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Epidural Neostigmine for enhanced Analgesia

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Epidural Neostigmine for enhanced Analgesia

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Table of Contents

Abstract

Background: The addition of medications for enhanced epidural analgesia is a well-known topic. Many medications have been studied including steroids, opioids, clonidine, precedex and others. Using Neostigmine has been hypothesized to enhance the efficacy of analgesia without some of the side effects associated with opioid use and risks of Local anesthetic systemic toxicity (LAST) from large Local Anesthetic (LA) requirements. Neostigmine administration in conjunction with alternative medications in neuraxial anesthesia is associated with a reduced dosage of LA required during labor and postoperatively following cesarean section. Studies have shown how neuraxial administration of neostigmine significantly minimized local anesthetic usage without causing serious negative side effects.

Methods: A detailed search strategy encompassed the databases CINAHL, Cochrane Library and PUBMED. Articles found to be eligible for review were found to fit within the constraints of the original PICO question. Population (P): Anesthesia Providers who participate in epidural management, Intervention (I): Educating about epidural Neostigmine analgesia, Comparison (C): Comparing epidural neostigmine knowledge before and after education, Outcome (O): Improve provider knowledge on methods to improve analgesia when additional local analgesia is contraindicated or opioid puritis is unwanted. These abstracts and titles were reviewed to include only randomized control trials. A total of seven articles were chosen and were deemed fitting within the PICO constraints.

Results: Participants were asked the likelihood to use alternative therapies rather than local anesthetics and opioids to enhance epidural analgesia. Two participants (40%) said extremely likely. An additional two participants (40%) said somewhat likely and one participant (20%) said neither likely nor unlikely. This showed that practitioners are willing to try alternative approaches to enhance epidural analgesia if patients will benefit. Additionally, participants were asked the likelihood that after watching the video on epidural neostigmine for enhanced analgesia, would the participant be willing to use neostigmine in their

daily practice. Based upon the results, two participants would be extremely likely to use epidural neostigmine. This result shows that the YouTube presentation provided a positive educational experience which may influence practitioners to consider epidural neostigmine in their pharmacological arsenal.

Keywords: EPIDURAL ANALGESIA; NEURAXIAL ANALGESIA; NEOSTIGMINE; OPIOID; ACETYLCHOLINE.

Problem Statement

Additional medications are often administered in addition to local anesthetics in efforts of enhancing epidural or spinal analgesia. These additional medications range from opioids to clonidine and even neostigmine. Pruritis can be a common unwanted side effect when intrathecal and epidural opioids are administered.[6] The incidence of pruritis can vary between 30% and 100%.[6] The exact mechanism of neuraxial opioid-induced pruritus is not totally understood.[6] The addition of opioids does enhance analgesia however the risk of pruritis can be severe for some. If patient preference opposes opioid usage due to their negative side effect profile, then practitioners can only rely on additional local anesthetics (LAs) or higher concentrations. However, epidural anesthesia and peripheral nerve blocks (PNBs) require high volumes of LAs and this inherently raises the possibility for local anesthetic systemic toxicity (LAST).[5] If a practitioner has already met the upper limits of allowable LA dosing then the extent of the block cannot be made denser if the patient refuses opioids due to past experiences such as pruritis.

Scope of the problem

A study was performed regarding the occurrence of pruritis among women receiving epidural management for cesarean section with the addition of opioids. From this study, 89% of the women who received morphine and 71% of the women who received fentanyl had severe pruritis

which required treatment.[7] These percentages show how common and frequent this undesirable side effect can occur. Additional problems that arise regard the issue of insufficient analgesia. Often, women who plan for a vaginal birth are forced to convert to cesarean for various reasons. Many of these women already have an epidural catheter in place. One study mentioned how many times epidural labor analgesia fails to convert to adequate epidural surgical analgesia.[8] The study found that epidurals fail to provide surgical analgesia 15% of the time while spinals fail 2% of the time.[9]

In addition to the failure of analgesia, if practitioners increase the dosage of LA, they run the risk of high levels and LAST. Current data indicated that the incidence of LAST associated with PNBs has decreased from 1.6–2 for every 1000 patients in the 1990s to roughly 0.9 for every 1000 between 2003 and 2013.[5] The incidence of LAST with epidural anesthesia decreased from 9.75 out of 1000 in the early 1980s to 0.1 out of every 1000 in the 1990s.[5] These trends show great improvements, but all possible risks are not eliminated.

Additional statistics show how dangerous LA dosages can be when handled incorrectly. A 2009 study revealed close-claim circumstances were anesthesiologist have been sued.[11] They reported 10 instances where a high spinal occurred due to epidural catheters placed intrathecally and were not recognized due to failure to aspirate or utilize a lidocaine test dose with epinephrine.[11] Additionally, there were two circumstances of high spinals and three instances of high epidural blockade.[11] The severity of consequences that can occur when regional anesthesia goes wrong cannot be underestimated. This study also revealed events where anesthesia providers were not adequately prepared to treat hypotension or airway emergencies when performing epidural placement.[11] Four of these cases resulted in patients requiring transfer to the operating room for resuscitation due to inadequate material in the labor room.[11]

Consequence of the problem

A high proportion of obstetric malpractice claims is the result of pain during anesthesia compared to nonobstetric claims.[9,] Circumstances arise were labor is escalating rapidly and the sacral blockade efficacy may not suffice. During these circumstances, large volumes of local anesthetic may improve sacral analgesia.[9] However if the efficacy of sensory blockade is optimal but the patient is still expressing pain, then the blockade's density may be inadequate.[9] These instances can be resolved with the administration of a more concentrated local anesthetic. [9] However these options in efforts of deepening the block run the possibility of high levels and possibly reaching the upper limit of safe LA dosages.

A review of cases since 1995 showed Anesthesia-related claims account for 2.5% of all claims and 2.4% of the value of all claims. Of 841 relevant claims, 44% were related to regional anesthesia, 29% obstetric anesthesia, and 20% were due to inadequate anesthesia.[10] This review was performed by the National Health Service Litigation Authority (NHSLA) which manages legal claims made against NHS Hospital Trusts, Foundation Trusts and Primary Care Trusts in the United Kingdom.[10] Claims-related costs have risen from $454 million in 2004-2005 to $585 million in 2006 through 2007.[10] The claims with the highest overall values were regional anesthesia recorded at $15 million and $10.38 million for obstetric anesthesia.[10]

Knowledge Gaps

Accidental subarachnoid injection of large doses of local anesthetics can have disastrous effects. These large unintentional doses can lead to a high spinal, which is characterized as extreme hypotension, syncope, and apnea due to brain stem hypoperfusion.[9] Therapy includes mechanical ventilation, fluid management and inotropes. Administration of ionotropic drugs

such as epinephrine may be required if cardiac sympathetic blockade occurs resulting in bradycardia.[9] Additionally, pregnant mothers are at higher risks for unintended intravenous catheter insertion during regional anesthesia because of epidural vein engorgement. Statistically, accidental intravascular epidural catheter insertion may occur in as many as 7% to 8.5% in the obstetric population.[9]

Proposal solution

The proposed solution for this DNP is the administration of neostigmine in efforts of enhancing analgesia while avoiding higher LA doses and the side effects of opioids. One study showed sampled Cerebrospinal fluid (CSF) via an indwelling spinal catheter in 12 volunteers receiving intrathecal neostigmine (50-750 mcg) and analyzed the presence of neostigmine and acetylcholine.[1] Analysis of the CSF samples were performed and found increased acetylcholine concentrations from <20 pmol/ml at baseline to >100 pmol/ml within 15 min of neostigmine injection.[1] A 2009 randomized control study by Ross and colleagues evaluated the requirements of epidural bupivacaine infused with neostigmine in obstetrics.[3] The data showed that adding 40 mcg/mL of epidural neostigmine reduced the hourly bupivacaine requirement by 19%-25% with patient-controlled epidural analgesia during labor.

Using Neostigmine can enhance the efficacy of analgesia without some of the side effects associated with opioid use and risks of LAST from larger LA requirements. The intravenous use of opioids reduce pain and increase the release of acetylcholine in the spinal cord's dorsal horn.[2] This effect has also been proven to be enhanced with the injection of intrathecal neostigmine.[2] Neostigmine administration in conjunction with alternative medication in neuraxial anesthesia is associated with a reduced dosage of LA required during labor and postoperatively following cesarean section.[4] This study showed how neuraxial administration of neostigmine significantly

minimized local anesthetic usage without causing serious negative side effects to the fetus or mother.[4] However, due to the occurrence of nausea and vomiting when given subarachnoid, neostigmine should only be given via the epidural route.[4]

An additional 1997 RCT by Hood and colleagues evaluated analgesia in intrathecal neostigmine and intravenous (IV) alfentanil.[2] IV alfentanil caused respiratory depression that was not observed via epidural neostigmine and additionally enhanced analgesia. Intravenous alfentanil increased cerebrospinal fluid ACh concentration, and neostigmine was noticed to enhance this change a well.[2] This data regarding neostigmine is consistent with the spinal cholinergic mechanism that is observed with IV opioid analgesia.[2]

Results

Study Characteristics

The six articles that were chosen were all Level I studies due to their RCT design. The articles all evaluated the use of epidural neostigmine, with one article, (Rocha et al., 2014) evaluating intrathecal neostigmine. This article was included due to the minimal dosage of neostigmine utilized and its literature review acknowledging the awareness of nausea and none of the participants experiencing nausea from intrathecal neostigmine. All the studies evaluated if less analgesics were required by the participants or if extended time was recorded before rescue analgesics were required after neostigmine administration.

Results of Individual Studies

The 2009 study from Ross and colleagues evaluated the hypothesis that epidural neostigmine in combination with bupivacaine via continuous infusion would minimize the amount of required bupivacaine. The study was of level one quality due to its randomized control trial. The study evaluated 40 women who blindly received solely 1.25 mg/ml

Bupivacaine or with the addition of 4 mcg/ml neostigmine. The primary outcome to be measured would be the hourly usage of bupivacaine. There findings revealed that the group that received neostigmine added to their infusion used 19% less bupivacaine in all participants and 25% in those who continued the infusion greater than 4 hours. The study also monitored for any possible negative muscarinic side effects on the fetus. They found no evidence of increased risk of nausea and vomiting, uterine contractions, or fetal heart abnormalities. The only side effect noticed was an increase level of sedation among the women. The first phase of this study was to find a safe dose of neostigmine that would not produce unwanted side effects for the mother or fetus. The first phase analyzed the safety between a 40 mcg and 80 mcg dose of neostigmine for 12 women. One woman in each group experienced nausea but was reported to be minimal on a 1-10 grading scale. The women for the second phase of the experiment ranged from ages of 21-36. There was no difference in demographic or labor characteristics. All women were cervically dilated roughly 3 cm. This could influence the efficacy of the block. If women were further along and experiencing more sever labor pain, thus requiring a stronger rescue of analgesia, maybe the addition of neostigmine wouldn't be enough to lower bupivacaine requirements. The women that were eligible for this study had to be ASA I or II, less than 114kg, single fetus, and cervical dilation less than 6 cm. The study was limited to healthy individuals and of women experiencing only labor pain. This study does not analyze the effectiveness of epidural neostigmine for postop analgesia used in other surgeries.

A 2014 article conducted between Rocha and colleagues, performed a Level one evidence study due to its RCT structure, evaluating 60 individuals. The study randomly selected 60 individuals to one of four groups. The control group (CG) received a spinal and epidural saline. The Neostigmine group (NG) received spinal neostigmine and epidural saline. The

Dexamethasone group (DG) received spinal saline and epidural dexamethasone. Lastly, the Neostigmine dexamethasone group (NDG) received spinal neostigmine and epidural dexamethasone. All groups received 15mg of Bupivacaine intrathecally and measured the time for their first rescue dose and amount of rescue medication required. The results concluded that DG had the longest time for first rescue dose compared to NG and CG. The results also concluded that the addition of neostigmine in the NDG group resulted in even longer times before rescue relief was required, and less medication needed. This study aimed at evaluating if additional medications could enhance analgesia compared to opioids which are known for their adverse effects. The study mentioned how neostigmine may be more effective in treating somatic pain versus visceral pain, and this could be beneficial for orthopedic procedures.[3] Additionally, epidural dexamethasone has been known to be more beneficial at treating visceral and neuropathic pain compared to somatic.[3] The candidates chosen were of ASA I and II, ranging from ages 15-60 years old. Their pain was ranked on visual analog score from 0-10. The rescue drug that could be requested at any time was 50 mg of ketoprofen every 4 hours, and the second rescue drug was 1 g dipyrone. Pain was recorded at the time of the spinal and the time of first requested rescue analgesia. Nausea and vomiting were recorded and ranked by the anesthesiologist who was blind to the treatment. The surgery the candidates underwent were minor orthopedic procedures ranging from knee arthroscopy, meniscus repair, and knee ligamental reconstruction. The use of 5-10 mg of epidural dexamethasone was the recommended dose. The study found that 30% of patients in the DG group did not request rescue medications and with the addition of 1 microgram of spinal neostigmine, this statistic was increased to 60% of the participants in the NDG group not requesting rescue medications. The study mentioned how they were the 3rd study to show evidence of enhancement of opioid analgesia after

neostigmine and the first clinical trial to show furth enhancement of analgesia in combination with epidural dexamethasone. The mechanism of action for which this study claims neostigmine has its analgesic effects is multimodal. It is believed to increase Acetylcholine concentration at the M1 and M3 receptors present in Laminae II and V in the dorsal horn. This affect was believed to be mediated partly by GABA receptors in the dorsal horn. Neostigmine was also shown to induce Nitric Oxide release which inhibited FOS expression and activated M2 receptors, which in turn released catecholamines, thought to produce anti-inflammatory effects at the tissues.

A 2017 randomized, double blind study was performed by Booth and colleagues. The study aimed at evaluating the efficacy between epidural neostigmine and epidural fentanyl when added to Bupivacaine. The study mentioned how epidurally placed opioids are known to decrease local anesthetic requirement up to 20% but at the expense of unwanted side effects. The hypothesis of the study was to see if epidural bupivacaine usage would be similar between neostigmine addition and fentanyl addition. The participants that were included were 215 ASA II laboring mothers, who were requesting epidural analgesia. The groups were to receive .125% Bupivacaine with 2mcg/ml fentanyl, or neostigmine (2, 4 or 8mcg/ml). The measured outcome was total hourly local anesthetic consumption, including top offs. The total amount of administered medication was divided by the number of hours administered. The results only found 151 participants to be eligible for evaluation in the study. The researchers monitored the maternal and fetal outcomes and found no significant difference between the groups. The evidence supported no hourly difference in Bupivacaine requirements whether the groups received fentanyl or neostigmine. The researchers mentioned how opioids are useful for minimizing local anesthetic dosages and minimizing hypotension and motor blockade, but they

themselves can cause puritits and decreases in fetal heart rate variability. They mentioned how neostigmine, since the 1990s, has been known intrathecally to provide effective analgesia, however at the cost of severe nausea and vomiting. The authors mentioned, how when neostigmine is administered epidurally rather than intrathecally, the unwanted side effects of nausea and vomiting are not observed. Additional inclusion criteria for this study were women with only single fetus, weight less than 115kg, cervical dilation less than 5cm, and not having received IV analgesics within 60 minutes of the epidural. If the women complained of pain greater than 3 on a pain score of 0-10, the women were excluded from the study and the catheter was removed and discretion was left to the anesthesiologist. All care members involved in the care were blind to the study and except for the anesthesiologist who mixed the epidural solutions. All participants were placed on a 6 ml/hr basal rate with a possible 5ml bolus with a 10 minute lockout period. Patients requiring more than one epidural bolus dose per hour or reporting inadequate analgesia after a bolus dose were excluded from the study. Level of sedation, motor blockade depth, nausea and vomiting, shivering, maternal hypotension, fetal Apgar scores were all monitored. There was no difference in degree of shivering, sedation, nausea and vomiting, and degree of motor blockade. Reported levels of puritis were significantly higher in the fentanyl group. Unfortunately, due to sample sizes the researchers were unable to find a difference between the bupivacaine usage among the 3 neostigmine groups who received either 2, 4, or 8 mcg. The researchers mentioned how it is possible that .125% of Bupivacaine was a strong enough dose to reach sensory blockade where fentanyl or neostigmine would not have made a difference. They also mentioned that the women who were evaluated in this study were all very pleased with their epidural and since any non-fully working epidurals were excluded, the

adequacy between fentanyl and neostigmine could have just been due to highly functioning epidural catheters.

An additional study conducted in 2004 evaluated the analgesia efficacy of epidural neostigmine. The study was performed by Kaya and colleagues, inclusive of 80 patients receiving elective cesarean section and receiving combined spinal epidural. All patients were to receive 8 mg of Bupivacaine with 10 mcg of fentanyl and then randomly selected to receive saline or 75, 150, 300 mcg of neostigmine after umbilical chord clamping. The researchers concluded that neostigmine could provide analgesia in women post caesarean delivery. This study mentioned that they were the first study to administer epidural neostigmine after a combine spinal-epidural approach was placed. Exclusion criteria were patients heavier than 110kg, ASA greater than 1, less than 18 years old and allergies to neostigmine or bupivacaine. The patients all received a spinal of bupivacaine and fentanyl and then an epidural catheter. The epidural catheter was only used to administer the studied dose once chord clamping was performed and removed after surgery. Patient's pain was managed post-op via morphine PCA pump. The number of demand doses and morphine consumption was monitored at 8, 16 and 24 hours. Neostigmine lowered pain but was not dose dependent. The time to the first pain complaint and PCA use was prolonged in the neostigmine group. However total 24-hour morphine use was no different between control and neostigmine groups. Additionally, results showed that time to ambulation was shorter and patient satisfaction was higher in the groups that received neostigmine. Neostigmine was administered after chord clamping when oxytocin was administered and therefore could not assess any uterine contractions from muscarinic side effects. The researchers stated that they found no negative maternal or fetal effects that would preclude epidural

neostigmine from future clinical investigation. The study found that doses of 300 mcg were associated with increased sedation among participants.

A 2003 study performed by Roelants and colleagues sought out to discover if epidural neostigmine could lessen anesthetic requirements. Epidural neostigmine (4 mcg/kg) was added to 10 ml of .1% ropivacaine with and without 10mcg of sufentanil. Pain score, sensory level, and motor blockade were all assessed 20 minutes after injection. The study concluded that when neostigmine was added to 10mg of ropivacaine, the level of analgesia was equivalent to 20mg of ropivacaine but was not as effective as sufentanil. There was no hemodynamic instability, or negative side effects that were recorded among researchers. The researchers choose to use the epidural route due to the spinal route having records of causing severe nausea. They also decided to make the inclusion criteria laboring women, because they stated how reports show neostigmine may be more efficacious in women compared to men, so gynecological and obstetrics would be fitting for its use. All women were of ASA I-II and requesting of epidurals. Exclusion criteria included, accidental dural puncture, multiple pregnancy, premature labor, and nonvertex presentation. All anesthesiologists and residents who administered the dose, were blind to the study. The recorded findings included hourly ropivacaine use, number of rescue doses and time of total delivery from initial dose to delivery. The participants were randomized into 4 groups. The first group received .2% 10ml (20mg ropivacaine), the others 3 groups received ropivacaine with sufentanil and neostigmine alone or ropivacaine with neostigmine and sufentanil. 101 patients participated in this study and 6 were excluded for requiring cesarean delivery. Neostigmine had no effects on mother or fetal heart rate. The researchers concluded that neostigmine with 10 mg of ropivacaine provided equal analgesia compared to 20mg of

Ropivacaine with less motor blockade. The researchers found that dose to be safe for epidural administration, however it had no effect on long term local anesthetic requirements.

A 2010 Randomized double blind study performed by Harjai and colleagues performed a study evaluating two different doses of epidural neostigmine for postop analgesia. The study included 90 females scheduled for lower abdominal surgery. The women were divided into three groups of 30. Group I (control) received 9 ml of 1% lidocaine with 1 ml of normal saline. Group II received 9 ml of 1% lidocaine and 100 mcg of neostigmine. Group III received 9 ml of 1% lidocaine and 200 mcg of neostigmine. The cases were all ran with N20 and relaxant. At the conclusion of the case, in recovery, all participants received their randomized dose. The conclusion of the study showed dose independent extended duration of analgesia and dose dependent sedation. Inclusion criteria included ASA level I-II women between the age 18-45 scheduled for lower intrabdominal surgery. Exclusion criteria included pregnant women, allergies to local anesthetics, and epidural contraindications. After 15 minutes of epidural administration; sensory and motor blockade were assessed. Level of sedation was also measured on a ranked scale of 0-3 by responses to increasing stimuli. The time for rescue analgesia was also monitored. The study stated there were no significant differences in participant characteristics including age, height, and weight. The time for rescue analgesia was significantly longer (210 min) in Groups II and III compared to Group I (130 min). Additionally, the amount of rescue injections (IM diclofenac) was less (1-2) for Groups II and III with group I receiving approximately 3-4. All candidates achieved approximately a T8 sensory level blockade with no extreme variances. No candidate in either of the groups experienced a change in vital signs greater than 15%. Groups II and III experienced mild levels of sedation with group I experiencing none. The researchers believed the sedation to be beneficial for postoperative care

due to enhanced analgesia and its ability to minimize cardiovascular and respiratory complications. No side effects of puritis or respiratory depression were seen amongst any of the participants, as is seen with opioid usage.

Authors	Purpose	Methodology/Research Design	Intervention/ Measures	Sampling/Setting	Primary Results	Relevant Conclusions
Ross et al., (2009)	To evaluate if neostigmine would minimize epidural Bupivacaine usage in Laboring women	The study was of level one quality due to its randomized control trial	They first phase analyzed the safety between a 40mcg and 80 mcg dose of neostigmine for 12 women	The women that were eligible for this study had to be ASA I or II, less than 114kg, single fetus, and cervical dilation less than 6cm	19% less bupivicane usage in all participants and 25% in those who continued the infusion greater than 4 hours. No evidence of increased risk of nausea and vomiting, uterine contractions or in fetal heart abnormalities	4mcg/mL of epidural neostigmine reduced bupivacaine usage by 19%-25%
Rocha et al., (2014)	To evaluate if spinal neostigmine, epidural dexmethasone enhanced spinal bupivacaine following orthopedic surgery	Level one evidence study due to its RCT structure	The control group (CG) received spinal and epidural saline. The Neostigmine group (NG) received spinal neostigmine and epidural saline. The Dexamethasone group (DG) received spinal saline and epidural dexamethasone. Lastly the	The study randomly selected 60 individuals to one of four groups. The candidates chosen were of ASA I and II, ranging from ages 15-60 years old. The candidates underwent were minor orthopedic surgeries, ranging from knee		The study found that 30% of patients in the DG group did not request rescue medications and with the addition of 1 microgram of spinal neostigmine, this statistic was increased to 60% of the

			Neostigmine dexamethasone group (NDG) received spinal neostigmine and epidural dexamethasone. All groups received 15mg of Bupivacaine intrathecally and measured time for their first rescue dose and amount of rescue medication needed. All groups received 15mg of Bupivacaine intrathecally and measured time for their first rescue dose and amount of rescue medication needed	arthroscopy, meniscus repair, to knee ligamental reconstruction		participants in the NDG group not requesting rescue medications
Booth et al., (2017)	To evaluate if epidural bupivacaine with neostigmine would lower LA usage compared to Bupi with fentanyl	Level I, randomized, double blind study. All care members involved in the care were blind to the study and drugs except for the anesthesiologist who mixed the epidural solutions	Groups were to receive .125% Bupivacaine with 2mcg/ml fentanyl, or neostigmine (2, 4 or 8mcg/ml). the measured outcome was total hourly local anesthetic consumption, including Top offs	215 ASA II laboring mothers, who were requesting epidural analgesia. Inclusion criteria for this study was women with only single fetus, weight less than 115kg, cervical dilation less than 5cm, and not having received	No negative maternal and fetal outcomes and found between the different groups. No difference in degrees in shivering, sedation, nausea and vomiting, and degree of	No hourly difference in Bupivacaine requirements whether the groups received fentanyl or neostigmine

				IV analgesics within 60 minutes of the epidural. If the women complained of pain greater than 3 on a pain score of 0-10, the women was excluded from the study and the catheter was removed	motor blockade. Reported levels of puritis were significantly higher in the fentanyl group	
Kaya et al., (2004)	Evaluate the efficacy and safe dose of epidural neostigmine for post labor analgesia	Level I, randomized double blind study	All patients were to receive 8mg of Bupivacaine with 10 mcg of fentanyl and then randomly selected to receive saline, 75, 150, 300 mcg of neostigmine via epidural catheter after chord clamping. Neostigmine was administered after chord clamping	80 patients receiving elective cesarean section and receiving combined spinal epidural. Exclusion criteria were patients heavier than 110kg , ASA greater than 1, less than 18 years old and allergies to neostigmine or bupivacaine	Time to the first pain complaint and PCA use was prolonged in the neostigmine group. Total 24 hour morphine use was no different between control and neostigmine groups. Time to ambulation was shorter and patient satisfaction was higher in the groups that received neostigmine	Neostigmine was capable of providing analgesia in women post caesarean delivery
Roelants et al., (2003)	To assess the duration and strength of epidural neostigmine analgesia and its ability to	Level I, RCT. All anesthesiologists, residents who administered the dose, were blind to the study	101 patients participated. participants were randomized into 4 groups. Epidural neostigmine (4	All women were of ASA I-II and requesting of epidurals. Exclusion criteria included, accidental dural puncture,	Neostigmine had no effects on mother or fetal heart rate. The researchers concluded that	The study concluded that when neostigmine was added to 10mg of ropivacaine the level of

	lessen LA requirements		mcg/kg) was added to 10 ml of .1% ropivacaine with and without 10mcg of sufentanil The first group received .2% 10ml (20mg ropivacaine), the others 3 groups received ropivacaine with sufentanil and neostigmine alone or ropivacaine with neostigmine and sufentanil	multiple pregnancy, premature labor, and nonvertex presentation	neostigmine with 10mg of ropivacaine provided equal analgesia compared to 20mg of Ropivacaine with less motor blockade	analgesia was equivalent to 20mg of ropivacaine but was not as effective as sufentanil was
Harjai et al., 2010	Evaluating two different doses of epidural neostigmine for postop analgesia	Level I, Randomized double blind study	Women were divided into three groups of 30. Group I (control) received 9ml of 1% lidocaine with 1ml of normal saline. Group II received 9ml of 1% lidocaine and 100mcg of neostigmine. Group III received 9ml of 1% lidocaine and 200mcg of neostigmine	90 females scheduled for lower abdominal surgery. Inclusion criteria included ASA level I-II women between the age 18-45 scheduled for lower intrabdominal surgery. Exclusion criteria included pregnant women, allergies to local anesthetics, and epidural contraindications	Time for rescue analgesia was significantly longer (210 min) in Groups II and III compared to Group I (130 min). Additionally, the amount of rescue injections (IM diclofenac) was less (1-2) for Groups II and III with group I receiving approximately 3-4	Epidural Neostigmine extended the duration and depth of analgesia without negative muscarinic side effects. The groups receiving neostigmine had dose dependent sedative effects.

Discussion

Summary of the Evidence

After reviewing the evidence, the usage of epidural neostigmine does seem to have a place in an anesthesia practitioner's arsenal. All seven RCTs showed an enhancement in patient analgesia and patient satisfaction without serious complications. Six of the seven articles included laboring women with one article included participants having orthopedic procedures. There have been well documented reports of severe nausea that is experienced when neostigmine is administered intrathecally. This fact is why only RCTs where neostigmine was administered epidurally were evaluated except for the one study. None of the RCTs showed harmful muscarinic effects towards the patient, mother, or fetus. This was a positive and reassuring result that supports the safety of this drug and route for further usages and studies to be conducted.

One of the studies by Roelant's and colleagues did not show neostigmine's analgesia effects to be as efficacious as sufentanil, but it was equivalent to doubling the LA dosage. This result supports the hypothesis that if opioids are not desired due to their negative profile, LAs are reaching their upper safe limit, or motor blockade is too dense then Neostigmine may be a beneficial option for a patient.

Purpose

Eligibility Criteria: Articles found to be eligible for review were found to fit within the constraints of the original PICO question.

Population (P): Anesthesia Providers who participate in epidural management

Intervention (I): Educating about epidural Neostigmine analgesia

Comparison (C): Comparing epidural neostigmine knowledge before and after education.

Outcome (O): Improve provider knowledge on methods to improve analgesia when additional local analgesia is contraindicated or opioid puritis is unwanted.

All articles that fit these constraints were evaluated. Any study regarding the epidural usage on animals or rats were not accepted for review.

Information Sources

Databases that were used for this study included The Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Library, and PUBMED.

Search Strategy

When searching CHINAL for "Epidural analgesia" and "neostigmine" 20 results were displayed. After further narrowing of results with full text and scholarly journal criteria, 16 results were populated and evaluated. Upon searching Cochrane Library, key words "epidural analgesia" and "neostigmine" were utilized. Initial efforts populated 10,500 results. When rephrasing Boolean terms to "epidural neostigmine" and "analgesia" 503 results were populated. When narrowing the time range within the past 10 years, 250 results were produced. These abstracts and titles were reviewed to include only randomized control trials. A total of seven articles were chosen and were deemed fitting within the PICO constraints.

Definition of terms

Neuraxial Analgesia: The goal of neuraxial anesthesia is to block pain transmission from area of injury, disease, or surgical intervention.[16] Spinal and epidural analgesia are known as central neuraxial blockade because they involve placement of local anesthetics onto or nearby the spinal cord. Spinal and epidural blockade share much of the same anatomy and physiology but are distinct in their anatomic, physiologic, and clinical features.[16]

Epidural: An epidural is an injection of a local anesthetic into the space directly outside the dura matter of the spinal cord. What is clinically important about spinal and epidural analgesia is that the primary site of action for local anesthetics is on the nerve roots within the spinal cord.[16]

Acetylcholine: In the autonomic nervous system, acetylcholine (ACh) is the neurotransmitter in the preganglionic sympathetic and parasympathetic neurons. In the peripheral nervous system, ACh is the neurotransmitter at the neuromuscular junction between the motor nerve and skeletal muscle. In the central nervous system, ACh is found primarily in interneurons.[16]

Neostigmine: Neostigmine is a carbamic acid ester of alcohols and contains a quaternary amino group. This agent forms a carbamyl-ester complex at the esteratic site of cholinesterase. The indirect effect of cholinesterase inhibitors is increasing the concentration of endogenous acetylcholine around cholinergic receptors.

Opioid: "The development of synthetic drugs with morphine-like properties has led to the use of the term opioid to refer to all exogenous substances, natural and synthetic, that bind specifically to any of several subpopulations of opioid receptors and produce at least some agonist (morphine-like) effects. Opioids are unique in producing analgesia without loss of touch, proprioception, or consciousness."[14]

Methodology

Goals and Outcomes

The goals and outcomes of this project are to identify any gaps or flaws in the current management of analgesia via the epidural route that may benefit from new research and

evidence. If there are any weaknesses in the hospitals current implemented protocols, then opportunities will be investigated for delivering evidence that will improve those protocols. Any currently implemented protocols that are strong or will assist in improving the implementation of the best current evidence-based practice will be further strengthened and encouraged to continue their practice.

Specific

Certified Registered Nurse anesthetists, student registered nurse anesthetist, anesthesiologists, and anesthesia residents will be educated on the benefits of epidural neostigmine.

Measurable

The participants will be educated on the topic and provided a voluntary questionnaire before and after an educational presentation, which will evaluate any gained knowledge on the topic. In addition, the questionnaire will analyze the likeliness that practitioners will utilize neostigmine epidurally in their future practice after having received the presentation.

Attainable

The completion of voluntary anonymous pre and post questionnaires should be attainable, especially if the questionnaires and education are presented in environments that are high-yielding for epidural procedures, such as obstetrics.

Realistic

CRNAs, SRNAs, anesthesiologists, and residents are in constant communication via email and daily meetings. Therefore, the opportunity to present this current evidence should be achievable.

Timely

Any participants that partake in this educational presentation and survey will be allotted six months to complete the pre-survey, read the educational power point, and complete the post-educational survey.

Description of the Program Structure

A SWOT analysis represents the strengths, weaknesses, opportunities, and threats of a project being designed. The purpose of the SWOT analysis is for a researcher to understand the project's strengths and weaknesses while being cognoscente of possible opportunities.[13] The strengths and weaknesses tend to arise from the project or organization itself.[13] In addition many of the opportunities and threats that arise tend to be external circumstances that arise to the project.

Strengths

The strengths of a SWOT analysis represent areas that an organization does exceptionally well and succeeds in.[13] The hospital takes exceptional pride in providing adequate analgesia during the perioperative and postoperative period. The addition of neostigmine into the daily practice of analgesia management aligns well with the organization's goal. The goal of providing pain relief while minimizing adverse side effects is at the foremost of this project's intent as well as the organization's daily mission.

Weakness

The weakness in SWOT analysis represents areas that need improvement. In one's analysis, these weaknesses need to be decided upon if their salvaging is possible and if required resources are even available.[13] In addition, when resolving these weaknesses, how will their resolution benefit the organization. A possible weakness towards the implementation of neostigmine with epidurals may be the fear of unwanted muscarinic side effects that come from

anti-cholinesterase medications. Another weakness is that there is no current evidence to show that neostigmine provides superior analgesia compared to opioids. This fact may lead practitioners to continue using their current regimen that has been successful. Additionally, enhanced and extended analgesia is well known to be exhibited with the supplemental addition of intrathecal steroids such as Decadron. This knowledge and current safety profile may make practitioners resistant to try alternate methods of enhancing analgesia compared to proven successful techniques. Lastly, there may be resistance due to personal beliefs and biases among individual practitioners.

Opportunities

The opportunities section analyzes the given strengths and any potential to grow these strengths to further improve one's goal.[13] Also, assessing the weaknesses and deciding how their resolution will create positive impacts on one's goal or if eliminating their status all together would be superior rather than attempting to rectify them altogether.[13]

A high proportion of obstetric malpractice claims are the result of pain during anesthesia compared to nonobstetric claims.[9.] Circumstances arise where labor is escalating rapidly and the sacral blockade efficacy may not suffice. During these circumstances, large volumes of local anesthetic may improve sacral analgesia.[9] However if the efficacy of sensory blockade is optimal but the patient is still expressing pain, then the blockade's density may be inadequate.[9] These instances can be resolved with the administration of a more concentrated local anesthetic. [9] However these options in efforts of deepening the block run the possibility of high neuraxial levels and possibly reaching the upper limit of safe LA dosages.

Using Neostigmine can enhance the efficacy of analgesia without some of the side effects associated with opioid use and risks of LAST from larger LA requirements. The intravenous use

of opioids reduces pain and increases the release of acetylcholine in the spinal cord's dorsal horn.[2] This effect has also been proven to be enhanced with the injection of intrathecal neostigmine.[2] Neostigmine administration in conjunction with alternative medication in neuraxial anesthesia is associated with a reduced dosage of LA required during labor and postoperatively following cesarean section.[4] This 2015 systematic review by Cossu and colleagues showed how neuraxial administration of neostigmine significantly minimized local anesthetic usage without causing serious negative side effects to the fetus or mother.[4] However, due to the occurrence of nausea and vomiting when given subarachnoid, neostigmine should only be given via the epidural route.[4]

Threats

The threats that may arise in one's analysis are going to be obstacles that one deems detrimental to the organization's goals or the project altogether.[13] These obstacles may consist of current competition, regulations, current practice beliefs, policies, and personal beliefs. The goal of neutralizing initial threats of resistance would be by educating practitioners regarding the rates and statistics of the negative side effects opioids produce when administered epidurally. Additionally, educating practitioners that if enhanced blockade is desired and local anesthetic dosages are maxed out, then neostigmine can be a valuable option; especially if the unwanted side effects of opioids are highly undesired. The biggest threat appears to be disrupting the current standards of practice that have a high profile for safety and effectiveness, while attempting to convince practitioners that there may be an additional safe option. The main strategy in mitigating this threat is through education and presenting strong evidence that supports the claims of neostigmine's epidural analgesic benefits.

Theoretical Framework

Selecting a Nursing Theory allows one to better focus efforts on research in a way that can be better suited for individual circumstances.[13] When one implements nursing theory into work, self, personal values, and assumptions then all of these factors can be evaluated to allow for a more holistic process. A theory that will be specifically utilized during this research is Johnson's Behavioral Systems Model Theory. This theory emphasizes how humans are systems that are behaving in an environment that is affected by internal and external factors.[13] This theory is excellent for evaluating the responses from anesthesia faculty after being educated on the current evidence regarding epidural neostigmine. This theory will help guide and understand the resistance to change or acceptance toward neostigmine's use. The resistance or acceptance may come from internal conflicts such as assumptions of best practice or external conflicts due to protocols, financial restraints, and even patient acceptance or refusal. Many circumstances can affect the acceptance or rejection of new evidence and this theory will assist in guiding and understanding how providers respond after receiving new evidence.

Methodology

Setting and Participants

This project will be conducted amongst the Florida International Alumni List. The participants included Certified Registered Nurse Anesthetist alumni. This group of participants routinely engages in the use of epidural analgesia and provides an excellent volume of knowledge. Currently, there are approximately 60 CRNAs enrolled on the list.

Description of approach and project procedures

This project will be conducted by inviting the previously mentioned participants to engage in an online survey via email. The data that will be conducted may include the years of employment and experience, age, location of training, and provider role. The providers will be

presented a questioner regarding their knowledge of supplemental medications that may be safely administered in combination with epidural local anesthetics to enhance analgesia. After the survey, an educational video will be presented on current research and knowledge of epidural neostigmine. After the video has been viewed, participants will be asked to complete a post-educational survey. The survey will evaluate any new knowledge gained and the possibility of providers implementing this new research into their practice.

Protection of Human Subjects

The subjects will all be emailed privately from the primary investigator. All responses will be anonymously submitted. The primary investigator will ensure all responses are confidential and the software used to collect responses ensures anonymous polls. All participants will have the option to withdraw their responses or not participate.

Data Collection

Questions will be presented in a manner which assesses practitioners beliefs in the benefits of additional pharmacological methods to enhance epidural analgesia. A 4-point Likert-type scale ranging from 1 (strongly disagree) to 4 (strongly agree) will be used to assess if they have heard of neostigmine epidurally, if they would use it after completing this survey, if they believe additional medications such as opioids, steroids enhance their epidural analgesia.

Data management and analysis plan

Data will all be held and evaluated by the primary investigator. The anonymous results will only be accessible by the primary investigator and be stored in an electronic database.

Discussion of the results with implications to advanced nursing practice

If the results from the survey conveyed that knowledge was gained, then the project would be deemed a success. In addition, if practitioners strongly agreed in implementing neostigmine into their pharmaceutical repertoire, then this would be a strong success. The purpose of this project is educating hospital staff who use epidurals daily for patient analgesia. If a competency course could show knew knowledge gained in the field of epidural management, then change could possibly occur in real practice. This educational competency has the potential to have a strong impact because the participants have great accessibility to these pharmacological supplies and possess advanced epidural management skills.

Timeline

Project Tasks

1. Develop the education intervention
2. Develop the questionnaire
3. Request CBMCS permission
4. Receive IRB approval
5. Choose an electronic database
6. Create and send study invitation
7. Administer pretest questionnaires
8. Perform educational intervention
9. Administer posttest questionnaire
10. Record participants responses
11. Analyze the anonymous data

Results

The patient demographics are depicted below in the table from the voluntary participants. There was a total of seven participants. Five (71%) of the participants were male, while two (28%) were female. The age range of the participants were asked. Two (66%) of the participants were between the ages of 25-30 and 1 (33%) was between the age of 31-40. Other age ranges were provided, but the remaining four participants preferred not to answer. The level of education was asked. Four (51%) participants had a bachelor's degree, while two (28%) had a Masters and 1 (14%) had a Doctorate degree. Lastly, the years of experience was asked. Four (57%) of the participants had 0-2 years of working experience, while two (28%) had 2-4 years of experience and one (14%) had 6-10 years of experience. Two participants did not complete the posttest survey and were therefore not included in the final assessment.

Demographics	N(%)
Gender	
Male	5 (71%)
Female	2 (28%)
Age	
25-30	2 (66%)
31-40	1 (33%)
Prefer not to answer	4
Level of Education	
Bachelors	4 (51%)
Masters	2 (28%)
Doctorate	1 (14%)
Years of experience	
0-2	4 (57%)
2-4.	2 (28%)
4-6.	0
6-10.	1 (14%)

All participants were consented for voluntary participation. After consent, patient demographics were collected. Then a pre-test consisting of eleven questions was provided. After the questionnaire, a link to an educational video regarding epidural neostigmine was provided. After the video was watched participants were provided a random ID number and given a post survey test that consisted of the original eleven pre-test questions. The same questions were provided to see if learning had occurred. The eleven questions that were provided in the pre and post survey consisted of:

1. Annual Medical Claims were the highest for what specialty, totaling $15million?

   a. Obstetrics b. Regional c. Cardiac d. Urology

2. The intravenous use of opioids reduce pain and increase the release of what in the spinal cord's dorsal horn:
   a. Dopamine
   b. Serotonin
   c. Acetylcholine
   d. Norepinephrine
3. What chemical is released by in the spinal chord when neuraxial neostigmine is administered?
   a. Dopamine
   b. Serotonin
   c. Acetylcholine
   d. Norepinephrine
4. What is a possible consequence of neuraxial opioids?
   a) Pruritis
   b) Respiratory depression
   c) Fetal Respiratory depression
   d) All of the above

5. What are the symptoms of Local Anesthetic Systemic Toxicity?
   a. Bradycardia
   b. Hypotension
   c. Respiratory Depression
   d. All of the Above

6. What additional Medications can be administered neuraxially in addition to local anesthetics to enhance analgesia?
    a) Clonidine
    b) Opioids
    c) Neostigmine
    d) Precedex
    e) Gabapentin
    f) All of the above
7. When compared to epidural opioids how efficacious has epidural neostigmine at providing analgesia proven to be?
    a. More effective
    b. Less effective
    c. Equally effective
8. What effect did neostigmine have when administered via the epidural route to pregnant mothers?
    a. Headache
    b. Sedation
    c. Nausea and Vomiting
    d. Confusion
9. What was an effective/ safe dose for epidural neostigmine administration?
    a) 40mcg
    b) 300mcg
    c) 1mcg
    d) 10mcg
10. How likely are you to use alternative therapies in to enhance epidural analgesia

    a) Most likely
    b) Somewhat likely
    c) Somewhat unlikely
    d) Most unlikely

11. How likely are you to utilize a single dose of epidural neostigmine to enhance the analgesia of a patient in addition to Local Anesthetics?
    1. Most likely
    2. Somewhat likely
    3. Somewhat unlikely
    4. Most unlikely

Pre Survey

The results from the pre and post survey are provided below. The randomized anonymous numbers provided were utilized to be able to compare the five participants pre and post survey

responses. Participant one scored an 11% on the pretest and after the educational video, a score of 44% was achieved. This participant showed that education had occurred. Participant two scored a 44% on the pre and posttest. They answered different questions correctly on the posttest than they did on the first, showing that some education did occur, but mistakes were still made. Participant three scored a 44% on the pre and an 88% on the post test, showing education did occur. Participant four scored an 11% on the pre and a 0% on the post. This participant may have not been paying full attention to the questions or did not possibly understand the material. Participant five scored an 11% on the pretest and an 88% on the posttest, showing a substantial difference in test scores after watching the educational video. In summary, three of the participants showed improvement in the test scores after watching the educational video while one did worse, and another received the same score. Provided below is the table comparing the answers of the five participants pre and post test scores.

Pre and Post Survey										
Patricipatint	1 Pre	1Post	2 Pre	2 Post	3 Pre	3 Post	4 Pre	4 Post	5 Pre	5 Post
Question 1	n	y	n	n	n	n	n	n	n	n
Question 2	n	n	n	n	y	y	n	n	n	y
Question 3	n	y	n	y	y	y	n	n	n	y
Question 4	n	n	y	n	y	y	n	n	n	y
Question 5	n	n	y	y	y	y	n	n	n	y
Question 6	n	y	y	n	n	y	n	n	n	y
Question 7	y	n	y	y	n	y	y	n	y	y
Question 8	n	y	n	n	n	y	n	n	n	y
Question 9	n	n	n	y	n	y	n	n	n	y
Score	11%	44%	44%	44%	44%	88%	11%	0%	11%	88%

Post Survey Test results are displayed in the Table below:

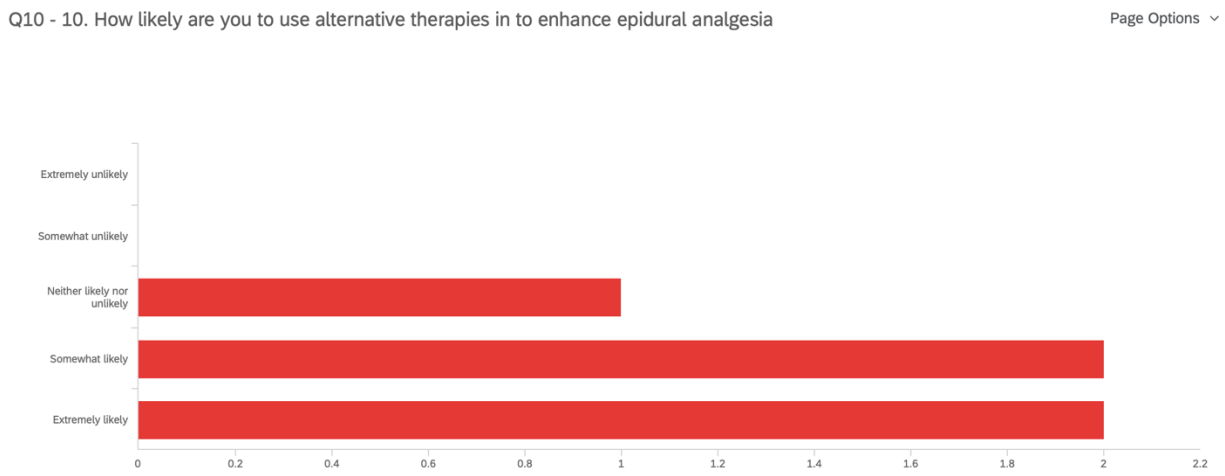
Post Test		
Question #	**Correct Answers**	**% Correct**
1	1	20%
2	2	40%

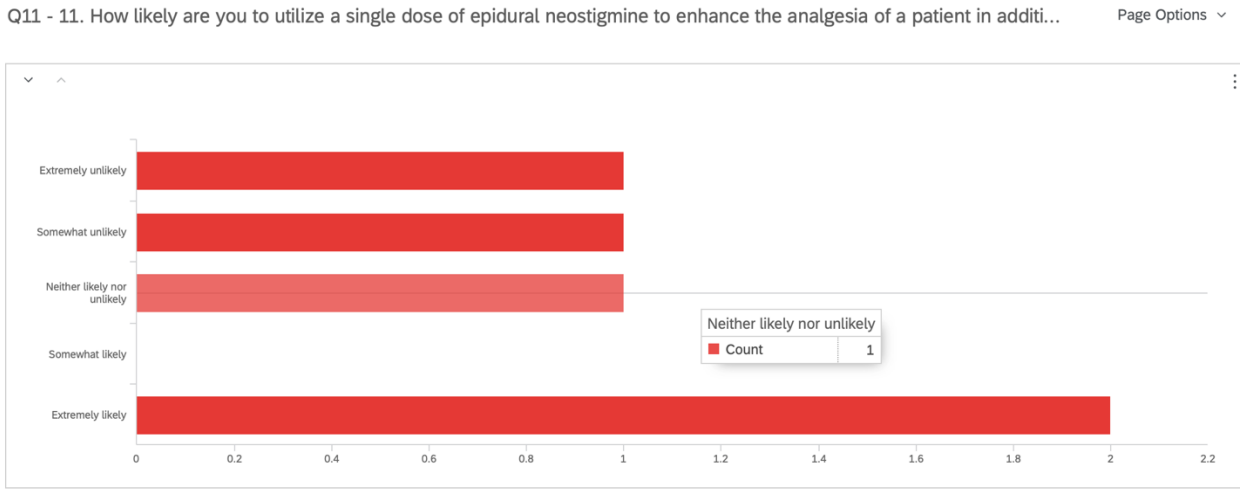
3	4	80%
4	2	40%
5	3	60%
6	2	40%
7	2	40%
8	3	60%
9	3	60%

Assessment Questions and Implications to Advanced Nursing Practice

Provided below are questions that assessed the participants likelihood to use alternative medications besides opioids and local anesthetics in the management of epidural analgesia. Question 10 asked how likely participants are to use alternative therapies rather than local anesthetic and opioids to enhance epidural analgesia. Two participants (40%) said extremely likely. An additional two participants (40%) said somewhat likely and one participant (20%) said neither likely nor unlikely. This showed that practitioners are willing to try alternative approaches to enhance epidural analgesia if patients will benefit. Additionally, question eleven, asked the likelihood that after watching the video on epidural neostigmine for enhanced analgesia, would the participant be willing to use neostigmine in their daily practice. Based upon the results, two participants would be extremely likely to use epidural neostigmine. This result shows that the YouTube presentation provided a positive educational experience which may influence practitioners to utilize epidural neostigmine. The categories extremely likely, somewhat unlikely, and neither likely nor unlikely all had one participant choose that response. These results showed that the video may not have provided enough evidence to convince a provider to alter their daily practice or they just may not be willing to change, their current practice base on the information provided. The participant that answered neither likely nor unlikely may not have been convinced either or possibly works in a department where they don't

perform many epidural such as a surgical center, or anesthesiologists perform the neuraxial anesthesia.





Limitations

One of limitations to the DNP project was the small size of participants. A larger participating group would have been more beneficial to assess the beliefs and evidence of learning achieved from the DNP educational module. Another limitation may have been the use of the internet. It is possible that many email invitations were not opened by FIU alumni. It is also possible that many CRNAs found this topic less beneficial and choose not to participate because they do not engage in obstetrics where there is a high use of epidurals.

Summary

Overall, the DNP project had a total of five participants fully complete the pretest, education video and posttest. The results showed that learning indeed did occur and based off of the responses, some practitioners would be willing to utilize neostigmine for enhanced epidural analgesia based upon the information provided. Question 10 from the post test survey asked how likely participants are to use alternative therapies rather than local anesthetic and opioids to enhance epidural analgesia. Two participants (40%) said extremely likely. An additional two participants (40%) said somewhat likely. This showed that practitioners are willing to try alternative approaches to enhance epidural analgesia if patients will benefit. Based upon the results, two participants would be extremely likely to use epidural neostigmine. This result shows that the YouTube presentation provided a positive educational experience which may influence practitioners to utilize epidural neostigmine. In conclusion, the DNP project showed that practitioners are willing to use alternate modalities when managing epidural analgesia and video modalities such as YouTube can be a beneficial way to present new learning material.

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Office of Research Integrity
Research Compliance, MARC 414

MEMORANDUM

To: Dr. Fernando Alfonso
CC: Frank Duffin

From: Maria Melendez-Vargas, MIBA, IRB Coordinator

Date: April 28, 2022

Protocol Title: "Educating on the benefits of Epidural Neostigmine for Epidural Analgesia"

The Florida International University Office of Research Integrity has reviewed your research study for the use of human subjects and deemed it Exempt via the **Exempt Review** process.

IRB Protocol Exemption #: IRB-22-0180 **IRB Exemption Date:** 04/28/22
TOPAZ Reference #: 111567

As a requirement of IRB Exemption you are required to:

1) Submit an IRB Exempt Amendment Form for all proposed additions or changes in the procedures involving human subjects. All additions and changes must be reviewed and approved prior to implementation.
2) Promptly submit an IRB Exempt Event Report Form for every serious or unusual or unanticipated adverse event, problems with the rights or welfare of the human subjects, and/or deviations from the approved protocol.
3) Submit an IRB Exempt Project Completion Report Form when the study is finished or discontinued.

Special Conditions: N/A

For further information, you may visit the IRB website at http://research.fiu.edu/irb.

MMV/em

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CONSENT TO PARTICIPATE IN A QUALITY IMPROVEMENT PROJECT

"Improve Knowledge in Epidural Neostigmine for Enhanced Analgesia"

SUMMARY INFORMATION
Things you should know about this study:

- **Purpose:** Educational module to improve knowledge in utilizing epidural neostigmine for enhanced analgesia
- **Procedures**: If you choose to participate, you will be asked to complete a pre test watch a voice PowerPoint and then a post test
- **Duration:** This will take about a total of 20 minutes total.
- **Risks**: The main risk or discomfort from this research is minimal. There will be minimal risks involved with this project, as would be expected in any type of educational intervention, which may have included mild emotional stress or mild physical discomfort from sitting on a chair for an extended period of time, for instance.
- **Benefits:** The main benefit to you from this research is increase the participants knowledge in utilizing epidural neostigmine for enhanced analgesia.
- **Alternatives:** There are no known alternatives available to you other than not taking part in this study.
- **Participation:** Taking part in this research project is voluntary.

Please carefully read the entire document before agreeing to participate.

PURPOSE OF THE PROJECT

You are being asked to be in a quality improvement project. The goal of this project is to improve health care provider knowledge on the use epidural neostigmine for enhanced analgesia

DURATION OF THE PROJECT

Your participation will require about 20 minutes of your time. If you decide to participate you will be 1 of 10 participants.

PROCEDURES

If you agree to be in the project, we will ask you to do the following things:
If you agree to be in the study, we will ask you to do the following things:
1. Complete an online 10 question pre-test survey via Qualtrics, an Online survey product for which the URL link is provided
2. Review the educational PowerPoint Module lasting 10 minutes via Qualtrics, an Online survey product for which the URL link is provided.
3. Complete the online 10 question post-test survey via Qualtrics, an Online survey product for which the URL link is provided.

RISKS AND/OR DISCOMFORTS

The main risk or discomfort from this research is minimal. There will be minimal risks involved with this project, as would be expected in any type of educational intervention, which may have included mild emotional stress or mild physical discomfort from sitting on a chair for an extended period of time, for instance.

BENEFITS

The following benefits may be associated with your participation in this project: An increased understanding regarding the use of epidural neostigmine to enhance ones level of analgesia.
The overall objective of the program is to increase the quality of healthcare delivery and improve healthcare outcomes for our patients.

ALTERNATIVES

There are no known alternatives available to you other than not taking part in this project. However, if you would like to receive the educational material given to the participants in this project, it will be provided to you at no cost.

CONFIDENTIALITY

The records of this project will be kept private and will be protected to the fullest extent provided by law. If, in any sort of report, we might publish, we will not include any information that will make it possible to identify you as a participant. Records will be stored securely, and only the project team will have access to the records.

PARTICIPATION: Taking part in this research project is voluntary.

COMPENSATION & COSTS

There is no cost or payment to you for receiving the health education and/or for participating in this project.

RIGHT TO DECLINE OR WITHDRAW

Your participation in this project is voluntary. You are free to participate in the project or withdraw your consent at any time during the project. Your withdrawal or lack of participation will not affect any benefits to which you are otherwise entitled. The investigator reserves the right to remove you without your consent at such time that they feel it is in the best interest.

RESEARCHER CONTACT INFORMATION

If you have any questions about the purpose, procedures, or any other issues relating to this research project, you may contact Frank Duffin at fduff004@fiu.edu or Dr. Fernando Alfonso at FAlfonso@FIU.edu.

IRB CONTACT INFORMATION

If you would like to talk with someone about your rights pertaining to being a subject in this project or about ethical issues with this project, you may contact the FIU Office of Research Integrity by phone at 305-348-2494 or by email at ori@fiu.edu.

PARTICIPANT AGREEMENT

I have read the information in this consent form and agree to participate in this study. I have had a chance to ask any questions I have about this study, and they have been answered for me. By clicking on the "consent to participate" button below I am providing my informed consent.

FIU
Department of Nurse Anesthesiology

Nicole Wertheim College of Nursing & Health Sciences

Use of Epidural Neostigmine for Enhanced Analgesia: An Evidence Based Educational Module

Dear FIU Alumni Anesthesia Providers:

My name is Frank Duffin and I am a student from the Anesthesiology Nursing Program Department of Nurse Anesthetist Practice at Florida International University. I am writing to invite you to participate in my quality improvement project. The goal of this project is to improve health care provider knowledge on use of epidural neostigmine for enhanced analgesia. You are eligible to take part in this project because you are a member of FIU's Alumni Anesthesia Department.

If you decide to participate in this project, you will be asked to complete and sign a consent form for participation. Next, you will complete a pre-test questionnaire, which is expected to take approximately 5 minutes. You will then be asked to view an approximately 15 minute long educational presentation online. After watching the video, you will be asked to complete the post-test questionnaire, which is expected to take approximately 5 minutes. No compensation will be provided.

Remember, this is completely voluntary. You can choose to be in the study or not. If you'd like to participate or have any questions about the study, please email or contact me at fduff004@fiu.edu or 9545511066

Thank you very much.

Sincerely, Frank Duffin SRNA, BSN, CCRN

Pretest and Posttest Questionnaire:

Epidural Neostigmine for Enhanced Analgesia

INTRODUCTION

The primary aim of this QI project is to improve the knowledge of CRNAs pertaining to the utilization of epidural neostigmine for enhanced analgesia.

Please answer the question below to the best of your ability. The questions include demographic information and knowledge of methadone utilization in adult surgical patients. Questions are either in multiple choice or likert style format and are meant to measure the CRNAs knowledge of the effectiveness of intraoperative methadone reducing post-operative opioid consumption.

PERSONAL INFORMATION

1. **Gender:** Male Female Other_____

2. **Age:** _____

3. Ethnicity: Hispanic, Caucasian, African American, Asian, Other_____

4. **Position/Title:** _____

5. **Level of Education:** Associates Bachelors Masters Doctoral (DNP, DNAP, EdD, PhD) _____

6. **Years of experience:** Less than 1 year 1 to 5 6 to 10 more than 10 years

QUESTIONNAIRE

12. Annual Medical Claims were the highest for what specialty, totaling $15million?

a. Obstetrics b. Regional c. Cardiac d. Urology

13. The intravenous use of opioids reduce pain and increase the release of what in the spinal cord's dorsal horn:

- **a. Dopamine**
- **b. Serotonin**
- **c. Acetylcholine**
- **d. Norepinephrine**

14. What chemical is released by in the spinal chord when neuraxial neostigmine is administered?

- **e. Dopamine**
- **f. Serotonin**
- **g. Acetylcholine**
- **h. Norepinephrine**

15. What is a possible consequence of neuraxial opioids?

- **e) Pruritis**
- **f) Respiratory depression**
- **g) Fetal Respiratory depression**
- **h) All of the above**

16. What are the symptoms of Local Anesthetic Systemic Toxicity?

- **e. Bradycardia**
- **f. Hypotension**
- **g. Respiratory Depression**
- **h. All of the Above**

17. What additional Medications can be administered neuraxially in addition to local anesthetics to enhance analgesia?

- **g) Clonidine**
- **h) Opioids**
- **i) Neostigmine**
- **j) Precedex**
- **k) Gabapentin**
- **l) All of the above**

18. When compared to epidural opioids how efficacious has epidural neostigmine at providing analgesia proven to be?

- **d. More effective**
- **e. Less effective**
- **f. Equally effective**

19. What effect did neostigmine have when administered via the epidural route to pregnant mothers?

- **e. Headache**
- **f. Sedation**
- **g. Nausea and Vomiting**
- **h. Confusion**

20. What was an effective/ safe dose for epidural neostigmine administration?

- **e) 40mcg**
- **f) 300mcg**
- **g) 1mcg**
- **h) 10mcg**

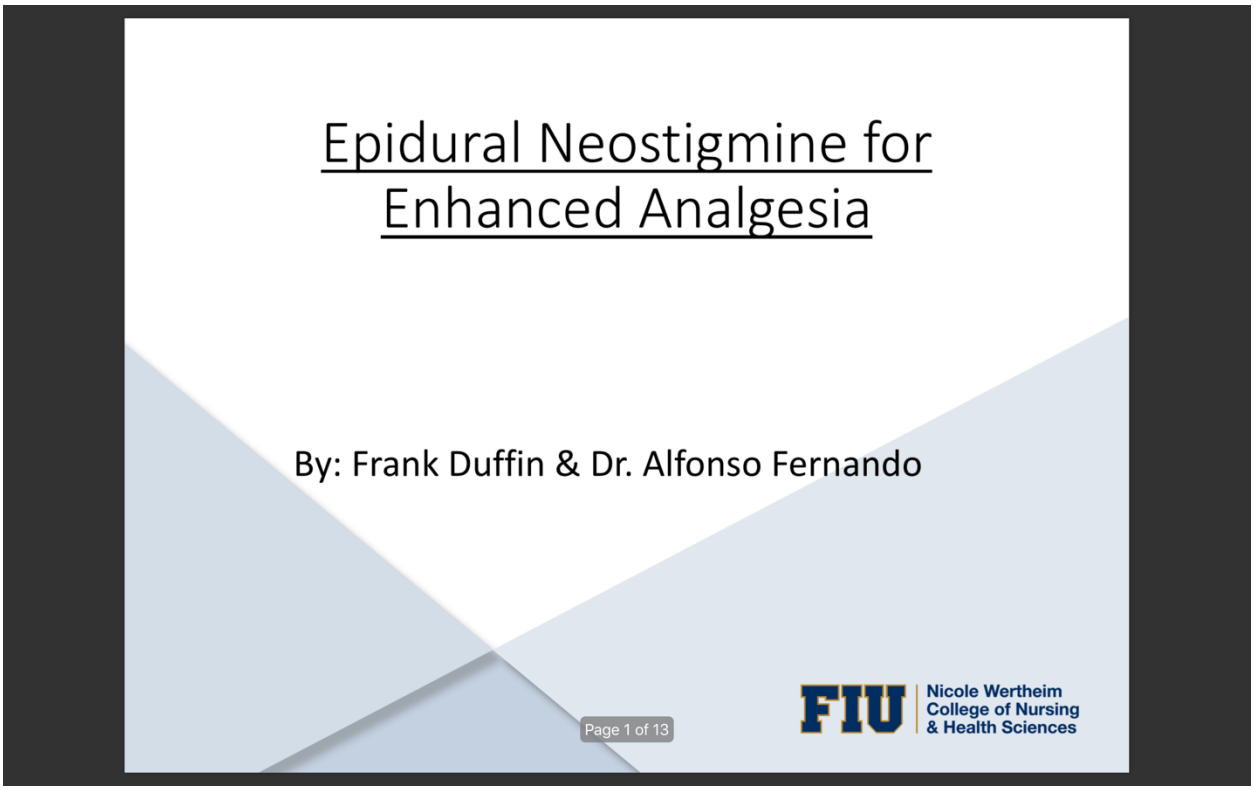
21. How likely are you to use alternative therapies in to enhance epidural analgesia

- **e) Most likely**
- **f) Somewhat likely**
- **g) Somewhat unlikely**

h) Most unlikely

22. How likely are you to utilize a single dose of epidural neostigmine to enhance the analgesia of a patient in addition to Local Anesthetics?

1. **Most likely**
2. **Somewhat likely**
3. **Somewhat unlikely**
4. **Most unlikely**



Goals

- Improve methods of Epidural analgesia
- Provide denser and longer blockade without having to use increased dosages of Local Anesthetics (LAs) and risking Local Anesthetic Toxicity
- Provide analgesia through additional alternatives when opioids are not warranted
  - Opioid dosage limit has been reached
  - Negative side effect profile of Opioids such as pruritis are unwanted
- Educate practitioners on the possible benefits of Epidural Neostigmine
- Neostigmine administration in conjunction with alternative medications in neuraxial anesthesia is associated with a reduced dosage of LAs required during labor and postoperatively following cesarean section.[4]
- This study showed how neuraxial administration of neostigmine significantly minimized local anesthetic usage without causing serious negative side effects to the fetus or mother.[4]

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Problem

- Additional medications are often administered in addition to local anesthetics in efforts of enhancing epidural or spinal analgesia. These additional medications range from opioids to clonidine and even neostigmine.[6]
- The incidence of pruritis from opioids can vary between 30% and 100%.[6]
- The exact mechanism of neuraxial opioid-induced pruritus is not totally inderstood.[6]
- Epidural anesthesia and peripheral nerve blocks (PNBs) require high volumes of LAs and this inherently raises the possibility for local anesthetic systemic toxicity (LAST).[5]
- If a practitioner has already met the upper limits of allowable LA dosing then the extent of the block cannot be made denser if the patient refuses opioids due to past experiences such as pruritis.

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Background of the problem

Current Practice Flaws:

- In a study, 89% of the women who received morphine and 71% of the women who received fentanyl had severe pruritis which required treatment.[7]
- The study found that epidurals fail to provide surgical analgesia 15% of the time while a spinal fails 2% of the time. [7]
- In addition to the failure of analgesia, if practitioners increase the dosage of LA, they run the risk of high levels and LAST.

LAST: Local Anesthetic System toxicity

- The incidence of LAST with epidural anesthesia decreased from 9.75 out of 1000 in the early 1980s to 0.1 out of every 1000 in the 1990s

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Complications

- Of 841 relevant claims, 44% were related to regional anesthesia, 29% obstetric anesthesia, and 20% were due to inadequate anesthesia[9]
- The claims with the highest overall values were regional anesthesia recorded at $15 million and $10.38 million for obstetric anesthesia [9]
- A high proportion of obstetric malpractice claims is the result of pain during anesthesia compared to nonobstetric claims.[9]
  - Circumstances arise where labor is escalating rapidly and the sacral blockade efficacy may not suffice.
  - During these circumstances, large volumes of local anesthetic may improve sacral analgesia.[9]
  - If the efficacy of sensory blockade is optimal but the patient is still expressing pain, then the blockade's density may be inadequate.[9] These instances can be resolved with the administration of a more concentrated local anesthetic. [9]
  - However these options in efforts of deepening the block run the possibility of high neuraxial levels and possibly reaching the upper limit of safe LA dosages.

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Intervention

- **Population (P):** Anesthesia Providers who participate in epidural management
- **Intervention (I):** Educating about epidural Neostigmine analgesia
- **Comparison (C):** Comparing epidural neostigmine knowledge before and after education.
- **Outcome (O):** Improve provider knowledge on methods to improve analgesia when additional local analgesia is contraindicated or opioid pruritis is unwanted.

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Epidural Neostigmine

- The intravenous use of opioids reduce pain and increase the release of acetylcholine in the spinal cord's dorsal horn.[2]
- This effect has also been proven to be enhanced with the injection of intrathecal neostigmine.[2]
- CSF samples before and after intrathecal neostigmine injection show increases of acetylcholine from <20 pmol/ml at baseline to >100 pmol/ml within 15 min of neostigmine injection.[1]
- Neostigmine administration in conjunction with alternative medications in neuraxial anesthesia is associated with a reduced dosage of LA required during labor and postoperatively following cesarean section
- A 2009 randomized control study by Ross and colleagues evaluated the requirements of epidural bupivacaine infused with neostigmine in obstetrics.[3] The data showed that adding 40 mcg/mL of epidural neostigmine reduced the hourly bupivacaine requirement by 19%-25% with patient-controlled epidural analgesia during labor.[3]
- However, due to the occurrence of nausea and vomiting when given subarachnoid, neostigmine should only be given via the epidural route.[4]

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Mechanism of Action

- It is believed to increase Acetylcholine concentration at the M1 and M3 receptors present in Laminae II and V in the dorsal horn. [3]
- This affect was believed to be mediated partly by GABA receptors in the dorsal horn. [3]
- Neostigmine was also shown to induce Nitric Oxide release
  - Thus inhibiting FOS expression and activated M2 receptors, which in turn released catecholamines, thought to produce anti-inflammatory effects at the tissues. [3]
- Neostigmine may be more effective in treating somatic pain versus visceral pain, and this could be beneficial for orthopedic procedures.[3] Side Note: Additionally, epidural dexamethasone has been known to be more beneficial at treating visceral and neuropathic pain compared to somatic.[3]

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Evidence

- A study by 2009 study from Ross and colleagues evaluated 40 women who blindly received solely 1.25 mg/ml Bupivacaine or with the addition of 4 mg/ml neostigmine.
- The primary outcome to be measured would be the hourly usage of bupivacaine.
- Their findings revealed that the group that received neostigmine added to their infusion used 19% less bupivacaine in all participants and 25% in those who continued the infusion greater than 4 hours.
- The study also monitored for any possible negative muscarinic side effects on the fetus.
- They found no evidence of increased risk of nausea and vomiting, uterine contractions, or fetal heart abnormalities. The only side effect noticed was an increase level of sedation among the women.
- The first phase of this study was to find a safe dose of neostigmine that would not produce unwanted side effects for the mother or fetus. The first phase analyzed the safety between a 40 mcg and 80 mcg dose of neostigmine for 12 women.

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Research Studies

- Ross et al., (2009)
  - 4mcg/mL of epidural neostigmine reduced bupivacaine usage by 19%-25%
- Rocha et al., (2014)
  - The study found that 30% of patients in the DG group did not request rescue medications and with the addition of 1 microgram of spinal neostigmine, this statistic was increased to 60% of the participants in the NDG group not requesting rescue medications
- Booth et al., (2017)
  - No hourly difference in Bupivacaine requirements whether the groups received fentanyl or neostigmine

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Studies Cont.

- Kaya et al., (2004)
  - Time to the first pain complaint and PCA use was prolonged in the neostigmine group. Total 24 hour morphine use was no different between control and neostigmine groups. Time to ambulation was shorter and patient satisfaction was higher in the groups that received neostigmine
- Roelants et al., (2003)
  - The researchers concluded that neostigmine with 10mg of ropivacaine provided equal analgesia compared to 20mg of Ropivacaine with less motor blockade
- Harjai et al., 2010
  - Epidural Neostigmine extended the duration and depth of analgesia without negative muscarinic side effects. The groups receiving neostigmine had dose dependent sedative effects

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Summary

- This DNP is aimed at educating anesthesia providers on the possible benefits of epidural analgesia
- Scenarios arise where analgesia depth may need enhancement and additional local anesthetics (LAs) or opioids are contraindicated
- LAST: additional LA's may not be suitable when upper limit dosages have been reached
- Opioids may be refused by a patient due to allergies, past experiences with pruritis or fear of neonate respiratory depression in pregnant parturients
- The Addition of Neostigmine to epidural LA's have been shown to enhance analgesia equally to opioids
- Having epidural Neostigmine in an anesthesia providers arsenal may be beneficial.
- None of the RCTs showed harmful muscarinic effects towards the patient, mother, or fetus. This was a positive and reassuring result that supports the safety of this drug and route for further usages and studies to be conducted.
- No standardized dose was used among studies and further evidence needs to be conducted but the 2009 study by Ross and colleagues found that 40mcg was safe.

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