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Utilizing Dexmedetomidine for a Patient with Prolonged Tourniquet Time to Decrease Sympathetic Effects

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UTILIZING DEXMEDETOMIDINE FOR A PATIENT WITH PROLONGED TOURNIQUET TIME TO DECREASE SYMPATHETIC EFFECTS

by

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ABSTRACT

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Background: A 48 year old male presented with bilateral calcaneus fractures requiring open reduction and internal fixation. Tourniquet times for the patient's right and left legs were 151 and 153 minutes respectively. It is known that prolonged tourniquet applications of greater than 45-60 minutes results in an increased sympathetic nervous system (SNS) response that is resistant to inhaled anesthetics and narcotics. In this case study, we compared the patient's blood pressure and heart rate between the left and right calcaneus surgeries. A dexmedetomidine infusion was administered during the left calcaneus surgery and not for the right calcaneus.

Purpose: To evaluate the use of a dexmedetomidine infusion for the attenuation of the sympathetic nervous system response associated with prolonged tourniquet use.

Process: A systematic search for articles published in the last ten years related to tourniquet induced sympathetic nervous system response and dexmedetomidine was performed using Pubmed and CINAHL. This information was synthesized and compared to the case study in order to develop evidence based recommendations for the use of dexmedetomidine in the attenuation of tourniquet induced sympathetic nervous system response.

Results: Dexmedetomidine does significantly attenuate the sympathetic nervous system response related to prolonged tourniquet use.

Implications: Hemodynamic control of patients is essential to prevent organ damage, most notably cardiovascular and neurological damage. Attenuation of the sympathetic nervous system related to prolonged tourniquet use can prove to be a difficult task for the anesthetist. Dexmedetomidine has been shown to be a viable option to attenuate the SNS response and thus may positively impact patient outcome.

Keywords: dexmedetomidine; tourniquet; tourniquet pain; sympathetic nervous system response; orthopedic surgery; sympatholytic

Utilizing Dexmedetomidine for a Patient with Prolonged Tourniquet Time to Decrease Sympathetic Effects

Pneumatic tourniquets are used in extremity surgeries with the goals of decreasing blood loss and allowing for better visualization of the surgical field. The lack of blood flow and oxygen delivery to the extremity is not without consequence as it can lead to acidosis and tissue hypoxia, which increases with the length of time the tourniquet is in use (Butterworth, Mackey, & Wasnick, 2013). At tourniquet times of approximately 45-60 minutes, tissue acidosis and hypoxia results in what is called tourniquet pain (Nagelhout & Plaus, 2014). Tourniquet pain manifests itself with an increased sympathetic nervous system (SNS) response, which results in hypertension and tachycardia (Nagelhout & Plaus, 2014). The exact pain pathway for tourniquet pain is unknown, but it is resistant to narcotics and anesthetic gases (Nagelhout & Plaus, 2014).

The definitive treatment for tourniquet pain induced hypertension and tachycardia is to shorten the tourniquet time (<45-60 minutes). This time variable is not controlled by the anesthesia professional, but rather the surgeon. Additionally, short tourniquet times are not always possible for specific procedures. Traditional treatments include the use of beta blockers to decrease the SNS response, but their efficacy is limited, and the potential for hypotension following tourniquet release is great. Allowing the blood pressure and heart rate to increase with no intervention is another common option in healthy individuals since the SNS response is transient and will resolve with tourniquet release. However, significant increases in blood pressure and heart rate are associated with some risk, and may not be tolerated by individuals with certain co-morbidities (e.g. congestive heart failure, coronary artery disease, abnormal bleeding, stroke risk). Dexmedetomidine appears to decrease the SNS response associated with tourniquet pain, which will be discussed further in this case report and literature review.

Case Report

A 48-year-old, 71 kg, 174 cm male presented to the pre-operative holding room for open reduction and internal fixation (ORIF) of bilateral calcaneus fractures. The injuries were sustained 35 days earlier after a fall from a ladder. His past medical history was significant for gastroesophageal disease (GERD), anxiety, depression, and one pack per day smoking habit. He denied alcohol use. He was allergic to penicillin, which manifested as a rash. His surgical history included lumbar fusion post L2 burst fracture and right tibia/fibula ORIF. He had no anesthetic issues except he stated he sometimes wakes up "wild." The patient had no neurological deficits. Prior to his injuries the patient took no medications, but post fall he had been taking hydrocodone 7.5 mg/ acetaminophen 325 mg two tablets every six hours, typically rating pain 7-9/10 before his medication administration.

Pre-operative airway evaluation included a Mallampati classification II, thyromental distance greater than 6cm, inter-incisor distance greater than 4 cm, and full range of motion of neck with no pain or stiffness. He was assigned an American Society of Anesthesiologists (ASA) classification of 2. Plans were made for general anesthesia with and endotracheal tube.

The patient received an 18 gauge peripheral intravenous (IV) catheter in the pre-operative area. Upon entry to the operating room (OR), the patient was connected to standard monitors, and received midazolam 2mg and fentanyl 150 mcg IV. He stated he was in "a lot of pain, 10/10" upon moving to the OR table. The patient was preoxygenated with 100% oxygen via mask for approximately 4 minutes. The patient then received the following medications IV: lidocaine 60 mg, fentanyl 100 mcg, propofol 180 mg, and rocuronium 50 mg. The patient was intubated utilizing a Macintosh #3 with a grade 1 view and a size 8.0 cuffed endotracheal tube was placed with no issues. Placement was confirmed with end-tidal carbon dioxide (ETCO2) and

auscultation of bilateral clear lung sounds. General anesthesia was maintained with Sevoflurane at a 2.2-3.0% expired concentration in a mixture of oxygen 1.5 L/min and air 1.5 L/min. A bispectral index (BIS) monitor was applied, which read 40-50 throughout the case.

Prior to incision, an additional dose of fentanyl 250 mcg was administered with a resulting blood pressure (BP) of 122/66 and a heart rate (HR) of 76 beats/minute. Immediately after right leg tourniquet inflation and incision the patient's BP increased to 151/76 and his HR increased to 98. Sevoflurane was increased from 2.4% expired to 3.0% expired, and hydromorphone 1 mg IV was administered. Fifteen minutes later the patient's blood pressure was 142/74 with a heart rate of 90. After another 30 minutes (45 minutes total tourniquet time) the patients BP increased to 162/82 with a HR of 105. The BIS was 40-42 at this time. Another 2mg hydromorphone IV was given resulting in a BP of 136/80 and a HR of 84. At a total tourniquet time of 90 minutes the patients BP was 155/82 with a HR of 102 and a BIS of 40-45. At total tourniquet time of 104 minutes the patient's BP was 164/91 with a HR of 105. At this time 10 mg Labetalol IV was administered resulting in a BP of 147/78 and a HR of 97. At a tourniquet time of 122 minutes the patient's BP was 163/96 with a HR of 104. Labetalol 5 mg IV was given at this time resulting in a BP of 152/91 and HR of 99. The patient's BP and HR slowly increased to 164/94 and 105 respectively until the release of the tourniquet at a total tourniquet time of 151 minutes. Immediately upon tourniquet release the patient's BP decreased to 124/72 and HR decreased to 82.

During surgery, it was discussed with the surgeon that the left calcaneus was more extensively damaged and may require a longer tourniquet time. Due to the expected long tourniquet time and narcotic requirements of the patient, we decided to start a dexmedetomidine infusion prior to the ORIF of the left calcaneus. The patient's BP prior to tourniquet inflation and

incision was 118/70 with a HR of 78. A dexmedetomidine bolus was not given and the infusion was started at 0.7 mcg/kg/hr. Total tourniquet time was 153 minutes with a patient max BP of 148/82 and HR of 95. No additional narcotics or labetalol was given, and Sevoflurane was slowly decreased from an expired concentration of 3.0% to 2.0%.

Dexmedetomidine was discontinued at approximately 20 minutes prior to the end of the procedure. Ondansetron 4mg IV was given at this time. Prior to extubation the patient produced tidal volumes of 400-600 ml at a rate of 14 breaths/min and opened eyes periodically to voice. The endotracheal tube was removed and oxygen at 4 LPM via nasal cannula was applied. The patient was then brought to the post anesthesia care unit (PACU). Report was given and care was transferred. Upon entry to the PACU the patient was drowsy but denied pain. One hour later, the patient was alert and calm rating pain 5/10, for which he was receiving IV fentanyl.

Discussion

Tourniquet Pain

Tourniquet pain is the result of mechanical compression to the underlying muscles, nerves, and blood vessels, along with ischemia to the distal tissues (Estebe, Davies, and Richebe, 2011). The specific metabolic and neuronal pathways that result in tourniquet pain are unknown, but they result in an aching pain that is associated with C-fibers, and a tingling/burning pain associated with A-delta fibers (Nagelhout & Plaus, 2014). Tourniquet pain is better controlled if adequate anesthesia is obtained prior to the application of the tourniquet, because of a hyperalgesia phenomenon, which results in an increased sensitization of pain receptors if they are previously activated (Estebe et al., 2011). Despite adequate anesthesia, tourniquet pain typically presents with a dull aching pain (C-fiber pain) at about 45-60 minutes (Nagelhout &

Plaus, 2014). As the duration of tourniquet time increases, so does the intensity of tourniquet pain.

SNS response to tourniquet use. The increased blood pressure and heart rate associated with prolonged tourniquet use are a result of the increased SNS response associated with tourniquet pain (Estebe et al., 2011). Tourniquet induced hypertension, which is defined as a blood pressure greater than 30% of baseline is found in approximately 67% of patients who undergo general anesthesia for lower extremity surgery requiring a tourniquet (Li et al., 2015). The SNS is activated by the acute pain pathway and results in the release of the catecholamines epinephrine and norepinephrine (Nagelhout & Plaus, 2014).

This case report depicts a clear picture of this SNS response with the tourniquet time on the right leg. As the case progressed and total tourniquet time increased, the patient's heart rate and blood pressure increased despite multiple doses of narcotics and labetalol. There was periodic decreases in heart rate and blood pressure with interventions, but overall the SNS response became more difficult to control the longer the tourniquet was in place.

Tourniquet Time

The maximum safe length of tourniquet time is controversial. Nagelhout & Plaus (2014) states that tourniquet time should not exceed two hours in order to avoid severe complications associated with ischemia. In a meta-analysis performed by Estebe et al. (2011), it is recommended that tourniquet time not exceed one hour in order to avoid ischemic injury. They further noted that up to 3 hours of tourniquet time does not typically result in irreversible ischemic damage, but over 1 hour can result in sublethal tissue injury (Estebe et al., 2011).

Dexmedetomidine

Mechanism of action. Dexmedetomidine is an alpha 2 adrenergic agonist with sedative properties, which reduces the SNS response by decreasing the release of norepinephrine and epinephrine into the circulation, thus decreasing blood pressure and heart rate (Lao, Tsai, Su, Kwok & Huang, 2013). This makes it an ideal adjunct for patients requiring prolonged tourniquet application, as was demonstrated by the patient's heart rate and blood pressure comparisons between his right and left calcaneous surgeries in the case study. Dexmedetomidine possesses the additional benefits of analgesia, reduction of postoperative shivering, and sedation with minimal effect on respirations (Lao et al, 2013). The drug also shows some benefit in reducing the effects of ischemic/perfusion injuries on the cellular level, which may results from extended tourniquet time (Cai, Xu, Yan, Zhang & Lu, 2014).

Emergence delirium. Dexmedetomidine is noted to decrease emergence delirium in elderly patients. In a randomized double blinded control study done by Kim et al. (2015), 115 patients over the age of 65 ASA I-II receiving lower extremity orthopedic surgery were examined. Half of the patients received a dexmedetomidine infusion of 0.4 mcg/kg/hr and half did not. The incidence of emergence agitation/delirium was 11.1% in the group that received dexmedetomidine infusions compared to 75% in the control group (Kim et al., 2015). Emergence delirium is common in elderly patients receiving orthopedic surgery, and can lead to self-injury, increased hemorrhage, and prolonged PACU/hospital stays (Kim et al., 2015).

There were no studies found examining the incidence of emergence delirium in orthopedic surgery with the use of dexmedetomidine in the age range that would be applicable to the patient in this case report. However, the anti-emergence delirium effects of dexmedetomidine appeared to be beneficial for the case. During the preoperative interview of the case study

patient, he stated he has been "wild" during emergence from anesthesia in the past. His emergence was smooth with no issues. He was calm throughout extubation to discharge from PACU.

Side effects. The main side effects of dexmedetomidine include bradycardia, heart block, and hypotension (Skidmore-Roth, 2014). These side effects appear to be dose dependent, but can be severe enough to cause asystole and possible death (Jaideep & Bhargava, 2015). It should be used cautiously in patients with severe hypotension, bradycardia, hypersensitivity, and dysrhythmias (Skidmore-Roth, 2014). Typical adult administration includes a loading dose of 1 mcg/kg over ten minutes followed by a continuous infusion of 0.2-0.7 mcg/kg/hr (Skidmore-Roth, 2014). Infusions of up to 1.5 mcg/kg/hr have been shown to be safe (Cai et al., 2014).

Half-life. Dexmedetomidine has a rapid onset with an elimination half-life of 2 hours (Skidmore-Roth, 2014). It is 94% protein bound, metabolized by the liver, and excreted by the kidneys (Skidmore-Roth, 2014). Dosages should be reduced in patients with abnormal kidney and liver function (Butterworth, Mackey, & Wasnick, 2013).

Cost. It is important for anesthesia professionals to consider cost when formulating a plan of care. Pricing for dexmedetomidine is approximately $541.28 for 200 mcg in 50 ml normal saline (D. Schmidt, personal communication, March 25, 2016).

Stable Hemodynamics

Adequate tissue perfusion is perhaps one of the most important goals for anesthesia professionals. One important way that we are able to judge adequate tissue perfusion is through blood pressure (Lonjaret, Lairez, Minville, & Geeraerts, 2014). Hypertension during the intraoperative period has been associated with myocardial ischemia, cerebral vascular complications, and increased bleeding (Lonjaret et al., 2014). Patients with bleeding disorders

and vascular disease are at an even higher risk of developing these complications due to intraoperative hypertension (Lonjaret et al., 2014). Lonjaret et al. (2014) also states, "in patients with known coronary artery disease or at high risk for coronary artery disease who are undergoing noncardiac surgery, preoperative hypertension increases risk for death by 3.8 times" (p. 50). Special care should be taken to maintain stable blood pressure in patients with these risk factors. It is difficult to determine an exact point in which hypertension is detrimental, and it is most likely patient specific. However, Lonjaret et al. (2014) defines intraoperative hypertension as being > 160 mmHg systolic and/or > 100 mmHg diastolic. They further defined a SBP ≥ 180 and a DBP ≥ 120 as being a hypertensive urgency requiring prompt intervention (Lonjaret et al., 2014). Maintaining a stable blood pressure throughout the perioperative period likely will help to maintain tissue perfusion. Ultimately, this potentially will improve patient outcomes by decreasing the risk of cardiovascular injury, stroke, and bleeding.

Increased heart rate can also be detrimental to tissue perfusion, specifically tissue perfusion of the heart. The heart is perfused during diastole. An increased heart rate not only increases the oxygen demand of the heart, it decreases the length of time the heart is able to perfuse (diastole). Tachycardia has also been associated with atherosclerotic plaque disruption leading to acute myocardial infarction (MI) (Wong & Erwin, 2016). Patients with coronary artery disease are especially at danger for MI with the contributing factor of an increased heart rate (Wong & Erwin, 2016). A heart already stressed from coronary artery disease may be pushed over the edge into infarction with the increased demands associated with tachycardia.

Dexmedetomidine Use in Surgery Requiring a Tourniquet

Lao et al. (2013) performed a prospective, randomized, placebo controlled, double blinded study on the sympatholytic effects of dexmedetomidine in patients undergoing general

anesthesia for lower limb surgery requiring a tourniquet. Seventy-two healthy adults were included in this study with 36 in the dexmedetomidine group who received a loading dose of 0.8 mcg/kg over 10 minutes followed by an infusion of 0.4 mcg/kg/hr, and 36 in the control group who received saline. After induction and prior to tourniquet application, patients in the dexmedetomidine group received their dexmedetomidine bolus and infusion, while the control group received normal saline. The tourniquet was then inflated to a pressure of 300-350 mmHg. Regardless of group, patients with blood pressure >160/90 for over five minutes received 5 mg of nicardipine repeated every five minutes as needed, and patients with SBP <90 or MAP <70 received ephedrine every five minutes in incremental doses. Hemodynamic parameters were measured and compared between the groups at inflation and every 15 minutes there after until tourniquet deflation. They found the average blood pressure was significantly lower in the dexmedetomidine group at inflation until about 90 minutes. At 90 minutes there was no significant difference in blood pressure. The blood pressure was again significantly lower in the dexmedetomidine group when the tourniquet was released.

The researchers determined that dexmedetomidine does in fact attenuate the increases in blood pressure associated with prolonged tourniquet use. They hypothesized that the meeting of the patients' blood pressure at the 90 minute mark was due to the steadily increasing SNS response, and that a titrating the dexmedetomidine infusion up would most likely help to combat the increased SNS response. Heart rate was significantly lower in the dexmedetomidine group at all points during tourniquet use. The average heart rate was 67-80 beats/min through tourniquet release in the dexmedetomidine group compared to 75-90 beat/min in the control group. Nicardipine supplementation was increased in the control group at an average of 0.4 mg ± 1.6 standard deviations (stdv) compared to 0.1 mg ± 0.3 stdv average for the dexmedetomidine

group. Ephedrine supplementation was increased in the dexmedetomidine group at 3.6 mg ± 5.8 stdv compared to 0.8 mg ± 3.7 stdv for the control group. This increase in ephedrine use was especially noted in the immediate period after the bolus dose. The researchers discussed that the synergistic effects of the inhalation agents, fentanyl, and midazolam, along with the dexmedetomidine, would probably warrant a smaller loading dose (Lao et al., 2013).

No loading dose was given to the patient in this case report involving bilateral calcaneous repair because the providers believed that the previous 3 hours of anesthetic drugs plus a loading dose may precipitate a hypotensive and/or a bradycardic event. However, dexmedetomidine does have rapid distribution with a steady state volume of distribution of approximately 118 L (Nagelhout & Plaus, 2014). This suggests the need for a bolus in order to obtain consistent drug levels in the blood stream.

The patient in the case report showed improved results in the attenuation of the SNS with the administration of the dexmedetomidine infusion without a bolus on the left leg compared to no dexmedetomidine infusion with the right leg. This is a peculiar case however, because the dexmedetomidine infusion was started in the middle of the surgery after the patient had already received approximately 3 hours of general anesthesia.

Another placebo controlled, randomized, double blind prospective study by Lu et al. (2013) examined the sympatholytic effects of dexmedetomidine. This study looked at 37 healthy individuals split into a dexmedetomidine group who received a bolus of 0.5 mcg/kg bolus prior to tourniquet inflation of 300 mmHg with no continuous infusion, compared to a control group who received saline. Blood pressure and heart rate where measured and compared every 10 minutes for a total of 60 minutes and at tourniquet deflation. They noted that there was no significant changes in HR between the groups until the tourniquet release time, where the

average HR of the control group was approximately 90 beats/min and the dexmedetomidine group was 78 beats/min. The blood pressure for the dexmedetomidine group was very stable at approximately 120/63 throughout the first 60 minutes and upon tourniquet release. Comparatively, the average SBP and DBP of the control group increased significantly at the 40, 50, and 60 minute marks with average pressures of 138/78, 142/81, and 150/90 respectively (Lu et al., 2013).

These findings appear to be consistent with the increased tourniquet pain at the 45-60 minute mark. Lu et al. (2013) discussed the importance of blunting the pain and sympathetic response to prolonged tourniquet use prior to its manifestation, because once it begins the feedback loop is difficult to control. This article seems to support the use of a dexmedetomidine bolus, which was not used during this papers presented case study. Unfortunately the Lu et al. (2013) study did not examine the hemodynamic effects of the dexmedetomidine group and the control group after 60 minutes. It would be beneficial to determine if and/or when the dexmedetomidine bolus would wear off, or the SNS response would overcome the sympatholytic effects of the bolus. The stable blood pressure and heart rate of the two groups up to the 40 minute mark indicates that total tourniquet time below this period would not warrant the need for dexmedetomidine.

The previously discussed research studies excluded patients with a history of hypertension. Hypertension is a common finding in patients that receive orthopedic surgery of the lower extremity. Li et al. (2015) performed a double blinded, placebo controlled study of 80 patients in which 43 of them had a history of hypertension. The patients were divided into hypertensive and non-hypertensive groups and within those groups the patients were randomly assigned to a dexmedetomidine group who received a bolus of dexmedetomidine of 1 mcg/kg

over 20 minutes followed by an infusion of 0.4 mcg/kg/hr until tourniquet release and a control group that received saline. They defined hypertension as > 160 mmHg systolic and determined the incidence of its occurrence. The incidence of hypertension was 71.8% for the control group and 34.1% for the dexmedetomidine group, which was significant. In the control group the incidence of hypertension was 66.7 % for the non-hypertensive patients and 77.8% for the hypertensive patients, which was not significant. In the dexmedetomidine group the incidence of hypertension was 12.5% of non-hypertensive patients compared to 48.0% of hypertensive patients, which was significant, but the incidence of hypertension in the hypertensive population between the control and dexmedetomidine group was substantial (Li et al., 2015).

This study shows that dexmedetomidine is beneficial in the patient population that has a history hypertension. However, there might be some consideration in increasing the dexmedetomidine rate in those populations that have hypertension. Theoretically, an increased rate of dexmedetomidine would increase the sympatholytic response and decrease patients' blood pressure.

Dexmedetomidine is not necessary for all patients having surgery requiring tourniquet use. Some individuals show no significant increases in heart rate and blood pressure depending on the length of the procedure and patient specific responses. It is sometimes difficult to predict the length of tourniquet application for certain procedures, and we are unable to determine the timing at which patients will have an exaggerated SNS response. Allee et al. (2011) discussed three case studies where they administered dexmedetomidine boluses of 0.5 mcg/kg over two minutes after patients exhibited tachycardia and hypertension secondary to tourniquet pain.

These studies demonstrated that dexmedetomidine is useful for tourniquet pain induced hypertension and tachycardia even after its manifestation. In all three studies, the providers first

attempted to administer more narcotics and increase the anesthetic gases with no results. After the administration of dexmedetomidine 0.5 mcg/kg over 2 minutes all of the patients' blood pressures and heart rates returned to baseline. In one of the three cases, the patient's vital signs remained stable throughout the procedure after one dose. For the other two procedures the patients' blood pressure and heart rate started to increase over the next 15-20 minutes, so a second bolus of dexmedetomidine 0.5 mcg/kg over 2 minutes were given followed by an infusion of 0.5/mcg/kg/hr with good results maintaining blood pressure and heart rate close to baseline. After tourniquet release there were no significant drops in the patients' blood pressure or heart rate for any of the cases.

Although there seems to be some advantage to starting dexmedetomidine prior to the manifestation of tourniquet induced hypertension and tachycardia, starting dexmedetomidine as needed appears to be a viable option. This was also demonstrated with the patient in this case report, where there appeared to be obvious benefits to attenuating the sympathetic response attributed to tourniquet pain despite starting the dexmedetomidine infusion half way through the procedure.

Adverse Reactions

Hypotension and bradycardia were the most common adverse reaction noted in the research studies involving the use of dexmedetomidine for the attenuation of tourniquet pain (Lu et al., 2013; Lao et al., 2013; Li et al., 2015). The hypotension and bradycardia appeared to be dose dependent. The Lao et al. (2013) study, which used a dexmedetomidine starting bolus of 0.8 mcg/kg over ten minutes, had the highest requirement of ephedrine and atropine use compared to its control group. The Lu et al. (2013) study, which used a staring bolus of 0.5 mcg/kg over ten minutes, showed no significant difference between the control group and dexmedetomidine

group in the requirement of rescue drugs for bradycardia and hypotension. However, both of these sample sizes are relatively small and more research is needed to determine the most appropriate loading dose. When hypotension and bradycardia are encountered with the use of dexmedetomidine, it responds well to the administration of ephedrine and/or anticholinergics (Lu et al., 2013; Lao et al., 2013; Li et al., 2015).

Caution is required when administering dexmedetomidine in patients who present with a heart less than 60 and/or are hypovolemic. Jaideep and Bhargava (2015) describe a case of prolonged asystole in a patient who received a dexmedetomidine infusion of 0.5 mcg/kg/hr after spinal anesthetic. The patient was a healthy 31 year old receiving a complex repair of his cruciate ligaments requiring a total tourniquet time of 150 minutes. His baseline heart rate was 55 beats/min and blood pressure of 113/71. After the initiation of the infusion his heart decreased to 47-52 beats/min, but there was no significant decrease in blood pressure. At the completion of the surgery the tourniquet was deflated and the patient's heart rate quickly decreased to 30 beats/min, 0.6 mg atropine IV where given. The patient was awake at this time and went unconscious followed by a 10 second episode of asystole. The patient's heart responded and he returned to consciousness with a heart rate of 60 beats/min. Jaideep and Bhargava (2015) warn of the use of dexmedetomidine in those patients that possess good vagal tone and have a slow baseline heart rate. The combination of the patient's vagal tone, the sympathectomy associated with the spinal anesthetic, and the quick changes in fluid status and acidosis associated with the release of the tourniquet, along with the bradycardic effects of dexmedetomidine most likely led to the patient's asystole.

An additional adverse effect to consider with the use of dexmedetomidine in surgery is the prolongation of time in the post anesthesia care unit (PACU). PACU time is expensive and

any intervention that prolongs it must be examined carefully to insure the benefits justify the cost. Although there are no research articles that examine PACU time in adult patients when dexmedetomidine is added to their anesthetic, Li et al. (2015) noted that PACU times for dexmedetomidine patients were most likely longer compared to the control group, but the design of their study did not allow for scientific confirmation of this. Kim et al. (2015) examined emergence in elderly patients receiving dexmedetomidine and noted that the time from anesthetic cessation to eye opening for a control group was approximately 10 minutes compared to a dexmedetomidine group being 14 minutes. Minutes to extubation was approximately 11 minutes for the control group compared to 15 minutes for the dexmedetomidine group. More research needs to be done on the time costs if any when adding dexmedetomidine to an anesthetic.

Dexmedetomidine and Ischemia/Reperfusion Injuries

Prolonged tourniquet use can lead to ischemia, the production of free oxygen radicals, and the increase of pro-inflammatory products (Estebe et al., 2011). Subsequent reperfusion leads to oxidative stress and the distribution of the pro-inflammatory products throughout the systemic circulation (Estebe et al., 2011). This occurrence is known as an ischemic/reperfusion injury. Dexmedetomidine has been shown to attenuate this type of injury. Dexmedetomidine has antioxidant abilities that neutralize the formation of free oxygen radicals (Cai et al., 2014).

Dexmedetomidine also seems to effect gene expression resulting in an increase of antiapoptotic proteins and decrease in proapoptotic proteins resulting in less cellular death (Cai et al., 2014). The sympatholytic effects of the drug also reduces the metabolic demands of the tissues resulting in ischemic resistance (Cai et al., 2014). Dexmedetomidine also diminishes the detrimental inflammatory response by decreasing the production of leukocytes (Cai et al., 2014). Yagmurdur et al. (2008) compared patients who received dexmedetomidine and regional

anesthesia for upper extremity surgery to patients who received regional anesthesia only, and found a significant reduction in ischemic/reperfusion injury markers. However, a study done by Bostankolu et al. (2013) noted no difference in ischemic injury markers with the addition of dexmedetomidine in patients having general anesthesia for lower extremity surgery with a tourniquet. The main difference between these two studies was the use of general anesthesia compared to regional anesthesia. Many of the anesthetics that practitioners use for general anesthesia attenuate ischemia/reperfusion injuries (Bostankolu et al., 2013). Studies have shown that propofol, thiopental, and sevoflurane all have the ability to decrease ischemic/reperfusion markers (Bostankola et al., 2013). Dexmedetomidine does have benefits for ischemia/reperfusion injuries, but more research is required to determine if those benefits are significant when compared to other general anesthetics.

Alternative Therapies for Tourniquet Pain

The most common therapy used to combat the SNS response from tourniquet pain is the administration of beta adrenergic blockers. Common beta blockers utilized in anesthesia practice include labetalol and esmolol.

Labetalol. Labetalol is typically administered in 5-10mg doses until desired effect is reached. The greatest concern with labetalol use to treat hypertension and tachycardia due to tourniquet pain is that the duration of action for the drug is approximately 6 hours. After the release of the tourniquet, there may be detrimental decreases in blood pressure and heart rate because the stimulus is gone, but the action of labetalol is still present. Due to this fact, many anesthesia professionals are hesitant to give labetalol and when they do they tend to be conservative, which may result in poor management of blood pressure and heart rate. This was noted in the case study where the patient received 5-10 mg boluses of labetalol with very little

lasting effect and swings in blood pressure. Labetalol is relatively inexpensive at $18.31 per 100 mg (D. Schmidt, March 25, 2016).

Esmolol. Esmolol may be a more appropriate beta blocker to attenuate the SNS response secondary to tourniquet pain because of its short half-life of 9 minutes and its ability to be quickly titrated as a continuous infusion (Skidmore-Roth, 2014). However, when compared to the price of labetalol, it is relatively more expensive at $63.05 per 100 mg (D. Schmidt, personal communication, March 25, 2016). Esmolol also does not have the sedative effects of dexmedetomidine and potential for as smooth as an emergence in some patient populations.

Haghighi et al. (2015) preformed a randomized double blinded control study examining the opioid reducing effects of esmolol when used in lower extremity surgery and found that narcotic requirements were significantly decreased during surgery and in the PACU. They also noted the stabilizing effect esmolol had on the hemodynamics of the patients. There are no studies that compare dexmedetomidine to esmolol infusions for the attenuation of the SNS response due to tourniquet pain.

Ketamine. Ketamine is another drug that has been shown to decrease blood pressure during surgeries requiring a tourniquet. Park et al. (2007) examined the administration of a bolus of 0.1 mg/kg of ketamine during general anesthesia prior to tourniquet inflation compared to a control group. They found that the patients in the ketamine group had a significant decrease in blood pressure during five minute intervals until the 60 minute mark where there was no significant difference in blood pressure. It is thought that the N-methyl-D-aspartic acid (NMDA) antagonist effects of ketamine decrease the pain response and subsequent SNS response due to tourniquet application. No studies were found that investigated the use of a ketamine infusion, but an infusion may result in a more stable and longer duration of blood pressure control in

patients receiving prolonged tourniquet times. There was no mention in the literature of heart rate control with the use of ketamine, but possible side effects of ketamine include tachycardia and/or arrhythmias. Other side effects include nausea/vomiting, hallucination, increased intra cranial pressure, tonic-clonic movements, and hyper salivation (Skidmore-Roth, 2014). The price of ketamine is approximately $56.38 per 100 mg (D. Schmidt, personal communication, March 25, 2016).

Evidence Based Practice Recommendations

There appears to be enough available evidence in the literature to determine that a dexmedetomidine infusion is beneficial in decreasing tourniquet induced hypertension and tachycardia caused by tourniquet pain. However, it is difficult to determine the cost effectiveness of this intervention and when it would be appropriate to implement it. When choosing an adjunct to attenuate the SNS response related to tourniquet pain, one must consider the efficacy of the drug, possible side effects (beneficial and harmful), and cost. Bearing this in mind, and based on the literature review, there are two recommendations.

First, it is recommended that patients who would benefit from tight blood pressure and heart rate control (e.g. coronary artery disease, stroke risk, increased chance of bleeding), and are projected to receive a tourniquet time greater than 45-60 minutes while under general anesthesia should be considered for a dexmedetomidine infusion. A bolus of 0.5-0.8 mcg/kg over 10 minutes should be initiated prior to tourniquet inflation followed by an infusion of 0.4 mcg/kg/hr and titrated up to 1.5 mcg/kg/hr to desired effect (Lao et al., 2013). The bolus dose may be reduced or held in those patients with labile blood pressure and/or bradycardia. Impediments for implementation of this recommendation include cost effectiveness, possible adverse side effects, and lack of practitioner knowledge. Dexmedetomidine is an expensive drug at about $541.28 per

200 mcg in 50 ml normal saline (D. Schmidt, personal communication, March 25, 2016). There is the potential that it increases post anesthesia care unit time, which may lead to higher costs, but this controversial (Lao et al., 2013). The benefits must outweigh the expense in order for nurse anesthetists and institutions to implement an intervention into practice. The main adverse side effects of dexmedetomidine includes bradycardia and hypotension, but this appears to be largely dose dependent (Alle et al., 2011; Jaideep & Bhargava, 2015; Lu et al., 2013; Lao et al., 2013). Educating nurse anesthetists on the benefits of dexmedetomidine in prolonged tourniquet cases will increase the likelihood of its use.

The second recommendation for practice is for nurse anesthetists to participate in and conduct more research, ideally randomized controlled trials, related to dexmedetomidine in prolonged tourniquet use. Although there appears to be sufficient evidence in the effectiveness of dexmedetomidine in reducing hypertension and tachycardia in prolonged tourniquet use, there is limited information on its cost effectiveness and potential for extending PACU times. Also, there needs to be a comparison of beta blockers and ketamine administration in attenuating the SNS response in prolonged tourniquet use, compared to the addition of a dexmedetomidine infusion. The key components in these studies would be the ability to control blood pressure, heart rate, associated side effects, and the total cost. Other trials that appeared to be absent in the review of the literature included the use of a dexmedetomidine bolus only compared to a bolus and infusion, and the incidence of emergence delirium in the adult population (age 18-65) having orthopedic procedures with the addition of dexmedetomidine. Impediments to implementation of this recommendation include the cost of research, the ethical considerations of testing medications on patients, and the size and scope of the sample size needed to truly represent the population.

Conclusion

Hemodynamic stability is essential to maintain adequate organ perfusion. This is especially true for patient populations that are at high risk for myocardial infarction, stroke, and increased bleeding. The increased SNS response associated with tourniquet times > 45-60 minutes is difficult to control. It is refractory to narcotics and inhaled anesthetics, and subsequently leads to hypertension and tachycardia, which can have a detrimental impact on morbidity and mortality.

Dexmedetomidine infusions have been shown to attenuate the SNS response associated with tourniquet pain in the literature as well as with the patient in this case report. The routine use of dexmedetomidine in general anesthetic surgeries requiring tourniquet times greater than 45-60 minutes may be prudent, but more research needs to be done to determine the efficacy and cost effectiveness of this intervention compared to other therapies.

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Utilizing Dexmedetomidine for a Patient with Prolonged Tourniquet Time to Decrease Sympathetic Effects

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Introduction

- Prolonged tourniquet use > 45-60 minutes results in an increased SNS response and subsequently an increase in heart rate and blood pressure.
- This SNS response, also referred to as tourniquet pain, is resistant to narcotics and anesthetic gases.
- Significant increases in blood pressure and heart rate may not be tolerated by individuals with certain co-morbidities (e.g. congestive heart failure, coronary artery disease, abnormal bleeding, stroke hx).
- Dexmedetomidine is an alpha 2 adrenergic agonist with sedative properties, which also reduces the SNS response by decreasing the release of norepinephrine and epinephrine into the circulation, thus decreasing blood pressure and heart rate.

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Case Information

- Open reduction and internal fixation (ORIF) of bilateral calcaneus fractures
- 48 year old
- 71 kg
- Male
- ASA 2

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Pre-operative Evaluation

- Past Medical History
  - GERD
  - Anxiety and depression
  - Smoker 1 ppd
- Surgical History
  - Lumbar fusion post L2 burst fracture
  - Right tibia/fibula ORIF
- Anesthesia History
  - Patient stated he sometimes wakes up "wild"
- Pre-op VS
  - 136/76, HR 78 NSR, Sats 98%, Pain "7-10/10"
- Airway Evaluation
  - Mallampati II
  - Full neck ROM
  - Thyromental distance greater than 6cm
  - Inter-incisor distance greater than 4 cm

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Anesthetic Course

- Induction
  - The patient was connected to standard monitors, and received midazolam 2mg and fentanyl 150 mcg IV
  - Preoxygenated with 100% oxygen via mask for approximately 4 minutes
  - Received the following medications IV: lidocaine 60 mg, fentanyl 100 mcg, propofol 180 mg, and rocuronium 50 mg
  - Intubated utilizing a Macintosh #3 with a grade 1 view and a size 8.0 cuffed endotracheal tube was placed with no issues. Placement was confirmed with ETCO2 and auscultation of bilateral clear lung sounds
- Maintenance
  - Sevoflurane 2.2-3.0%
  - ETCO2 30-34
  - BIS 40-50
  - PRN Fentanyl, Hydromorphone, Labetalol
  - Dexmedetomidine infusion (started prior to left calcaneus fixation).

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Intraoperative Issues

- Right Calcaneus Fixation
  - Prior to incision an additional 250 mcg fentanyl given for a total of 500 mcg. BP 122/66 with a HR of 76 beats/min at this time.
  - During the first 45 minutes of total tourniquet time 3mg hydromorphone was titrated on in response to increased blood pressure and heart rate. Max blood pressure and heart rate during this time was 162/82 and 105 respectively.
  - Tourniquet time 45 min BP 136/80, HR 84
  - Tourniquet time 104 min BP 164/91, HR 105
    - Labetalol 10 mg IV given with resulting BP 147/78, HR 97
  - Tourniquet time 122 min BP 163/96, HR 104
    - Labetalol 5 mg IV given with resulting BP 152/91, HR 99
  - BP and HR slowly increased to 164/94 and 105 respectively until the release of the tourniquet at a total tourniquet time of 151 minutes
  - Immediately upon tourniquet release the patient's BP decreased to 124/72 and HR decreased to 82.

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Intraoperative Issues

- Left Calcaneus Fixation
  - During surgery, it was discussed with the surgeon that the left calcaneus was more extensively damaged and may require a longer tourniquet time. Due to the expected long tourniquet time and narcotic requirements of the patient, we decided to start a dexmedetomidine infusion prior to the ORIF of the left calcaneus
  - Dexmedetomidine infusion was started at 0.7 mcg/kg/hr. No bolus was given.
  - Total tourniquet time was 153 minutes for the left leg with a max BP of 148/82 and a max HR of 95
  - No additional narcotics or labetalol were given during the left calcaneus fixation
  - Sevoflurane was slowly decreased from 3.0% to 2.0% expired, with the BIS remaining 40-50.

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PACU

- Dexmedetomidine was discontinued at approximately 20 minutes prior to the end of the procedure. Ondansetron 4mg IV was given at this time.
- Prior to extubation the patient produced tidal volumes of 400-600 ml at a rate of 14 breaths/min and opened eyes periodically to voice
- The endotracheal tube was removed and oxygen at 4 LPM via nasal cannula was applied
- Upon entry to the PACU the patient was drowsy but denied pain
- One hour later, the patient was alert and calm rating pain 5/10, for which he was receiving IV fentanyl
- No emergence delirium was noted

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Discussion

Tourniquet pain

- Tourniquet pain is the result of mechanical compression to the underlying muscles, nerves, and blood vessels, along with ischemia to the distal tissues.
- The specific metabolic and neuronal pathways that result in tourniquet pain are unknown
  - C-fibers = aching pain
  - A-delta fibers = burning/tingling pain
- Despite adequate depth of anesthesia, tourniquet pain typically presents with a dull aching pain (C-fiber pain) at about 45-60 minutes, which causes an increase in the SNS response and subsequent increase in BP and HR.
- Tourniquet pain is frequently refractory to narcotics and anesthetic gases
- Significant increases in blood pressure and heart rate may not be tolerated by individuals with certain co-morbidities (e.g. congestive heart failure, coronary artery disease, abnormal bleeding, stroke hx), which may lead to poor outcomes.

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Discussion Cont'd

Dexmedetomidine

- Alpha 2 adrenergic agonist
- Sympatholytic effects by decreasing the release of norepinephrine and epinephrine, resulting in a decrease in BP and HR.
- Additional beneficial effects: sedation, analgesia, reduction of postoperative shivering, decrease in postoperative delirium, minimal respiratory effects, reduces ischemia/reperfusion injury markers due to prolonged tourniquet use.
- Main adverse effects: Severe bradycardia, heart block, hypotension
  - Dose dependent but can be damaging and potentially lethal
- Cost: $541.28 for 200 mcg in 50 ml normal saline

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Discussion Cont'd

Dexmedetomidine Use in Surgery Requiring a Tourniquet

- Three separate, randomized, placebo controlled, double blinded studies on the sympatholytic effects of dexmedetomidine in patients undergoing general anesthesia for lower limb surgery requiring a tourniquet, determined that blood pressure and heart rate were significantly reduced in patients that received a dexmedetomidine infusion compared to the control groups who did not.

- Lao et al. (2013) Study, 72 adults
  - Dexmedetomidine group received 0.8 mcg/kg bolus over ten minutes followed by 0.4 mcg/kg/min infusion.
  - The average heart rate was 67-80 beats/min through tourniquet release in the dexmedetomidine group compared to 75-90 beat/min in the control group.
  - The average BP was 118/68 through tourniquet release in the dexmedetomidine group compared to 130/73 in the control group.

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Discussion Cont'd

- Lu et al. (2013) Study, 37 adults
  - Dexmedetomidine group received 0.5 mcg/kg bolus over ten minutes with no continuous infusion
  - There was no significant changes in HR between the control and dexmedetomidine groups until the 60 minute mark, where the average HR of the control group was approximately 90 beats/min and the dexmedetomidine group was 78 beats/min
  - The blood pressure for the dexmedetomidine group was very stable at approximately 120/63 throughout the first 60 minutes and upon tourniquet release. Comparatively, the average SBP and DBP of the control group increased significantly at the 40, 50, and 60 minute marks with average pressures of 138/78, 142/81, and 150/90 respectively

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Discussion Cont'd

- Li et al. (2015) Study, 80 adults
  - 43 patients had a diagnosis of HTN and 37 did not. These two groups were separated equally into a control group and dexmedetomidine group that received 1 mcg/kg bolus over 20 minutes followed by a 0.4 mcg/kg/min infusion
  - HTN diagnosis: Incidence of hypertension between the control versus dexmedetomidine groups was 77.8% and 48.0% respectively.
  - No HTN diagnosis: Incidence of hypertension between the control versus dexmedetomidine groups was 66.7% and 12.5% respectively.

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Discussion Cont'd

Dexmedetomidine Use in Surgery Requiring a Tourniquet

- Most common side effects found in the literature were hypotension and bradycardia soon after the initial bolus
- Dexmedetomidine has a steady state volume of distribution of 118 Liters suggesting the need for a bolus prior to infusion
- The study by Lu et al. (2013) gave a 0.5 mcg/kg bolus over ten minutes prior to tourniquet inflation, and showed much less hypotension and bradycardia requiring intervention compared to the Lao et al. (2013) study which used a 0.8 mcg/kg bolus over ten minutes prior to tourniquet inflation. Both the studies had similar results in controlling BP and HR due to tourniquet pain.

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Discussion Cont'd

Alternatives

- Labetalol
  - Beta blocker
  - Half life approximately 5.5 hours
  - $18.31 per 100 mg
  - Side effects: Hypotension and bradycardia
- Esmolol
  - Beta blocker
  - Half life 9 minutes
  - $63.05 per 100 mg
  - Side effects: Hypotension and bradycardia
- Ketamine
  - NMDA antagonist
  - Half life 10-15 minutes
  - $56.38 per 100 mg
  - Side effects: Tachycardia, arrhythmias, nausea/vomiting, hallucination, increased intra cranial pressure, tonic-clonic movements, and hyper salivation

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Recommendations

- Patients who would benefit from tight blood pressure and heart rate control (e.g. coronary artery disease, stroke risk, increased chance of bleeding), and are projected to receive a tourniquet time greater than 45-60 minutes while under general anesthesia should be considered for a dexmedetomidine infusion.
- A bolus of 0.5-0.8 mcg/kg over 10 minutes should be initiated prior to tourniquet inflation followed by an infusion of 0.4 mcg/kg/hr and titrated up to 1.5 mcg/kg/hr to desired effect.
- The bolus dose may be reduced or held in those patients with labile blood pressure and/or bradycardia.

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Recommendations

- Areas Where More Research Needed:
  - Cost effectiveness of dexmedetomidine
  - Effects of dexmedetomidine on PACU length of stay
  - Comparison of beta blockers and/or ketamine administration in attenuating the SNS response in prolonged tourniquet use, compared to the addition of a dexmedetomidine infusion.

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Conclusion

- The increased SNS response associated with tourniquet times > 45-60 minutes is difficult to control. It is refractory to narcotics and inhaled anesthetics, and subsequently leads to hypertension and tachycardia, which can have a detrimental impact on morbidity and mortality.
- Dexmedetomidine infusions have been shown to attenuate the SNS response associated with tourniquet pain in the literature as well as with the patient in this case report.

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