphine: PNB/Epidural groups used much less morphine. Although there was no significant difference in morphine usage between epidural and PNB, there was a significant difference in the incidence of side-effects: those in the PNB group had a much lower incidence than the epidural group.[29]

Lastly, a group of studies done by White et al in 2003, Ilfeld et al in 2002, and Siddiqui et al in 2007 compared the use of PNB to a saline control. Each patient received a similar anesthetic for surgery, however the trial group received a PNB during the surgery, and the control group received saline. Although the studies varied and sets of patients were tested using different procedures, they agreed that, compared to saline, PNBs used in conjunction with local anesthetics provided significantly better pain relief and decreased postoperative narcotics use. [9,18,19] Ilfeld et al[9] noted that the PNB provided such powerful analgesia that 80% of the patients receiving the local anesthetic did not require a single opioid tablet during their infusion. More specifically, these patients had an average resting pain of less than 1 on a 0-10 scale. Siddiqui et al. also noted that, like prior studies, there was less vomiting, nausea and respiratory depression in the trial group than the control group.[19]

Although not all literature agrees that PNBs can reduce pain and narcotic use,[30] most of the literature has shown that PNBs have the ability to reduce postoperative narcotic consumption (Figure 3), as well as give better maximal pain scores for patients postoperatively. Not only can PNBs decrease health care expenditures, they may also reduce the prevalence of narcotic dependence. PNBs, further, are advantageous because they provide an avenue by which the comorbidities associated with opioid use can be avoided.

INFLAMMATORY RESPONSE

Inflammation after surgery is a major contributor to postoperative pain. Pro-inflammatory cytokines are involved at the site of inflammation, in the dorsal root ganglion, and within the spinal cord, resulting in neurogenic pain.[31-35] After a tissue stressor, such as surgical insult or trauma, leukocytes are activated and migrate into the circulation. These leukocytes gather at the site of inflammation, causing the release of cytokines, resulting in a more robust local immune responss.[36] Surgical trauma has been shown to provoke an inflammatory state that causes the release of inflammatory cytokines. This cytokine release results in inflammation at the sight of injury as well as inflammation that cause systemic effects. Such systemic effects are tachycardia, tachypnea, leukocytosis, and pyrexia.[37] Prostaglandin E2, COX-2, and cytokines such as IL-1β, IL-6, and TNFα induce nociception by stimulating the free nerve endings of small fiber axons (A delta and C fibers) causing hyperalgesia and allodynia.[20,31,33,37-43] Tissue stressors, such as surgery or trauma, provoke a neuroendocrine stress response resulting in local and systemic inflammation. The neuroendocrine stress response is regulated *via* the hypothalamic pituitary axis, adreno-medullary axis, and the parasympathetic nervous system. Similarly, synthesis of acute phase proteins produced in the liver also play a role in the stress response, as well as the modulation and release of inflammatory cytokines.[36] Reducing the inflammatory response can lead to decreased immunosuppression which enhances recovery.[36,44] Release of substance P and neurokinin have been shown in murine models to induce peripheral inflammation. This increase in peripheral inflammation led to a quick rise in axonal transport of the neurogenic substances (substance P and neurokinin) that peaked on the first day after insult, and subsequently returned to normal one week after insult.[45,46] The initial activation of inflammation in the periphery results in the activation of the systemic

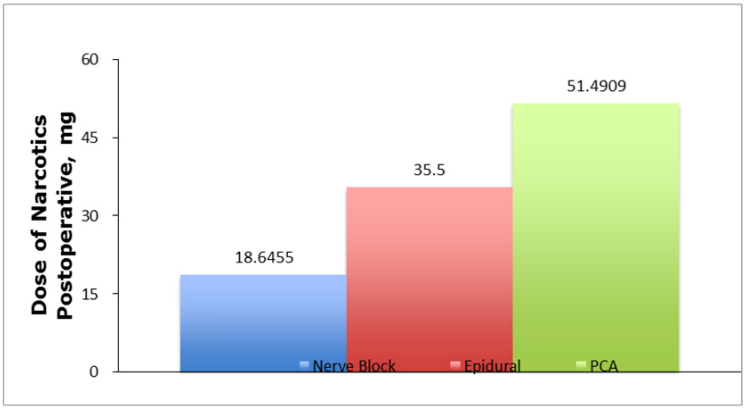

Figure 3: Compilation of data from the literature comparing the average amount of narcotics used postoperatively between nerve blocks, epidurals and PCA. That data shows that when comparing to PCA, both epidural and nerve blocks have lower amounts consumed narcotics postoperatively.

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responses. Administration of anesthetics surrounding the nerve or tissue near the initial site of inflammation halts the development of swelling and reduces systemic effects.[47]

Using a knee arthroplasty model, Bagry et al[36] studied the effect of a continuous PNB on the inflammatory response. Specifically, they compared PNB to the patient-controlled analgesia inflammatory response. These researchers measured plasma glucose, serum insulin, serum cortisol, C-reactive protein, leukocytes, and interleukin-6 at 3, 8, 24, and 48 hours after surgery. Bagry et al[36] observed no difference in glucose, insulin, and cortisol levels measured between the two groups. C reactive protein and leukocyte counts were reduced in the patients receiving a nerve block. These results showed a correlation between maximal leukocyte count and inflammatory mediators IL-6 and CRP was identified.[39] This research suggests that PNBs are able to suppress the inflammatory response by decreasing CRP and leukocytes. Since leukocytes were correlated with decreases in IL-6 and CRP, it may be possible that PNBs are able to repress the body's cytokine-mediated inflammatory response.

Deruddre et al used a murine model to gauge the effect of nerve blocks on the axonal transport of TNFα, edema, and TNFα receptor expression. Using carrageenan injections to induce inflammation, the study revealed that, relative to mice without nerve blocks, those with nerve block had markedly decreased edema after injection.[48] To study the influence of PNBs on axonal transport, they used five study groups: one received a saline nerve block (control), the second received drug-free microspheres (control), the third received bupivacaine, the fourth received colchicine, and the fifth received an epinephrine block. During the 36-hour study period a significant decrease in the transport of TNFα occurred when comparing the controls to the bupivacaine nerve block. The colchicine group had levels of TNFα transport that were statistically different from controls; however this difference only lasted during the first 24 hours.[48] By hour 30, the difference was gone.[48] In the three hours after carrageenan injection, there was a significant increase in TNFα-receptor 1 levels which plateaued at the 3 hour mark. When treated with bupivacaine, the TNFα-receptor 1 levels maintained their basal concentration.[48] This concentration differed significantly from the control mice.[48] TNFα-receptor 2 levels were also found to have low concentrations at baseline. Additionally, these levels did not increase when inflammation was induced with carrageenan.[48] This seems to evidence clinical value in using PNBs as in this model it was able to reduce both edema and transport of inflammatory mediators at the axonal level.

Studies by Beloeil et al[49,50] in 2006 and 2009 showed that nerve blocks performed with bupivacaine reduce thermal hyperalgesia, mechanical hyperalgesia, edema, and markers of inflammation. Using injections of carrageenan to induce inflammation in mice, they investigated the formation of edema, thermal nociceptive withdrawal, production of PGE2, and COX1/2 expression in the spinal cord and dorsal root ganglion.[50] It was observed that bupivacaine significantly decreased edema.[38,50] When comparing thermal nociceptive withdrawal reflex in the mice with and without the block, they noticed significant hyperalgesia in those treated with carrageenan without a nerve block.[50] The study also showeda significant PGE2 increase in subjects that received carrageenan without nerve block. When carrageenan was injected after the nerve block was placed, the levels of PGE2 did not vary significantly from the basal levels.[50] There were also marked differences in COX1 and COX2 expression. In control mice, COX1 was expressed at low levels and COX2 was almost completely absent in the spinal cord and dorsal root ganglion.[38] Throughout the entire experiment, COX1 levels were unchanged the entire time.[50-53] COX2 mRNA levels were increased in mice treated with carrageenan that did not receive nerve block.[50,52,53] The COX2 levels significantly increased throughout the spinal cord (both sides) but only increased on the side of injection at the dorsal root ganglion.[50] Animal models showed that when given a bupivacaine block, levels of COX-2 mRNA was impaired. This impairment was seen on the same side of the dorsal root ganglion. This was significantly less compared with the non-block group. Furthermore, the bupivacaine block was able to impair contralateral COX-2 expression in the dorsal root ganglion.

Figure 4 shows how the inflammatory markers interact with each other when causing pain. Nerve blockades in the murine models were shown to decrease levels of TNFα as well as COX1 expression. PNB's are known to stop the pain transmission, which has a regulatory affect on the arachidonic acid pathway. The findings in the studies mentioned above have been promising. By seeing decreases in inflammatory cytokines after administration of PNBs gives hope that these anesthetic methods may help dampen the inflammatory response and speed up recovery time. However, current research involving these inflammatory markers in human subjects is lacking. Investigating similar processes in human subjects would be beneficial for understanding how regional anesthesia can dampen the inflammatory response.

POST OPERATIVE HORMONAL STRESS RESPONSE

Pain directly triggers hormonal stress responses. During surgery or traumatic injury, tissue destruction results in local and systemic release of signaling molecules that activate a neuroendocrine and inflammatory response. A number of systems are affected resulting in significant pituitary hormone secretion, insulin resistance, cytokine production, neutrophil leukocytosis, lymphocyte proliferation, and other responses.[54-56] The severity of a patient's stress response to surgery depends on a variety of factors. A patient's age, the severity of pain or trauma, the location of the injury, and the type of anesthesia they receive affects the management of surgery and or pain.[61,62] These hormonal responses are mediated by afferent nerve pathways and the central nervous system and they are linked *via* complex signaling networks.[62]

Opioids are known to suppress the secretion of hypo-

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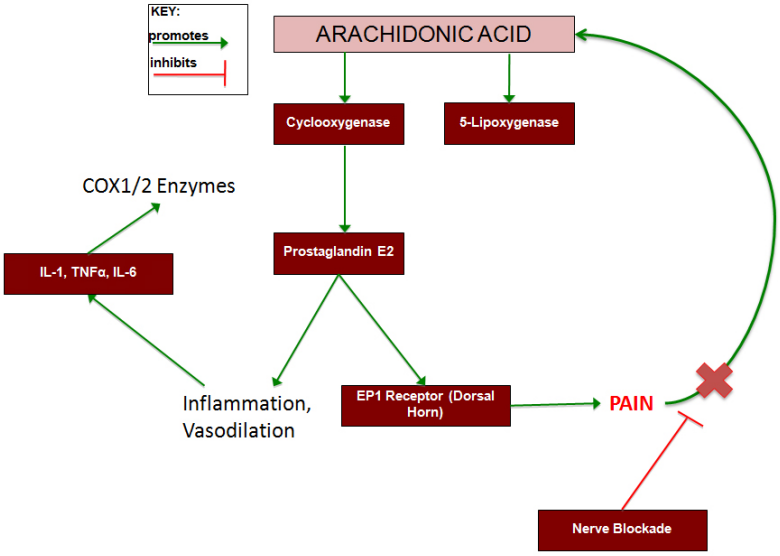

Figure 4: Regulation of pain by arachidonic acid pathway. This schematic diagram shows how arachidonic acid pathway could further modulate the pain response. Cyclooxygenase (COX) converts arachidonic acid into prostaglandin E2, which causes inflammation and vasodilation leading to inflammatory cytokine release. Inflammatory cytokines, IL-1, TNFα, and IL-6, can up-regulate the activity of the COX1/2 enzymes further producing PGE_2. PGE_2 is also sensed by EP1 receptors in the dorsal horn causing pain, which modulates the activity of the AA pathway.

thalamic and pituitary hormone during general anesthesia.[56] McDonal et al[57] demonstrated this by looking at morphine's effect on the hypothalamus. Patients who received morphine showed suppression of corticotrophin release, which resulted lower cortisol levels. Similarly, morphine has also been shown to inhibit cortisol release in cardiac bypass patients and during upper and lower abdominal surgeries.[58-60]

Regional anesthetic techniques, such as epidural anesthesia, can inhibit endocrine and metabolic responses in surgeries taking place in the lower half of the body. Epidural blockade of T4-S5 preoperatively prevents cortisol release and modulates the hormonal response.[54] Epidurals can block both the hypothalamic pituitary axis and the efferent autonomic pathways to both the liver and the adrenal medulla. This inhibits the hormonal responses from both organs, stopping the hormonal stress response from being activated.[54]

Studies have shown that different anesthetic techniques have different affects on the body's hormonal reaction to pain and surgical stimuli. Celic-Spuzic et al[61] showed that the use of epidural anesthesia lowered the peak levels of cortisol during and after surgery when compared with patients who underwent general anesthesia. It was also shown that levels of ACTH, which accelerates the rate of catecholamine release, were much lower in patients who underwent regional techniques when compared with general anesthesia patients. Similarly, Breslow et al[63] showed that patients with regional anesthesia had lower levels of cortisol and norepinephrine release both during surgery and postoperatively (compared with those who underwent general anesthesia).[25] Pflug and Halter[64] compared the effects of spinal and inhalation anesthesia. Their results showed that spinal anesthesia dampened the endocrine response and the adrenergic tone. They noted suppression in norepinephrine, epinephrine, and cortisol for patients with spinal anesthesia compared with inhalational anesthesia. Similarly, Soto et al[65] showed that intraoperative levels of cortisol, noradrenaline and total catecholamine levels were significantly lower when an epidural anesthetic was used compared to a general anesthetic.

Reducing the body's response to pain and stress, although a useful way to hasten recovery may place the patients at risk of becoming immunocompromised or decrease their capability to respond to stress. The benefits of using regional anesthesia and general anesthesia still outweigh possible side-effects. Literature has shown that, compared to spinal anesthesia, the use of general anesthetics maintains less desirable levels of catecholamines, epinephrine, norepinephrine, and cortisol in the plasma.[2] General anesthesia, however, is still able to diminish the surgical stress response *via* the opioid pathway.[2]

Further studies are needed to determine how peripheral nerve blockade can be employed to further suppress the surgical stress response during the postoperative period.

HOSPITAL LENGTH OF STAY

Turker et al[66] showed that, when comparing PNB to epidurals, nerve blocks provided decreased motor block and limb anesthesia. Although negative side effects of PNB's exist, including motor loss, anesthesia of limbs, and anesthetic toxicity[10,67] these side effects can be managed through careful titration of local anesthetic infusions.

PNBs have been shown to reduce postoperative narcotic consumption and can help to provide sustained analgesia

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for patients after major surgery. Together these variables have a significant impact on the length of hospital stay. Several studies have shown that postoperative pain control is an important determinant of hospital length of stay.[7,14-16] Chelly et al.[16] investigated differences in outcomes based on postoperative pain control modalities. In comparison to epidural analgesia or CPNB, patients receiving morphine PCA had an increase in respiratory depression, constipation, pruritus and sedation, which led to a prolonged hospital stay. Likewise, Bingham et al[7] also showed that, when coupled with rehabilitation, CPNBs facilitate early hospital discharge. In another study, Edkin et al[14] showed that the use of CPNBs facilitates same-day discharge for several surgery types that would normally require overnight admission for pain control. The average time of hospitalization was significantly decreased for patients using femoral nerve blocks as a means of analgesia, instead of morphine PCA. In results from patient questionnaires after a femoral nerve block, the majority of the patients felt that they could have been discharged even earlier. However, two of the patients who did not believe they were ready for early discharge due to muscle weakness.[14]

Singelyn et al[17] compared PCA, femoral nerve block and epidural analgesia to see which method had the greatest efficacy for total hip arthroplasty. The analgesia was comparable between the femoral nerve block and the epidural groups. Both epidural and PNB groups showed significantly better analgesia than the patients receiving morphine. Although analgesia was comparable between the epidural and PNB groups, side effects were less frequent and less severe in the femoral nerve block group compared to the epidural and PCA group. This observation led investigators to the conclusion that the femoral nerve block appeared to be the best analgesia technique for total hip arthroplasty. Although, Singelyn et al[17] did not study how each technique compared in relation to length of hospital stay, it is fair to assume that patients who have fewer side effects generally have shorter hospital stays. Maurer et al[68] evaluated the effect of single injection blocks, continuous injection blocks, and patient-controlled analgesia for hip arthroplasty. Although the study did not gauge discharge time specifically, they noted that pain scores with continuous injection blocks were significantly lower when compared to single injection blocks and patient controlled analgesia. Maurer et al also noted a significant difference in hemodynamic stability between the groups: continuous injection blocks kept postoperative blood pressure more stable.

White et al.[18] investigated effects of PNBs on the length of hospital stay. Using bupivacaine and a saline control, they compared postoperative narcotic use in patients that were allowed to supplement their pain with narcotic PCA. Results showed that patients who received intra-operative bupivacaine higher satisfaction scores, less narcotic use, lower maximal pain scores, and 40% of the patients were able to be discharged on the same day as the surgery. The study found that the average length of stay for patients with the bupivacaine PNB was 0.7 days, whereas patients without the bupivacaine spent an average of 1.4 days in the hospital.[16] The authors also noted that patients who received the PNB spent less time in the PACU after surgery; however, this relationship was not found to be statistically significant.[18] In a similar study, Hadzic et al[69] showed that, when comparing PNBs with general anesthesia for hand surgery, patients anesthetized with PNB were able to ambulate significantly earlier (82 +/- 41 min) while the general anesthesia group ambulated slower (145 +/- 70 min). Also, the time to discharge was significantly shorter for patients in the PNB group.

A recent study conducted by Ilfeld et al[70] examines pain control following total knee arthroplasty. The study shows that continuous femoral nerve block offers a viable, alternative option as compared to opioid or epidural analgesia. They noted that patients who received a continuous block instead of epidural (or patient-controlled analgesia) were able to reach their discharge criteria significantly faster (25 hours as compared to control averages of 71 hours). A similar study by Chelly et al[16] found that, in total knee arthroplasties, the PNBs reduced postoperative morphine consumption and provided a reduction in recovery time compared to epidural and patient-controlled analgesia. Specifically, there was a 90% reduction in adverse events and length of stay was reduced by 20%. Two reasons emerged to explain these findings. The first was the decrease in serious complications such as postoperative bleeding, constipation, pruritus, and respiratory depression. The second was that the use of femoral block led to increased passive knee flexion during the first three postoperative days, allowing earlier mobilization of the limb.[16] Capdevila et al[71] performed another study on the effect of femoral nerve blocks on knee surgery. They showed that a femoral nerve block and epidural analgesia provided better postoperative knee mobilization compared to patient-controlled analgesia. As a result, the average stay in the rehabilitation center was shorter: 37 days for epidural, 40 days for femoral block and 50 days for patient-controlled analgesia.[71] Although the epidural had the shortest average stay at the rehabilitation center, side effects were more frequent in epidural anesthesia (compared to femoral block).[71]

Salinas et al[72] compared the use of single injection and continuous femoral nerve blocks on hospital stay. They found that, although the analgesia did improve with continuous femoral blocks, the length of stay was unchanged when compared to single injection femoral nerve block. The study concluded that changing a single treatment modality will not have an effect on the total hospital time because of the improved ability of physical therapy and rehabilitation. However, this study did not compare the length of stay between multiple modalities of analgesia. If the nerve block groups were compared to other modalities such as PCA or epidural techniques, there may be a significant difference in length of stay.

Hadzic et al[59] performed a study that compared brachial plexus nerve block with general anesthesia for hand surgery. The results showed that 79% of the nerve block patients met criteria to bypass the Post-Anesthesia Care Unit (PACU) compared to only 25% of patients who received a general anesthetic. Similar-

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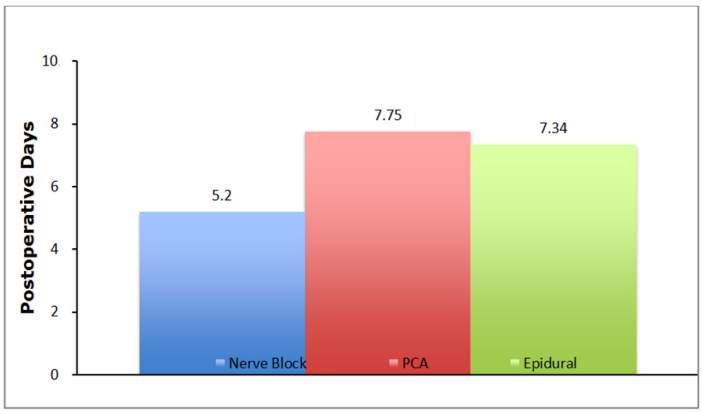

Figure 5: Compilation of data from multiple studies in the literature showing the average length of stay postoperatively comparing nerve blocks, epidurals and opioid PCA. The data shows that the average length of stay when using nerve block analgesia is shorter when compared to PCA and epidural analgesia.

ly, none of the patients in the PNB group required pain medications during hospitalization whereas 48% of general anesthetic patients did.[59] The patients who received nerve blocks were also found to ambulate earlier and were discharged sooner.

According to the literature reviewed and compilation of the data in Figure 5 it seems that PNBs are efficacious in reducing the length of stay compared to PCA. This difference could be attributable to a few variables. First, reducing the patient's perceived pain leads to earlier discharges. Second, because it decreases opioid use, PNBs tends to have fewer opioid-related side effects. Lastly, although data is lacking in human models, PNBs reduce inflammatory mediators, allowing them to increase the speed of recovery. Additional research is needed to compare the relative length of stay in PNBs and epidurals.

CONCLUSION

Adequate perioperative pain control is essential for the recovery of surgical patients. Pain associated morbidity reduces healing, increases healthcare costs and prolongs hospital length of stay. The data collected and presented in this review demonstrate the utility of PNBs in a muti-modal pain management regimen.

PNBs decrease opioid consumption resulting in less opioid related side effects. This benefit alone leads to shortened length of stay and improved patient satisfaction just by avoidance of opioid related side effects.

In regards to inflammation and surgical stress response, more research is needed. Murine studies demonstrate PNBs influence on modulating the inflammatory response to surgical trauma. Further studies are warranted to see how this research translates to humans. While epidural and spinal anesthetics have been shown to decrease the stress response, the data is limited on PNBs. Further studies are needed on the ability of PNBs to limit the surgical stress response and to determine which outcomes are affected by doing so.

With increased economic pressure for improved quality of care, lower expenditures, and shortened duration of hospitalization, a perioperative pain regimen that can control pain as well as decrease comorbidities associated with pain and or its treatment is ever so important. In many cases, including PNBs in a multimodal approach is an important part of meeting these goals.

CONFLICTS OF INTEREST: None.

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Case Report

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Positioning and Anesthesia Challenges In a Morbidly Obese Patient Undergoing Cervical Spine Surgery

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ABSTRACT

Background Context: By itself, the perioperative anesthesia management of morbidly obese patients is challenging; this task is further complicated when such patients have to be placed in the prone position for surgery. In these cases, challenges may include positioning, intubation and ventilation.
Purpose: Herein, we describe the safe perioperative anesthesia care of a morbidly obese patient undergoing cervical spine surgery for an enlarging schwannoma.
Study Setting: Morbidly obese patient care at a tertiary cancer institute.
Patient Sample: Single case report.
Methods: Describing the preparation and planning for this complex case and the perioperative care of a patient with several comorbidities. No conflict of interest to report for any of the authors.
Results: Good patient outcome.
Conclusion: Careful multi-disciplinary planning facilitates, good patient outcome, given the challenging nature of the case. Highlighting the use of a trial run in the operating prior to the day of surgery.

INTRODUCTION

Obesity is associated with increased rates of surgical complications, wound healing problems, and re-operation.[1] Obesity also is associated with increased risk of pressure injuries, obstructive sleep apnea and medical comorbidities like hypertension and diabetes which poses some challenges to these patients' perioperative anesthesia management. Although others have reported the challenges in providing anesthesia care to obese patients, few have described such challenges in morbidly obese patients.[2] To our knowledge, none have described such challenges in a morbidly obese patient with a BMI over 75 undergoing spine surgery that requires the patient to be in a prone position. The patient has given written consent for this report to be published.

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CASE DESCRIPTION

A 41-year-old woman with an enlarging cervical Schwannoma was scheduled to undergo a C2-C3 cervical laminectomy with intradural and extradural exploration with complex muscle flap closure. With a weight of 188 kg and a height of 157 cm, the patient had a body mass index (BMI) of 76.2 kg/m², indicating morbid obesity. Her past medical history included obstructive sleep apnea, for which she used a continuous positive airway pressure device at night. A pulmonology consultation suggested the need for bi-level positive airway pressure (BIPAP) both before surgery for lung recruitment and after surgery to meet the patient's postoperative respiratory requirements. Because morbidly obese patients have a higher incidence of medical comorbidities such as diabetes, chronic obstructive pulmonary disease, hypertension, and coronary artery disease, an internal medicine consultation was also obtained as per our institutional practice, which helped rule out any cardiac pathology and identified a plan for post-operative glucose management. Since obtaining peripheral intravenous access is challenging in obese patients, to avoid delay on day of surgery a central venous double lumen 8 French line was placed the day before surgery by interventional radiology. (Figure 1)

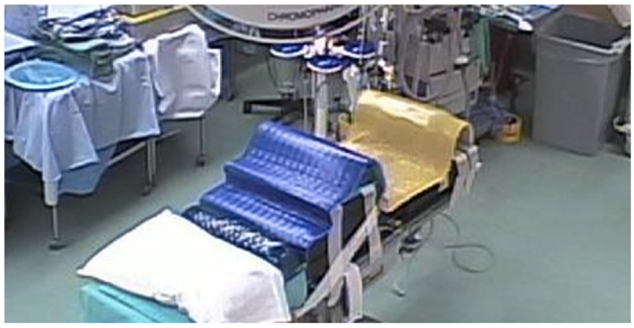

Figure 1: Operating table set up prior to surgery after the trial of positioning the day before.

We anticipated that placing this patient in a prone position would be very challenging. Therefore, we performed a trial run the day before surgery. We did this primarily to identify the adjustments we would need to make to minimize pressure related injuries, get adequate surgical exposure and to unfold potential pitfalls in delivering this optimal care. We chose to use the Hercules bed 6702 Hercules (Skytron) which has a weight capacity of 1200 pounds (1000 pounds flexed or offset center), and bilateral lateral extension attachments, which made the bed 8 inches wider than a regular surgical bed, to accommodate the patient's wider torso and the wider knee placement.

After the goals of the trial run and the plan for the next day's surgery had been communicated to the nursing, surgery, and anesthesiology teams the patient was brought into the operating room, where she moved herself from the gurney to the operating table and placed herself in the prone position. She provided feedback on roll placement and comfort, and we identified possible pressure areas and aligned the rolls to accommodate her height. For example, when the patient flexed her knees and her pelvis (which was supported on gel rolls), her knees did not reach the bed; therefore, we added padding to support them. Extended straps were attached to the operating table and were determined to be sufficiently long and secure to be effective. (Figure 2)

Figure 2: Patient positioned on operating room table and secured.

At this time it was discovered the patient's body habitus and positioning foam brought patients head too far away from the bed for usual Mayfield pinning. We needed an extra 6 inches of Mayfield frame to reach the patients head. By reversing the table attachment and adding a "dog bone" attachment and carefully positioning the locking mechanism to not impinge on the face, we were able to gain the necessary height and anticipated using the Mayfield. (Figure 3)

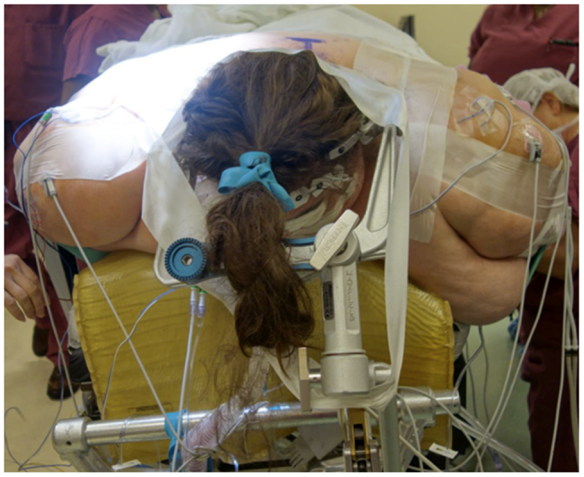

Figure 3: Patient head in Mayfield pins.

After the patient left the operating room, the anesthesia and nursing teams discussed findings and next-day plans. The

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operating table was prepared, and additional padding and positioning gel for arm placement on the arm boards were procured. The teams determined that full-length gel padding would be used to prevent sores and that a rolling action would be used to prevent the abrasions that can result from traditional transfers.

The next morning, the patient was brought to the operating room and preoxygenated with continuous positive pressure until her tidal oxygen concentration was >90% to compensate for her very poor pulmonary reserve due to decreased lung volume and functional residual capacity.[3,4] Ramped position used to assist with intubation. After intravenous anesthesia induction, with propofol 300 mg, succinylcholine 140 mg and fentanyl 100 mcg, she was intubated using a C-MAC video laryngoscope. To prevent intra-operative atelectasis during mechanical ventilation, we performed recruitment maneuvers using an intermittent positive end-expiratory pressure of up to 20 mmHg very 30-60 minutes throughout the case.[5-7] Prior to positioning Rocuronium 30 mg was given, after which no further muscle relaxant given due to motor evoked potential monitoring. A slow rolling transfer was performed to place the patient in the prone position. The eyes were taped shut and we ensured that there was no pressure on the eyes.

Total intravenous anesthesia along with multimodal analgesia was utilized as intra-operative neurophysiology monitoring was to be performed. The hemodynamic monitoring included invasive arterial blood pressure and central venous pressure, BIS monitor was utilized to determine depth of anesthesia We used lidocaine (1.5 mg/minute), ketamine (5 mg/hour), dexmedetomidine (0.5 mcg/kg/hour), Sufentanil (0.15 mcg/kg/hour) and propofol, (75-150 mcg/kg /min) along with intravenous acetaminophen (1 gm every 6 hours) during surgery. We adjusted the doses of the above medication, empirically, for the body weight of 100 kg not utilizing either lean body weight or Allometric scaling but titrating to effect of BIS between 30 to 55.[7] Throughout the whole operation her oxygen saturations stayed between 99-100% and end tidal carbon dioxide was between 33 to 38 mmHg. Thus, at the end of the 9.5-hour surgery, we had given Ketamine 30 mg, Sufentanil 130 mcg, hydromorphone 2 mg total, along with a fluid balance of 1700 ml of crystalloid in and Output of 810 ml of urine and 500 ml blood loss. At the end of surgery she was transferred to the bed in a sitting position, there was minimal facial edema and leak around the endotracheal tube was noted and then she was extubated in the operating room. She woke up comfortable and was able to follow commands. We helped prevent atelectasis by using the Boussignac CPAP system (Vitaid), which creates positive end-expiratory pressure that can be adjusted by changing oxygen flows. The patient was taken to the intensive care unit for monitoring and was placed on Bilevel Level Positive Airway Pressure (BIPAP) to prevent atelectasis. This period was crucial and required multimodal analgesia with hydromorphone, intravenous acetaminophen and pregabalin to provide adequate pain control and prevent somnolence. Multidisciplinary teams assisted in the patient's recovery.

DISCUSSION

The coordinated efforts of the day before surgery, which included establishing a communication pattern and identifying potential problems, helped facilitate successful anesthesia care.

There are several challenges in the perioperative anesthetic management of the morbidly obese. In the literature are highlighted various strategies of managing the potentially difficult airway, ventilation difficulties and risk of excessive sedation.

In positioning the patient, our primary goals were to expose the surgical site, facilitate ventilation, and stabilize the head and neck; immobilize the body to prevent intra-operative shifting; and perform interventions to prevent pressure sores and/or nerve injury.

Techniques for achieving the above include immobilizing the head in a neutral position, properly placing chest rolls, and providing abdominal support with pelvic gel rolls to eliminate pressure on the abdomen.

Here we showcase the importance of planning ahead of time. With the placement of central line the day before with help of interventional Radiology made that safer for the patient and decreased the time spent in the operating room.

To our knowledge a "trial run" for positioning has not been described for positioning of morbidly obese patients for spine surgery. As stated, we did identify several issues like the knee support and the Mayfield frame fit. As we had done this, the day before surgery, it gave us time to get the additional attachment for the frame.

Another lesson learned was that once the patient had muscle relaxant administered her legs had little tone and tilted to the side in the prone position, this required some support and additional padding.

The prone position is actually advantageous for ventilation, as it increases blood flow to the dependent lung, increases functional residual capacity, better drainage of secretion and the heart is against the sternum thus less of the lung is compressed.[8]

Thus, planning for positioning in the operating room, judicious fluid management, multimodal pain management and intermittent lung recruitment methods during surgery helped our patient have an uneventful perioperative course.

CONFLICTS OF INTEREST: None.

CONSENT

The patient has provided written permission for publication of the case details.

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Case Series

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Isolated Prolonged Activated Partial Thromboplastin Time and Contact Factor Deficiencies: Case Series and Management Review

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ABSTRACT

Background: Contact factor deficiencies are rare disorders that can cause grossly prolonged activated partial thromboplastin time (aPTT) and activated clotting time (ACT) while rarely affecting *in vivo* hemostasis. This *in vitro* laboratory phenomenon poses a particular challenge in surgical procedures that require anticoagulation monitoring.
Case: Here we report two cases of contact factor deficiencies; a 67-year-old morbidly obese female with factor XII deficiency requiring revascularization of a graft and a 58-year-old female with prekallikrein (PK) deficiency undergoing routine muscle biopsy.
Conclusion: Peri-operative anticoagulation monitoring poses a significant challenge in contact factor deficiency patients. Awareness of the challenges of contact factor deficiencies allows for optimal peri-operative management. Emerging literature supports that contact factors play a role in fibrinolysis. Increased surveillance of thrombotic events as well as avoidance of fibrinolytics may be necessary in these patients.

KEYWORDS: Prekallikrein (PK), Factor XII, Activated partial thromboplastin time (aPTT), Contact factors; Fibrinolysis; Anticoagulation; Prolonged clotting time; Thrombosis.

CASE 1

A 67-year-old morbidly obese (BMI=49.3) white female, status post recent aortobifemoral bypass, was transferred to our medical center for an emergent right axillary to bifemoral bypass following a newly diagnosed thrombosis of her graft. The patient had no previous records in our health system and limited preoperative laboratory workup revealed an isolated prolonged activated partial thromboplastin time (aPTT) (HemosIL™ SynthASil on ACL TOP 500 CTS, Instrumentation Laboratory, Bedford, MA, USA) of >200 seconds (normal range 25.8-37.9 seconds), which was attributed to the UFH administration during her outside hospitalization. The patient was brought emergently to the operating room where her baseline activated clotting time (ACT) (Hemochron®, International Technidyne Corporation; Edison, NJ, USA) was 567 seconds (normal range 105-167 seconds; with a target therapeutic level of 300-400 seconds); suggesting adequate anticoagulation. During surgery, the ACT was repeated twice at 1 and 2 hours and results were consistent with adequate anticoagulation (524 and 480 seconds, respectively) without the use of UFH.

Thirty-seven minutes later, following the 2-hour ACT, a thrombus was detected and the surgeon requested an immediate bolus dose of 10,000 units of UFH. ACT was then repeated and found to be >1500 seconds, exceeding the assay detectable limit. Instrument malfunctioning was suspected; however, a repeated ACT test on a different analyzer revealed similar results. Both analyzers were evaluated intra-operatively by a point of care quality assurance

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supervisor and were found to be performing within the standard limits. Intra-operative hemostasis was further managed by empirically dosing the patient with1000 unit/hour of UFH. Surgery was concluded 5 hours later without further complications and with a final postoperative ACT of 586 seconds. The patient's post-operative course was unremarkable with no incidence of excessive bleeding or thrombotic events.

Post-operative workup was initiated to identify the underlying etiology contributing to her abnormal laboratory findings. In addition to her peripheral vascular disease, her past medical history revealed hypertension, chronic obstructive pulmonary disease with an incidental left lower lung lobe mass (later found to be a moderately to well-differentiated squamous cell carcinoma), hyperlipidemia, bipolar disorder, and vitiligo. The patient had no family history of excessive bruising or bleeding and she had previously undergone surgical interventions without bleeding complications. Laboratory workup of the isolated prolonged aPTT is shown in Table 1. UFH effect was ruled out by Hepzyme (Siemens, Marburg, Germany); an enzyme that neutralizes UFH in the plasma sample. Lupus antibody panel (Instrumentation Laboratory) was performed and found to be negative. Mixing studies showed immediate correction of aPTT with a slight prolongation at 1 hour, suspicious for a factor deficiency. Further intrinsic factor analysis (Instrumentation Laboratory) revealed a FXII level of 0.0 U/mL (normal range 0.57-1.63 U/mL) with all other intrinsic factors within normal limits except a high FVIII level. FXII dilutions ruled out a specific factor inhibitor (Table 1). The patient was diagnosed with FXII deficiency and discharged on post-operative day 15.

CASE 2

A 53-year-old African American female with a past medical history of hypertension presented to her primary care physician with diffuse myalgias, elevated creatine kinase levels of 976 U/mL (reference range 34-145 U/mL) (Roche/Hitachi analytes, Indianapolis, IN, USA), and a positive anti-nuclear antibody at 1:360 with nucleolar staining (Zeus Scientific, Branchburg, NJ, USA). Muscle biopsy was recommended and the routine blood workup revealed a normal prothrombin time (PT) and a markedly prolonged aPTT (Instrumentation Laboratory) of >200 seconds (Table 2). The patient has no previous history of a prolonged aPTT and no recent history of anticoagulation use. She denied any history of excessive bleeding, bruising, or epistaxis. She reported having an older sister with an "abnormal coagulation disorder", but no other known family history of bleeding or thrombosis.

Lupus antibody panel was performed as part of the prolonged aPTT workup and was found to be negative. The aPTT mixing study showed immediate correction without subsequent prolongation, indicating a factor deficiency. Factor analysis revealed normal levels of FXII, FXI, FIX, and FVIII (Table 2). These findings suggested a deficiency in an upstream precursor of the intrinsic pathway such as HMWK or PK, both which would require a send out to a reference laboratory. During this time, our lab performed a PK screening test utilizing prolonged pre-incubation times with aPTT reagents as previously described.[1] Briefly, patient plasma sample is pre-incubated with an activator (silica in our case) (STAGO Compact, Diagnostica

Test	Normal Range	Units	Pre-operative	Post-operative
Prothrombin Time (PT)	9.2-12.3	Seconds	13.6	10.4
INR	1.0-1.2	-	1.3	1.0
Activated Partial Thromboplastin Time(aPTT)	25.8-37.9	Seconds	>200	>200
aPTT with Hepzyme	25.8-37.9	Seconds	-	>200
Lupus Anticoagulant	Negative	Seconds	-	Negative
aPTT mixing study				
- at 0 min	25.8-37.9	Seconds	-	36.0
-at 30 min	25.8-37.9	Seconds	-	37.3
- at 60 min	25.8-37.9	Seconds	-	40.3
Fibrinogen	172-409	mg/dL	-	563
Thrombin Time	11.7-15.0	Seconds	-	15.6
FVIII	0.68-1.56	U/mL	-	3.12
FIX	0.92-1.61	U/mL	-	1.59
FXI	0.60-1.54	U/mL	-	0.95
FXII	0.57-1.63	U/mL	-	0.0
- at dilution (1:10)			-	0.01
- at dilution (1:20)			-	0.0
- at dilution (1:40)			-	0.0

Table 1: Preoperative and postoperative laboratory findings of case 1 patient.

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Test	Normal Range	Units	Results
PT	9.2-12.3	Seconds	11.6
aPTT	25.8-37.9	Seconds	>200
aPTT with Hepzyme	25.8-37.9	Seconds	>200
Lupus Anticoagulant		Negative	Negative
aPTT mixing study			
- at 0 min	25.8-37.9	Seconds	36.3
- at 30 min	25.8-37.9	Seconds	35.6
- at 60 min	25.8-37.9	Seconds	37.2
FVIII	0.68-1.56	U/mL	0.88
FIX	0.92-1.61	U/mL	1.28
FXI	0.60-1.54	U/mL	1.22
FXII	0.57-1.63	U/mL	0.74

Table 2: Laboratory findings of case 2 patient.

Stago, Parsippany, NJ, USA) for a longer period of time prior to the re-calcification step; resulting in a normalization of aPTT.[1] This unique *in vitro* phenomenon is thought to be due to the auto activation of FXII in the absence of PK.[1,2] In our case, the patient's plasma was incubated at the aPTT standard incubation time of 240 seconds and then subsequently at 480 seconds, 960 seconds, and 1440 seconds prior to re-calcifications with final aPTT values of >235, 140.1, 67.8, and 53.6 seconds, respectively (Figure 1). Our results yielded the characteristic normalization of aPTT suspicious of PK deficiency. In addition to our qualitative screening studies, PK deficiency was also quantitatively confirmed to be <15% (normal range 55-207%) by a reference laboratory utilizing STA-R Evolution (Diagnostica Stago, France). The patient underwent a routine muscle biopsy without any complications. Of note, one year later our patient experienced bilateral pulmonary embolisms with a negative malignancy workup, and was placed on warfarin.

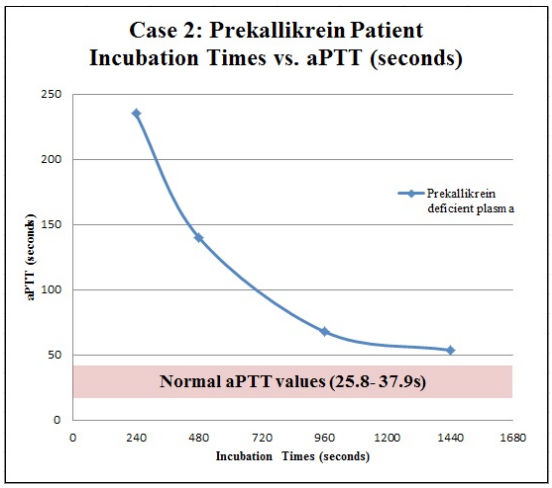

Figure 1: Incubation times versus aPTT (seconds) of second patient (PK deficiency). Patient plasma was preincubated prior to the addition of calcium with silica activator for a series of different times, and aPTT was subsequently measured after addition of calcium. The times measured were 240 seconds (standard time), 480 seconds, 960 seconds, and 1440 seconds yielding aPTTs of >235, 140, 67.8, and 53.6 seconds, respectively. Results below show a characteristic normalization curve of aPTT with prolonged incubations suspicious of PK deficiency.

DISCUSSION

Contact factor deficiencies are rare disorders that are usually detected incidentally during peri-operative screening. As opposed to the other intrinsic coagulation factor deficiencies (FVIII, FIX, and FXI), which cause hemorrhagic diathesis, contact factor deficiencies do not cause excessive bleeding.[3] Contact factors are however essential for *in vitro* initiation of coagulation screening tests utilizing negatively charged surfaces, such as aPTT and ACT.[3] A grossly prolonged aPTT (>120 seconds) is very common in contact factor deficiencies as compared to the downstream intrinsic factor deficiencies (i.e. FXI, FIX, or FVIII). Thus, a contact factor deficiency interference with ACT poses a greater challenge in surgical or invasive medical procedures that require UFH monitoring.

Factor XII Deficiency

The pathogenesis of FXII deficiency can be either congenital or acquired. The former is usually inherited autosomal recessively.[4] Acquired FXII deficiency is commonly seen in nephrotic syndrome but has also been described in autoimmune entities, malignancy, and after liver transplantation.[5] The prevalence of FXII deficiency is unknown, as most patients remain asymptomatic and undiagnosed. Epidemiologic literature studies estimate a 1-3% prevalence,[6] with a higher incidence reported in patients with coronary heart disease as high as 10%.[7] FXII deficiency is also linked to high incidences of thrombosis (e.g., acute coronary syndrome, miscarriages, and deep venous thrombosis).[7,8]

Prekallikrein Deficiency

PK deficiency can be either acquired or inherited; the latter is generally autosomal recessive.[9] PK is also essential for *in vitro* initiation of the intrinsic pathway of the coagulation cascade. As discussed in the second case, the grossly prolonged aPTT in PK deficiency can be normalized by a prolonged incubation with the aPTT activator before the re-calcification step.[1] This phenomenon is believed to be due to the auto-activation of FXII.

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PK plays a significant role in fibrinolysis through the activation of Kallikrein which can convert plasminogen to plasmin.[10] As in FXII, PK deficiency has been associated with increased risk of arterial and venous thrombosis. Evidence recommends the avoidance of anti fibrinolytics in these patients due to their potential underlying impaired fibrinolysis.[11]

Peri-operative Monitoring of UFH in Contact Factor Deficiency Patients

Numerous approaches have been suggested to monitor UFH in these patients peri-operatively,[11,12] including empiric dosing of UFH without monitoring anticoagulation effect,[13] measuring UFH concentrations directly through blood heparin concentrations utilizing a protamine titration protocol[14] or indirectly by anti-Xa levels,[15] administration of fresh frozen plasma (FFP) to obtain a normal baseline ACT and then subsequent monitoring of ACT levels,[11,16] and more recently using a modified ACT test utilizing *in vitro* mixing of patient samples with FFP to calculate normal ACT values.[17] Each method inherently has its own advantages and limitations and the optimal strategy is based on the complexity of the surgical procedure as well as the hemodynamic status of the patient.

The simplest and most commonly used method is empirically dosing the patient with UFH without monitoring (i.e., ACT) during the procedure.[13,16] Once the procedure is completed, UFH anticoagulation effect can then be reversed by protamine sulfate. Although abnormal, a baseline ACT may be helpful in this method to target the UFH reversal.

Utilization of anti-Xa levels was also used to indirectly monitor UFH. However, this method is labor intensive, time consuming and expensive.[11] Blood heparin levels using a protamine titration curve can be measured in the peri-operative period. This is also a time consuming method and requires special instrumentation such as Hepcon (Medtronic Perfusion Systems, Minneapolis, Minnesota, USA) that may not be readily available.[14]

Peri-operatively transfusion of FFP is another common method used to normalize baseline aPTT and ACT values. Administration of FFP to increase FXII levels was first proposed by Wood et al. and has been successfully implemented in several procedures.[11,16] It is estimated that an initial dose of 10 mL/kg of FFP should raise all coagulation factor levels by about 0.25 U/mL unless the patient is bleeding or experiencing an active thrombosis and/or sepsis that surges coagulation factor consumption (e.g., disseminated intravascular coagulopathy - DIC). Thus, an estimated starting dose in a 70-kg patient with FXII or PK levels of 0.0 U/mL would be approximately 5-6 units of FFP, which is clinically impractical. Furthermore, 50% of this dose may need to be repeated every two days in some cases where a longer monitoring of UFH is required (FXII and PK half-life is 40-50 and 58 hours, respectively). It is questionable that infusing such large volume of FFP solely for anticoagulation monitoring without any known therapeutic advantage outweighs the risk of rare but serious transfusion-related complications such as transfusion associated circulatory overload (TACO), transfusion related acute lung injury (TRALI), and infection. This method is best considered for those patients at high risk of thrombosis (e.g., malignancy, previous thrombotic events) and/or low weight patients who require close peri-operative monitoring of UFH.

To avoid exposure to FFP a modified ACT method was proposed by Gerhardt et al.[17] In this method, an individualized dose of FFP is added to an *ex vivo* blood sample prior to establishing a baseline ACT. This method however is time consuming, requiring preoperative generation of a patient-specific FFP curve, and the ACT values may not be accurate due to differences in ATIII levels in both FFP and patient plasma.[17]

In addition, viscoelastic tests, such as thromboelastography (TEG), have also been studied in cases of contact factor deficiencies, however they yield mixed results. In one study of PK deficiency, TEG parameter values failed to detect a contact factor deficiency whereas ACT and aPTT were abnormal.[14]

In summary, we report two case reports of contact factor deficiencies incidentally diagnosed during peri-operative workup. In case 1, empiric dosing of heparin intra operatively allowed for successful continuation of bypass graft surgery. In case 2, routine muscle biopsy was performed successfully without any significant adverse events. Coincidentally, both patients experienced thrombotic events during the time of having a deficient coagulation factor, supporting the notion that these patients are not protected against thrombotic events at may be at risk for prothrombotic tendencies. Thus contact factor deficiencies are a rare but important differential diagnosis for an isolated prolonged aPTT that must be recognized early for anticoagulation monitoring and surveillance of thrombotic events.

AUTHORSHIP CONTRIBUTIONS

N. Patel and M.A. Refaai analyzed the data and drafted the manuscript. G.W. Conley and L.A. McElroy contributed to the collection and interpretation of the data and critical review of the manuscript.

CONFLICTS OF INTEREST

The authors do not declare any conflicts of interests.

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Case Report

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Case Report in Anesthesiology: Essential Pulmonary Hypertension in a Primigravida

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CASE REPORT

A 21-year old gravida 1, para 0, female with a past medical history of Pulmonary Hypertension (PH) secondary to a congenital heart disease (patent foramen ovale), diaphragmatic hernia status post repair, asthma, and attention-deficit/hyperactivity disorder presented to a tertiary care hospital at 30 weeks gestation for a right heart catheterization. The catheterization was completed without complications and it was found that the patient's Pulmonary Arterial Pressure (PAP) was 54/32 with a mean value of 39. The PAP was only minimally improved to 46/30 with a mean of 35 after nitric oxide administration.

When the patient presented for follow up, she was complaining of shortness of breath for the last two months and she is unable to walk up a flight of stairs. Due to her history, the patient was admitted to the hospital and was seen by a pulmonologist and an obstetric consultation was ordered. It was determined that the only medications the patient was taking at home were Symbicort, Prenatal Vitamins, Lovenox, Xoprenex, and an iron supplementation. On physical exam, the only pertinent positive was shortness of breath. Her pulmonary history was also significant for a FEVI of 36.6%, and a FEV1/FVC ratio of 62.6%. Given her history of pulmonary arterial hypertension, she was placed on sildenafil 20 mg TID, an epoprostenol drip and lovenox was started after central line placement. An echocardiogram showed an ejection fraction of 60-65%, mild to moderate right ventricular hypertrophy, severe tricuspid valve regurgitation, a right to left shunt and a right ventricular systolic pressure of 104 mmHg (increased from 73 recorded a few weeks prior). Due to her declining right ventricle function, she was started on steroids to induce fetal lung maturity. Over the next few days, the patient developed chest pain, jaw pain, decreased fetal variability, increased oxygen and epoprostenol requirements and hypotension treated with IV fluid boluses. A multidisciplinary care conference including maternal fetal medicine, anesthesia, SICU/PICU surgery team, pulmonary NICU, Labor and Delivery RN, and a pastor was held in order to determine a plan for delivery given the 50% risk of maternal mortality. It was concluded that the patient would undergo an elective cesarean section and bilateral tubal ligation in two days time.

At the time of delivery, the patient was 31 5/7 weeks gestation on 8 liters of oxygen and an epoprostenol drip infusing a 14 mg/kg/min. The morning of surgery, the patient was brought to the preoperative area five hours prior to her surgery. An arterial line was placed in her left dorsalispedis. An epidural was placed at the L3-L4 level without incident. The lidocaine epidural was slowly infused epidural over a period of one hour, mindful to monitor the patient's hemodynamics with the arterial line. The patient was brought to the operating room where she was placed in a supine position with a leftward tilt to avoid inferior vena cava compression. The cesarean section was completed without complications and one dose of methergine was given to control uterine bleeding. Next, a bilateral tubal ligation was carried out without difficulty. Post-partum, the patient did very well. She received dilaudid for pain control and heparin for DVT prophylaxis. Over the next couple of days, her DVT prophylaxis was switched to lovenox, her epoprostenol was increased to 16 mg/kg/min and her oxygen requirement dropped to room air at rest, 3 liters on exertion and 1 liter at night. The patient recovered well and was discharged 5 days after delivery.

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A patient with pulmonary arterial hypertension has substantial risks associated with pregnancy.[1] Pulmonary hypertension is defined by a resting mean pulmonary artery pressure greater than 25 mmHg and a pulmonary capillary wedge pressure less than 15 mmHg in the absence of other causes of precapillary pulmonary hypertension. Clinical classification of PH has been updated in 2008 and divided into five groups by the World Health Organization (WHO). The groups include pulmonary arterial hypertension (Group 1), pulmonary veno-occlusive disease and/or pulmonary haemangiomatosis (Group 1), PH due to left heart disease (Group 2), PH due to lung disease and/or hypoxia (Group 3), Chronic thromboembolic PH (Group 4), and PH with unclear multifactorial mechanism (Group 5).[2] Mortality in pregnant women with PH is has been quoted as 30% for primary PH, 36% for Eisenmenger's syndrome and 50% for secondary PH. Despite this improved mortality, recent practice guidelines from the European Society of Cardiology and the American Heart Association/American College of Cardiology strongly discourage pregnancy in patients with PH and advise termination in early pregnancy.[3]

Pregnancy is heavily discouraged and contraception emphasized due to the difficulty for patients with PH to cope with the hemodynamic changes related to pregnancy. The changes include increased blood volume, red cell mass, heart rate, cardiac output, left ventricular mass, and decreased pulmonary vascular resistance. The blood volume increases through pregnancy until a plateau occurs between 28 and 34 weeks gestation and remains stable until delivery. The circulating blood volume is increased to 30-50% above the normal state and red blood cell mass is increased to 25% above the non-pregnant state. In order to accommodate for these physiological changes, there is a decrease in peripheral vascular resistance. However, patients with pulmonary arterial hypertension are unable to make this adjustment,[4] restricting the normal progressive increase in pulmonary plasma volume and further stressing the right ventricular load. The drop in systemic vascular resistance increases cardiac output and renal blood flow, which cannot be handled by a failed right ventricle. In addition, in patients with right-to-left shunts, the shunting of blood worsens due to the increased pulmonary pressure, exacerbating hypoxia and pulmonary vasoconstriction.

Furthermore, additional challenges are presented during labor and delivery. During delivery, approximately 500 ml of blood is diverted from the uterine to the material circulation with every uterine contraction, leading to increased cardiac output and venous return. The pain of parturition stimulates the sympathetic nervous system leading to an increase in heart rate, blood pressure and myocardial oxygen consumption, which is further exaggerated during valsalva maneuvers. The pain, acidosis, hypoxia and hypercarbia associated with delivery may increase pulmonary vascular resistance. In addition, acute hypotension from blood loss or vasovagal response during delivery may acutely drop systemic pressure and produce right ventricular ischemia. After delivery, the relief of inferior vena cava compression and auto transfusion from the emptied uterus causes a transient increase in cardiac output and venous return. As a result of the extreme changes to the maternal circulatory system, the highest mortality rate is seen within the first month after delivery.

As of today, there is no consensus on the gold standard management for essential pulmonary hypertension in pregnancy with regards to timing of delivery, choice of delivery technique, and anesthetic choice. Most of the recommended practices are based on case reports and what has been successful for individuals in the past. If a patient with pulmonary hypertension does become pregnant life style changes such as rest, low salt diet and quitting smoking should be implemented. Due to ongoing research, there have been more medications available for the treatment of pulmonary hypertension and aggressive intervention early on may improve outcomes. There are three classes of medication that have entered clinical practice in recent years, resulting in improvements in both functional status and survival.[5] One class of medication is the endothelial receptor antagonist (bosentan, sitaxsentan, and ambrisentan). The second class of medication is the phosphodiesterase-5 inhibitors (sildenafil and tadalafil). These medications have the convenience of being taken orally and sildenafil received FDA approval for the treatment of pulmonary arterial hypertension in 2005. The third class of medication is prostacyclin/ the prostacyclin analogues (epoprostenol, iloprost, treprostinil). Epoprostenol is given IV, iloprost can be administered IV or nebulized, and treprostinil is given *via* subcutaneous route. The use of inhaled prostacyclin analogues results in greater concentration of the medication in the pulmonary circulation, and has a theoretical advantage of avoiding some systemic side effects such as hypotension and inhibition of platelet aggregation. Calcium channel blockers are also a treatment option, but should only be used in patients with a functional class II or III in the setting of a positive response to a vasodilation trial. These medications should only be used in a subset of patients and hypotension should be avoided. In addition, a number of case studies report the successful use of nitric oxide around the time of delivery to minimize right ventricular afterload and acutely drop pulmonary vascular resistance.

Even though diuretics are avoided in pregnancy, torsemide or furosemide can be carefully used to manage right heart failure. Antithrombolytic therapy is also recommended for patients with pulmonary arterial hypertension. Warfarin should be avoided between 6 and 12 weeks due to embryonic toxicity. Low molecular weight heparin is the drug of choice since it does not cross the placenta and most physicians will switch to unfractioned heparin near delivery because it is more readily reversible in the event of a hemorrhage.

The mode of delivery is another controversial topic in patients with pulmonary hypertension. The advantages of a vaginal delivery are there are smaller shifts in blood volume, fewer clotting and bleeding complications and a lower risk of infection. However, the disadvantages are a prolonged second stage of labor, uncontrolled vaginal hemorrhage, and adverse hemodynamic effects of the valsalva maneuver. In comparison, the advantages of a caesarian section are it can be performed at

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a suitable time under relative stable conditions, and it can be utilized in urgent deliveries. The disadvantages include increased risk associated with anesthesia, larger shifts in blood volume, more clotting and bleeding complications, higher risk of infection and increased peripheral vascular resistance and right ventricular afterload imparted by positive pressure ventilation in the setting of endotracheal intubation.

A caesarean section is necessary in cases of maternal hemodynamic deterioration or fetal distress requiring emergent delivery. In one study, a planned caesarean section at 34 weeks (the time when blood volume increases by 50%) was the preferred method of delivery in stable patients. The justification was a caesarean section can be scheduled during the day with specialists on hand, timing and bimanual compression and suture compression can aid in blood loss. Some studies suggest that if a vaginal delivery is going to be attempted, it should be done in the operating room or in the intensive care unit.

There is no gold standard approach to anesthesia management in a patient with pulmonary arterial hypertension.[6] During the peripartum period, patients require careful monitoring of oxygen saturation, blood pressure, and heart rhythm. An arterial line and central venous catheter should be placed to monitor blood pressure and right atrial pressure. There is lack of evidence supporting the use of a pulmonary arterial catheter and it is not advised due to its potential complications. During the time of delivery, general anesthesia is mostly avoided. General anesthesia is associated with a higher mortality and it is known to depress cardiac contractility, increase pulmonary vascular resistance, decrease venous return due to positive pressure ventilation, and may result in increased pulmonary arterial resistance during laryngoscope and intubation.[7] Adequate oxygen, slight hypocapnia, adequate anesthesia level, continuous nitric oxide inhalation and infusion of prostacyclin may all be supportive and help prevent right heart failure caused by the stress of intubation and the operation. After delivery, increasing the nitric oxide dose and maintaining anesthesia with propofol and fentanyl minimizes right ventricular afterload and volume centralization respectively.

Due to the risk associated with general anesthesia, epidural anesthesia or combined spinal anesthesia is recommended. Epidural anesthesia has less effect on cardiac contractility and pulmonary vascular resistance, but the blocks are contraindicated in anticoagulated patients and if used in a caesarean section, it may produce a large decrease in venous return because of the large sympathetic block. Cardiovascular compromise may occur during delivery, which can be treated with dobutamine, norepinephrine or a combination of the two, which provides positive inotropic effects and beneficial right ventricular – pulmonary coupling.

In conclusion, even though the risk of mortality for a patient who becomes pregnant with pulmonary hypertension has decreased, the risk is still substantial enough to advice against it. However, due to further research and medication options physicians are better able to manage pregnancies complicated by pulmonary arterial hypertension. The consensus guidelines recommend the use of epoprostenol and sildenafil to lower pulmonary resistance prior to delivery and aggressive therapy prior to clinical deterioration. This approached worked well for the patient presented. In addition, there is debate over the preferred delivery method as well as the anesthesia management. The patient at hand received a slow infusing epidural and a scheduled caesarean section with arterial line and central line monitoring. The patient and her infant survived the delivery and were discharged home in good condition. Furthermore, the use of lovenox for DVT prophylaxis and unfractioned heparin near the time of delivery was shown to be successful in the case presented. It is unanimously agreed that a multidisciplinary approach is needed to order to properly care for a patient who is pregnant with pulmonary arterial hypertension. Additional research and clinical trials on pulmonary hypertension complicated by pregnancy in needed in order to decrease the risk or mortality since more young women with the disorder are able to reach child bearing age.

CONFLICTS OF INTEREST: None.

CONSENT

The patient has provided written permission for publication of the case details.

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A Comparative Study of Ropivacaine Alone *Versus* Ropivacaine With Dexmedetomidine in Supraclavicular Brachial Plexus Block

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ABSTRACT

Background and Aims: Supraclavicular brachial plexus block is frequently used procedure to provide anaesthesia and good post-operative analgesia for surgery on upper limb. The purpose of this study was to compare the hemodynamic, sedative and analgesic effects of ropivacaine alone *versus* ropivacaine given along with dexmedetomidine.
Materials and Methodology: This prospective, randomized and double-blinded study included total 60 patients of either sex with age between 18-60 years posted for various elective upper limb surgery and randomly allocated into 2 equal groups of 30 each. Control Group-R received injection ropivacaine (0.75%) 30 ml plus 1 ml normal saline and Group-RD received injection ropivacaine (0.75%) 30 ml plus dexmedetomidine 25 µg (1 ml) for supraclavicular brachial plexus block using the peripheral nerve stimulator. Sensory and motor block, monitoring of vitals (systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR)), presence of any side effect, Ramsay sedation score and visual analogue scale or visual analog scale (VAS) score were determined every 5 mins in 1st 30 mins and then every 15 mins during 1st hr followed by every 2nd hourly during 24 hrs.
Results: There was no significant difference in the study groups with regards to demographic profile and duration of surgery. The onset of sensory and motor blockade was faster in Group-RD than Group-R. {Onset of sensory block: (Group-R=14.133±1.676 min and Group-RD=12.667± 1.213 min) (p=0.000), Onset of motor block: (Group-R=25.967±2.748 min and Group-RD=23.333±3.467 min) (p=0.002). Also total duration of sensory blockade {Group-R=547.833±26.152 mins, Group-RD=811.667±25.405 mins (p value=0.000)}, motor blockade {Group-R=509.667±24.703 mins, Group-RD=760.667±28.062 mins (p value=0.000)} and number of rescue injections in 24 hrs {Group-R=2.733±0.450, Group-RD=1.400±0.498 (p value=0.000)} was significantly different in 2 groups. There was good haemodynamic stability in both groups. SBP and DBP in Group-R and Group-RD with p values 0.416 and 0.784 were comparable between the groups. The difference was statistically not significant. There was no incidence of any side effects like hypotension and bradycardia in any of the 60 patients.
Conclusion: Dexmedetomidine in a dose of 25 µg added to ropivacaine in supraclavicular brachial block for upper limb surgery significantly shortens the onset time and prolongs the duration of sensory and motor block without producing sedation in patients.

KEYWORDS: Ropivacaine; Dexmedetomidine; Adjuvant; Supraclavicular brachial plexus block.

ABBREVIATIONS: IEC: Institutional Ethics Committee; BMI: Body Mass Index; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; ECG: Continuous Electrocardiogram.

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INTRODUCTION

Various approaches of brachial plexus block have been used for upper limb surgeries but supraclavicular brachial plexus block is mainly used for any surgery in the upper extremity that does not involve the shoulder because it is a safe technique with rapid onset and reliable anesthesia.[1]

Various local anesthetics have been used to provide brachial plexus block. Ropivacaine, a long-acting amide local anaesthetic related structurally to bupivacaine, has been used for supraclavicular block in upper limb surgery. It provides pain relief with less motor blockade and is less cardiotoxic than bupivacaine, which makes it a more suitable agent for supraclavicular brachial plexus block.

A variety of adjuvant has been already studied for brachial plexus blockade. Dexmedetomidine, a highly selective α-2 agonist with a relatively high ratio of α-2:α-1 activity (1620:1 as compared to 220:1 for clonidine), possesses all these properties but lacks respiratory depression, making it a useful and safe adjunct in diverse clinical applications. Presynaptic alpha-2 adrenoceptors are present in sympathetic nerve endings and noradrenergic neurones in the central nervous system (CNS) where dexmedetomidine binds and inhibits the release of noradrenaline. Dexmedetomidine has been already used for intravenous regional anesthesia.[2] Dexmedetomidine has shown greater affinity as an α-2 adrenoreceptor agonist than clonidine. The effect of dexmedetomidine when added to lidocaine for intravenous regional anaesthesia, demonstrated that addition of 1 mcg/kg dexmedetomidine to lidocaine improves quality of anaesthesia and intraoperative as well post-operative analgesia without causing side effects.[3]

Dexmedetomidine has not been associated with respiratory depression, despite frequently profound levels of sedation. It decreases sympathetic tone, with attenuation of neuroendocrine and haemodynamic responses to anaesthesia and surgery, reduces anaesthetic requirement, causes sedation and analgesia. Because of arousable sedation, lack of respiratory depression and analgesia sparing effect, dexmedetomidine might prove useful in post-operative period for patient undergoing surgical procedures that are associated with significant pain.

The purpose of this study is to compare the hemodynamic, sedative, and analgesic effects of ropivacaine alone *versus* ropivacaine given along with dexmedetomidine.

The present study was carried out on patients undergoing elective upper limb surgery during the period from May, 2013 to May, 2014 for period of 12 months.

The study was carried out to compare haemodynamic, sedative, sensory and motor effects of ropivacaine alone and ropivacaine along with dexmedetomidine in supraclavicular brachial block in upper limb surgery. Institutional Ethics Committee (IEC) approval was obtained. It was prospective, randomized and double-blinded study. The study included total 60 patients belonging to ASA grade I and II of either sex with age between 18-60 years posted for various elective upper limb surgery. Sample size was decided in consultation with a statistician. Most of the past studies on brachial plexus block were done with the sample size of total 60 patients. After observing results of various similar studies, it was considered that a clinically significant benefit of using dexmedetomidine would be a prolongation in sensory block duration of 15% (minimum) compared with the control group. Based on these estimates, we calculated a sample size that would permit a type I error of α=0.005 and power of 80%. Enrolments of 25 patients in each group was required. Considering the dropouts, 30 patients were selected in each of the group.

MATERIALS AND METHODS

Informed consent was taken from each patient who meets the following inclusion and exclusion criteria's. Inclusion criteria's were ASA I-II adult subjects, age between 18-60 years, of either sex, elective upper limb surgery, willingness to be contacted post-operatively. Exclusion criteria were age<18 or >60, body mass index (BMI)>35, ASA grade>II, any upper limb surgery involving shoulder, inability to understand protocol due to language barrier, hypersensitivity to amide local anesthetics or dexmedetomidine, uncontrolled anxiety, schizophrenia or bipolar disorder, pre-existing nerve damage in the extremity to be blocked, significant cardiovascular disease, renal impairment (creatinine>2.0 mg/dL), pregnancy.

Patients meeting the inclusion criteria during the pre-anaesthetic evaluation were randomly assigned into 2 groups of 30 each with the help of a computer-generated table of random numbers by simple randomization method. Total 31 ml of solution for supraclavicular brachial plexus blockade was administered as follows: patients of Group-R received injection ropivacaine (0.75%) 30 ml and 1 ml normal saline. Patients of Group-RD received injection ropivacaine (0.75%) 30 ml and dexmedetomidine 25 µg diluted in 1 ml normal saline.

Pre-anaesthetic evaluation was done on the evening before surgery. All patients included in the study were premedicated with tablet alprazolam 0.5 mg and ranitidine 150 mg orally at night before surgery.

On arrival of patients in the operating room, a 20 gauge intravenous cannula was inserted on the non-operating hand and infusion of normal saline was started. The patients were connected with monitor to record heart rate (HR), non-invasive measurement of systolic blood pressure (SBP), diastolic blood pressure (DBP), continuous electrocardiogram (ECG) monitoring and haemoglobin oxygen saturation (SpO_2). The baseline systolic BP, diastolic BP and HR were recorded.

One of the anaesthesiologists not involved in the care

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or monitoring of the patient, prepared the local anaesthetic study solutions. The patients and the observing anaesthesiologist as well as the physicians and nurses of the acute pain service were blinded to the study drug used.

The patients were placed in dorsal recumbent position with the head turned away from the site of injection. The injection site was infiltrated with 1 ml of lidocaine 2% subcutaneously. A nerve stimulator was used to locate the brachial plexus. Nerve stimulator "B Braun Stimuplex Dig RC" with needle length of 5 cm was used for the study. The location end point was a distal motor response with an output lower than 0.6 mA. During injection, negative aspiration was performed after every 6.5-7.0 ml to avoid intravascular injection.

Sensory and motor block along with monitoring of vitals was determined every 5 mins in first 30 mins and then every 15 mins during 1st hr followed by every 2nd hourly during 24 hrs. Any hypersensitivity reaction for the drugs, evidence of pneumothorax, and other adverse events were also monitored. To evaluate duration sensory block and motor block, patients were asked to inform the time when incisional discomfort as a sensation of pain began and also the time when full power returned to the shoulder. In the post-operative period, when the patient complained of pain at the operative site, injection Diclofenac 75 mg I/M was given. Patients were followed-up for 24 hrs for any side effects.

Sensory block was determined by the response to pin prick method using a visual analogue scale (VAS): [0-no pain, 2-mild pain, 5-moderate pain, 8-severe pain, 10-unbearable pain]. Assessment of motor blockade was done by bromage 3 point score. Assessment of sedation was done by Ramsay Sedation Scale.

Study parameters were defined as:

Onset of Sensory Blockade

Sensory block was assessed as loss of pinprick sensation using the blunt needle. Dermatomes C5 to T1 were assessed. Onset time is the time from the completion of injection of study drug till the loss of pinprick sensation completely.

Onset of Motor Blockade

Onset time of motor blockade is defined as the time from the completion of injection of study drug to paralysis of the upper limb.

Duration of Sensory Blockade

Duration of sensory blockade is the time from the onset of sensory blockade to till the patient's complaints of pain at the site of surgery. Rescue analgesia was given after that only.

Duration of Motor Blockade

Duration of motor blockade is the time from the onset of motor blockade to complete recovery of motor power.

Haemodynamic parameters were recorded at 0, 5, 10, 15, 20, 25, 30, 45 mins, 1st hr, 2nd hr and thereafter every second hourly till 24 hrs.

Post-operatively, all patients received routine analgesic intramuscular injection Diclofenac 75 mg when they started feeling pain (VAS>3). Time for first dose of rescue analgesic in post-operative period and total rescue analgesic requirement in 24 hrs were recorded. The maximum pain scores and Ramsay sedation score at different time intervals (at 0, 5, 10, 15, 20, 25, 30, 45 mins, 1st hr, 2nd hr and thereafter every second hourly till 24 hrs in post-operative period) for each patient were recorded.

Incidences of nausea and vomiting, respiratory depression and sedation were noted. All the parameters were recorded as per the proforma and subjected to statistical analysis.

Statistical Analysis

Data were expressed as mean values±standard deviation/standard error, percentages (%), and numbers (n). The statistical analysis was performed by a statistician using Windostat Version 9.2. Two statistical tests were primarily used to analyze the data and p value<0.05 was considered as statistically significant.

1) t-tests were used to analyze differences between 2 groups.

2) Analysis of variance (ANOVA) to analyze differences in parameters such HR, SBP, DBP, VAS score and Ramsay sedation scores over a period of time.

RESULTS

There was no significant difference in the study groups with regards to demographic profile and duration of surgery (Table 1). The onset of sensory and motor blockade was faster in Group-RD than Group-R. Onset of sensory block was (Group-R=14.133±1.676 min and Group-RD=12.667±1.213 min) (p=0.000), Onset of motor block was (Group-R=25.967±2.748 min and Group-RD=23.333±3.467 min) (p=0.002)} (Table 2). Total duration of sensory blockade and motor block was longer in Group-RD. Total duration of sensory blockade was Group-R=547.833± 26.152 mins, Group-RD=811.667±25.405 mins (p value=0.000)}, and motor blockade was Group-R=509.667±24.703 mins, Group-RD=760.667±28.062 mins (p value=0.000)} (Table 2) (Figure 1). The total number of rescue injections in 24 hrs was less in the study group, Group-R=2.733±0.450, Group-RD=1.400±0.498 (p value=0.000) which was significantly different in 2 groups

(Table 3). There was good haemodynamic stability in both groups. Heart rate in Group-R and Group-RD were compa-

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Demographic profile	Group-R(n=30)	Group-RD(n=30)	*p* value
	Mean±SD	Mean± SD	
Age (years)	38.233±11.723	35.633±9.661	0.352
Weight (kgs)	58.1±6.472	58.4±5.763	0.850
Height (cms)	159.5±4.632	159.8±3.881	0.787
Gender ratio(M:F)	17:13	14:16	0.446

Table 1: Demographic profile of patients.

Variables	Group R (n=30) Mean±SD	Group RD (n=30) Mean±SD	*p* value
Onset of sensory block (in min)	14.133±1.676	12.667±1.213	0.000
Onset of motor block (in min)	25.967±2.784	23.333±3.467	0.002
Duration of sensory block (in min)	547.833±26.152	811.667±25.405	0.000
Duration of motor block (in min)	509.667±24.703	760.667±28.062	0.000
Duration of surgery (in min)	101.633±31.012	103.500±33.040	0.822

Table 2: Onset time and duration of motor and sensory block and duration of surgery.

Total number of rescue injection in 24 hours	Group-R (n=30)	Group RD (n=30)	*p* value
	Mean±SD	Mean±SD	
	2.733±0.450	1.400±0.498	0.000

Table 3: Comparison of number of rescue injections in 24 hours.

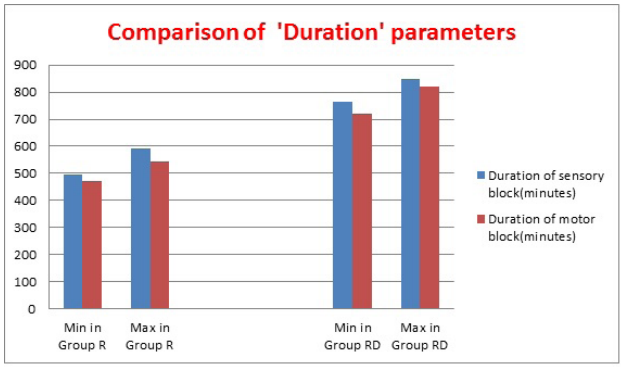

Figure 1: Bar graph showing comparision between duration of sensory and motor blockade.

rable. The difference was statistically not significant (p=0.476). There was no fall or rise in heart rate more than 15 beats in both groups (Figure 3). SBP and DBP in Group-R and Group-RD with p values 0.416 and 0.784 were comparable between the groups. The difference was statistically not significant (Figures 4 and 5). We found that there was no significant difference among the 2 groups in total 24 hrs of duration with respect to parameters like HR, SBP, and DBP. There was no incidence of any side effects in both groups. There was no incidence of hypotension and bradycardia in any of the 60 patients. The mean Ramsay sedation scores (RSS) of Group-R was almost equal to Group-RD. The difference was not significant (p=0.169) (Figure 2). Patients in Group-RD had zero VAS score for a longer duration than those in Group-R. Differences in VAS scores of the 2 groups was statistically significant (p=0.000) (Figure 6).

DISCUSSION

Dexmedetomidine is being used for intravenous regional anesthesia (Bier's block), intravenous sedation and analgesia for intubated and mechanically ventilated patients in intensive care units and non-intubated patients for surgical and other procedures. It has been reported to improve the quality of intrathecal and epidural anaesthesia. Its use in peripheral nerve blocks has been described. However, the reports of its use in supraclavicular brachial plexus block are limited. In this study, we investigated whether adding dexmedetomidine to ropivacaine for supraclavicular brachial plexus block would affect the sensory and motor blocks and duration of analgesia. Results in a study done with end stage renal disease showed that the motor and sensory block was longer in the dexmedetomidine group.[4] In a prospective double-blinded study on 70 patients, it was found that dexmedetomidine gives better haemodynamic stability and greater post-operative analgesia.[5] The effect of dexmedetomidine on brachial plexus block with ropivacaine and upper extremity ischemia-reperfusion injury in patients undergoing upper extremity surgery showed that dexmedetomidine can not only enhance the efficacy of brachial plexus block with ropi-

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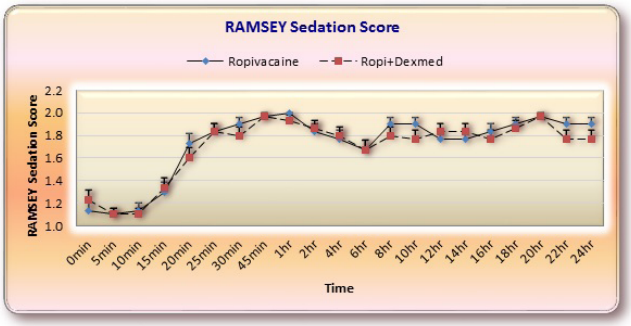

Figure 2: Comparision between sedation scores both the groups.

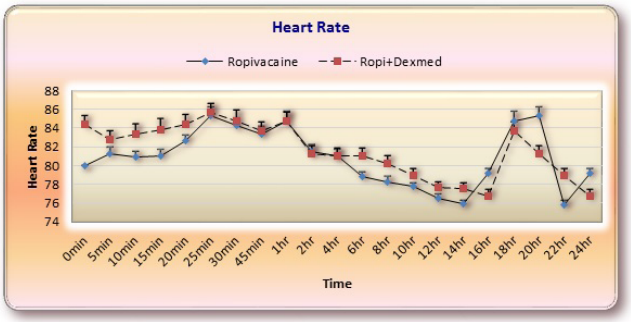

Figure 3: Heart rate at different time intervals in both groups.

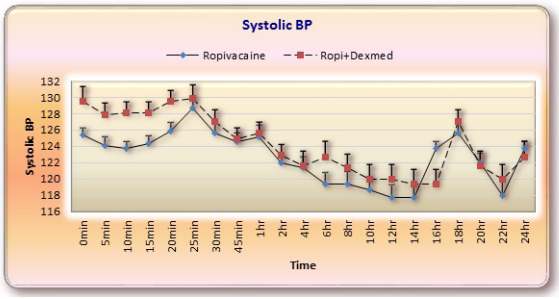

Figure 4: Systolic blood pressure (mmHg) at different intervals in both the groups.

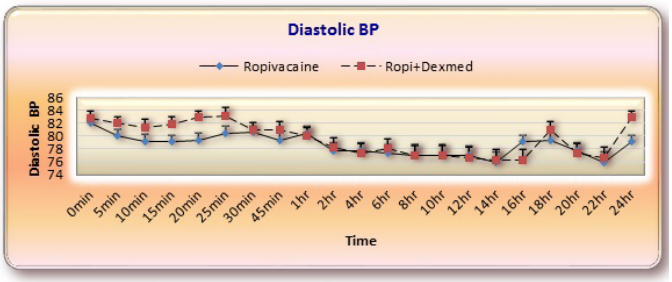

Figure 5: Diastolic blood pressure (mmHg) at different time intervals in both the groups.

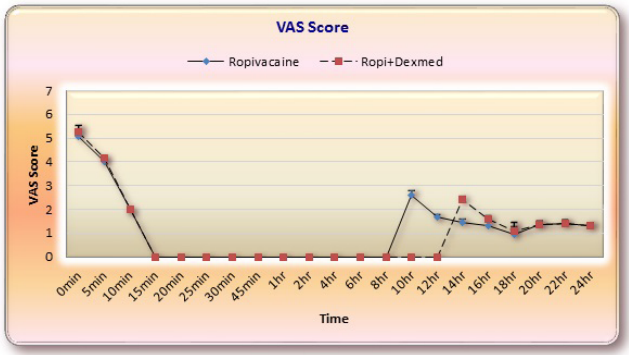

Figure 6: VAS scores at different time intervals.

vacaine, but also reduce the upper extremity ischemia reperfusion injury caused by tourniquet in patients undergoing upper extremity surgery.[6] A prospective, randomized, double-blinded, placebo-controlled trial on 50 patients, undergoing upper limb surgery under supraclavicular brachial plexus block to compare the effects of adding dexmedetomidine to a 30 ml solution of 0.325% bupivacaine in supraclavicular brachial plexus block showed that dexmedetomidine when added as an adjuvant to bupivacaine for supraclavicular brachial plexus block significantly shortens the onset time and prolongs the duration of sensory and motor blocks and duration of analgesia.[7]

The duration of analgesia, when only local anaesthetic is used is very short and does not extend into post-operative period for more than 3-4 hrs. Various drugs have been tried as adjuvant to local anaesthetics for prolonging the analgesia and improving the quality of block. Dexmedetomidine has been introduced in India in parenteral form and the effectiveness of the same for supraclavicular brachial plexus block has not been investigated in India, as very few studies have been done regarding the same. Hence, we selected dexmedetomidine as an adjuvant to ropivacaine in our study.

Ropivacaine has been found to be equally effective as bupivacaine for brachial plexus block by various authors.[8,9] Hence, ropivacaine was selected as local anaesthetic for our study.

In our study we used only 25 µg dexmedetomidine as adjunct to ropivacaine, because there are more chances to have bradycardia and hypotension with higher doses of dexmedetomidine.[10]

Various authors have used different volumes of ropivacaine for brachial plexus block. We used 30 ml of local anesthetic solution for brachial plexus block basing on few papers

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selected for our study.[11-13]

In a randomized double-blinded study of effects of dexmedetomidine added to caudal ropivacaine in paediatric lower abdominal surgeries found that caudal dexmedetomidine with 0.25% ropivacaine for paediatric lower abdominal surgeries achieved significant post-operative pain relief that resulted in better quality of sleep and prolonged duration of arousable sedation and produced less incidence of emergence agitation following sevoflurane anaesthesia.[14]

In our study haemodynamic parameters (HR, SBP, and DBP) were recorded at 0, 5, 10, 15, 20, 25, 30, 45 mins, 1st hr, 2nd hr and thereafter every second hourly till 24 hrs. There wasn't any incidence of fall in blood pressure more than 20 mmHg compare to baseline reading. No patient had respiratory depression, bradycardia or tachycardia. This shows that dexmedetomidine is not producing side effects like bradycardia and hypotension if it is used in small doses (less than 30 mg) as an adjuvant with local anesthetics in supraclavicular brachial plexus block.

CONCLUSION

Dexmedetomidine in a dose of 25 µg added to ropivacaine in supraclavicular brachial block for upper limb surgery significantly shortens the onset time and prolongs the duration of sensory and motor blocks without producing sedation in patients. Total number of rescue analgesics required in post-operative period is also less with use of dexmedetomidine as an adjuvant to ropivacaine.

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CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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