The Effect of Clonidine as an Adjuvant on Onset of Action of Levobupivacaine Epidural Anesthesia among Patients Undergoing Elective Lower Limb Orthopedic Surgery*

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ABSTRACT

Background: Epidural anesthesia is a widely used anesthesia technique commonly for surgeries involving the lower extremities up to the abdomen. It is beneficial for long duration surgeries because the epidural catheter in place allows additional of local anesthetic as needed. However, this technique has a slower onset of action and requires a larger volume of local anesthetic compared with spinal anesthesia. This study aims to determine if clonidine when used as an adjuvant can hasten the onset of action of levobupivacaine epidural anesthesia thus allowing the early commencement of surgery.

Methodology: This is a double blind randomized controlled trial. After approval from the institution's research ethics and review committee, a total of 36 patients of American Society of Anesthesiologist Classification I or II for elective lower limb orthopedic surgery under levobupivacaine epidural anesthesia were purposively enrolled in this study and randomly assigned by match pairing of characteristics to two groups: Group A-Clonidine and Group B- plain normal saline solution. Group A were given 0.5% levobupivacaine 15cc with 30 μg (0.2cc) clonidine and group B were given 0.5% levobupivacaine 15cc with 0.2cc plain normal saline solution. In both groups the onset of levobupivacaine epidural anesthesia (sensory block at T10 dermatomal level/ Bromage 1) were observed. Side effects such as hypotension, decreased in respiratory rate, oxygen saturation, and any untoward incidence were noted. All data gathered: statistical mean, median, standard deviation, and T test were analyzed using the SPSS software at 5% significance level.

Results: The mean onset of action of group A-Clonidine group (5.62 minutes) was faster compared to group B-control (11.33 minutes), which was statistically significant ($P<0.05$). The highest dermatomal level for the clonidine group was at T6 and T7 for the control group. Two segments regression was at 180 minutes for the Clonidine group while 60 minutes for the control group. The patients given clonidine experienced side effects such as sedation, bradycardia (20% decrease in cardiac rate from baseline), and shivering. Hypotension was not observed in both clonidine and control groups.

Conclusion: Clonidine at a dose of 30 μg when used as an adjuvant to levobupivacaine epidural anesthesia can hasten its onset of action among patients undergoing elective lower limb orthopedic surgery.

Keywords: *epidural anesthesia, clonidine, adjuvant*

Disclosures: *The author has formally acknowledged and signed a disclosure affirming the absence of any financial or other relationships (including personal connections), intellectual biases, political or religious affiliations, and institutional ties that could potentially result in a conflict of interest.*

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INTRODUCTION

Background of the Study

Anesthesiology is the practice of medicine that provides insensibility to pain during surgical, obstetric, therapeutic and diagnostic procedures. It has become progressively safe due to the availability of advance patient monitoring devices and delivery technology.[1] One such anesthetic technique is epidural anesthesia. In a skilled anesthesiologist it is easy to learn and safe to perform. Epidural is useful for surgical anesthesia of different specialties such as orthopedic, obstetric, gynecologic, general surgery, cardiothoracic, among others.2 It is also useful for pain management both intraoperatively and postoperatively. Furthermore it has also been shown to decrease the surgical risk and morbidity of patients such as those with cardiac diseases.[3]

Epidural anesthesia involves the insertion of a hollow needle in the epidural space. This is a potential space located between the dura mater and the vertebrae spine.4 Its contents are the lymphatics, spinal nerve roots, loose connective tissues, adipose tissue, small arteries and a network of internal vertebral venous plexuses.5 A small, flexible catheter inserted into epidural space in the lumbar, thoracic, or cervical level. The anesthetic agent is injected into the catheter. It then diffuses into the epidural space and coat the dural sac while partly passing through the foramina before it is able to cause motor and sensory blockade).[6]

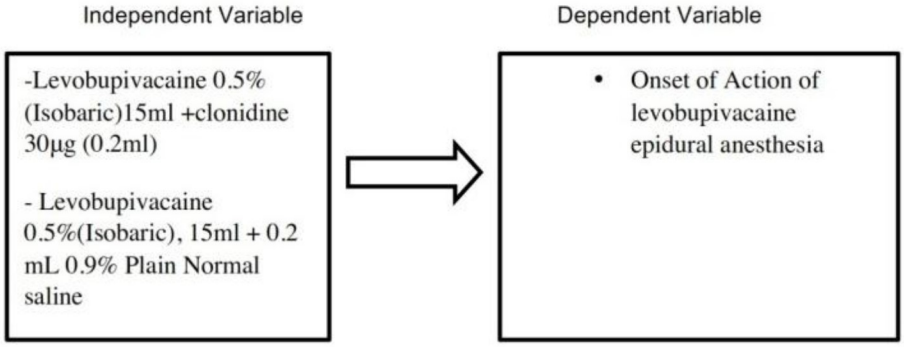
On the other hand, in spinal anesthesia, the anesthetic agent is directly injected into the cerebrospinal fluid into the subarachnoid space. This direct bathing of the nerve root with a local anesthetic agent allows a relatively small dose and volume of local anesthetic to attain a dense sensory and motor blockade.

For epidural anesthesia to achieve the same local anesthetic effect with spinal anesthesia, a larger volume of local anesthetic is given. Adults require 1-2 ml of local anesthetic per spinal segment to be blocked. For instance, to achieve a T4 sensory level blockade from an L4-L5 injection would require about 12-24 ml of local anesthetic. Furthermore, epidural anesthesia has a slower onset of action at around 10-20 minutes and may not be as dense as spinal anesthesia.[7]

Because epidural anesthesia requires larger volume of local anesthetic and a slower onset of action, it is imperative to find an adjuvant that will help to hasten the onset and prolong the duration of action of levobupivicaine epidural anesthesia. This will allow the early commencement of the surgery and use of lower volume of local anesthetic.

One such adjuvant is clonidine. It is a derivative of imidazoline and exerts its action on the alpha 2 adregenergic receptor as an agonist. Once this receptor is activated it can lead to inhibition of excitatory cardiovascular neurons and a reduced sympathetic outflow from the central nervous system. It can also decrease transmission of pain, hence producing analgesia. If added as an adjuvant to epidural, aside from reducing pain transmission in the dorsal horn, it can also cause vasoconstriction of the blood vessels, which slows the removal of local anesthetics. Lastly, there is an additive effect when it is combined with other adjuvants such as opioids leading to a reduced dose of each component by as much as 60% for postoperative analgesia.[8]

Conceptual framework



Objectives

General Objective

To determine the effect of clonidine as an adjuvant on levobupivacaine epidural anesthesia

Specific Objectives

- To determine the effect of clonidine on the onset of sensory blockade and motor blockade of levobupivacaine epidural anesthesia
- To determine if there is significant difference on onset of action of levobupivacaine epidural anesthesia with clonidine adjuvant versus levobupivacaine alone

Definition of Terms

Levobupivacaine - a local anesthetic belonging to the amino amide group and the S enantiomer of bupivacaine. Indicated for infiltration, nerve block, ophthalmic, epidural, and intrathecal anesthesia

Epidural anesthesia - a local anesthetic is injected into the epidural space around the spinal cord using an epidural catheter, the injection can result in a loss of pain sensation by blocking the transmission of signals through nerve fibers in or near the spinal cord

Dermatome - an area of skin that is mainly supplied by afferent nerve fibers from a single dorsal root of spinal nerve, which forms a part of a spinal nerve.

Pinprick test- a gross test to check the actual ability to feel a pinprick and the ability to determine the difference between sharp and dull

Bromage scoring- measures the intensity of motor block by assessing the patient's ability to move their lower extremities: Grade I (complete block-100%)-unable to move feet or ankle, Grade II-(Almost Complete-66%)-able to move feet only, Grade III (Partial-33%)- just able to flex/move the knee, IV (NONE-0%) full flexion of knee and feet

Onset of action- - inability to feel pinprick at T10 dermatome and Bromage I or unable to move feet or legs

Top-up- the addition of anesthetics via epidural route to maintain anesthesia at the desired dermatomal level

Scope and Limitation of the Study

This study is limited to patients admitted at a tertiary level hospital undergoing an elective lower limb orthopedic surgery who are ASA (American Society of Anesthesiologist) I-II, aged 19-50 years old.

Significance of the Study

The result of this study will benefit anesthesiologists for they will be given a possible adjuvant to hasten the onset of sensory and motor blockade of levobupivacaine epidural anesthesia. For the surgical team, because faster onset of epidural anesthesia means early commencement of surgery thus saving time. For the patients, this will help lessen the risk of local anesthetic systemic toxicity. For the "tertiary level hospital", more patients will be catered because of the faster transit time at the operating room and this will serve as a baseline study for future researchers.

MATERIALS AND METHODS

Research Design

This was a double blind randomized controlled trial. An experimental form of research in which the population receiving the intervention was chosen at random from the eligible population, and a control group was also chosen from the same eligible population.

Participants

Thirty-six participants scheduled for elective orthopedic surgery under epidural anesthesia were included in this study.

Sample Size and Randomization Technique

The 36 recruited subjects were purposively enrolled in this study and randomly assigned by match pairing of characteristics to groups two groups (Group A and Group B).

Sample size computation

The result of the study was recorded in "minutes". This was a continuous variable, with a minimum and maximum value; hence this formula for continuous variable was used for the sampling size computation:

$$N = 2 \times \left(\frac{z_{1-\frac{\alpha}{2}} + z_{1-\beta}}{\delta} \right)^2 \times s^2$$

Parameter definitions

N=sample size; p=the response rate of standard treatment group; p_0= the response rate of new drug treatment group; z_x= the standard normal deviate for a one or two sided x; d= the real difference between two treatment effect; δ_0= a clinically acceptable margin; S^2= Polled standard deviation of both comparison groups.

$$N_{\text{statistical superiority}} = 2 \times \left(\frac{1.96 + 0.845}{4} \right)^2 \times 6^2 = 36$$

COVID 19 Precautions and Protocols

The safety of both the patient and the researcher was the utmost priority of this study. The hospital's existing COVID 19 guidelines were strictly followed. Patients who were scheduled for operation underwent a preoperative risk assessment. This was a screening form from the Infection and Prevention and Control unit of the "tertiary level hospital" which was adapted from the Philippine Society for Microbiology and Infectious Diseases and Philippine Hospital Infection Control Society. The following details were obtained from the patient: signs and symptoms, history of travel, preexisting medical conditions, physical examination, vital signs, laboratory including COVID 19 RT PCR result. From these, the patients were then classified as either low risk or high risk for COVID 19 transmission.

Based on the risk for COVID-19 transmission during surgery, there was a minimum recommended personal protective equipment to be used by the anesthesiologist and the surgeon. For low risk for transmission, the following were the recommended personal

protective equipment: Fit tested N95 mask and goggles/face shield.

At the wards, patients were placed in isolated cubicles and were mandated to wear facemask at all times.

For this study, only patients who were classified as low risk for COVID-19 transmission were included. The use of appropriate personal protective equipment was observed during preoperative visit, recruitment process, and operation proper. The patient at the operating room was required to wear facemask at all times.

Recruitment

The Department of Orthopedics submitted a list of patients for elective surgery a day before their scheduled operation. Hence, the recruitment was done a day before the scheduled elective surgery. The principal investigator did the recruitment process and this was done at their respective wards. Those who were eligible to become a participant of the study were visited and recruited. During the recruitment process it was ensured that the participant was in a quiet room or surrounding.

COVID 19 safety protocols such as wearing of proper protective equipment were strictly observed during recruitment process.

Inclusion criteria

- Patients admitted for elective orthopedic lower limb surgery
- Patients who were assessed as low risk for COVID 19 transmission during operation
- ASA (American Society of Anesthesiologists) I-II patient
- Ages 19-50 years old
- Voluntary with written informed consent

Exclusion criteria

- Pregnancy
- Unsuitable condition for lumbar puncture/epidural anesthesia such as: patient refusal, severe coagulation abnormalities, sepsis, elevated intracranial pressure, anticoagulant use, thrombocytopenia, other bleeding diathesis, preexisting central nervous system disorder such as multiple sclerosis, infection at lumbar function site, previous back surgery, preexisting neurologic injury, back pain, placement in anesthetized adult, needle placement through tattoo
- Untreated psychiatric disorder, preexisting psychotic disorder and non compliance to pyshiatric medications and no follow-up
- Those who had sedative or analgesic medications 24 hours prior to surgery
- Epidural block failure (unable to reach sensory block at T10 and motor block-Bromage grade I) after 30 minutes of epidural injection
- Allergy to local anesthetic

Withdrawal criteria:

- Request of patient to withdraw from the study
- COVID positive/exposure to COVID 19 positive patients while at the wards
- Cancelation of surgery
- Change in anesthetic technique

Risk

The level of risk in this study was more than minimal because of the use of an adjuvant drug. Expected side effects were the following: hypotension, sedation, bradycardia, with little effect on respiratory drive. The risks were assessed by the use of standard monitors recommended by the American Society of Anesthesiologists such as pulse oximeter,

electrocardiography, noninvasive blood pressure device, and a temperature probe. These monitors were used during the operation and at the post anesthesia care unit until full recovery from anesthesia was attained. Emergency drugs were made available at all times in order to address these possible side effects.

Benefit

Surgeons and anesthesiologists- faster onset of epidural anesthesia is equivalent to faster commencement of surgery.

Patient - clonidine is known to prolong the duration of action of local anesthetics, lower amount of local anesthetic was given to the patient hence lessening the risk of local anesthetic systemic toxicity. Furthermore, it can also reduce the cost of surgery

The Tertiary Level Training Hospital – a baseline for future researchers. Furthermore, the institution's operating room could cater more patients due to faster transit time of patients.

Study Setting

This study was conducted at the operating room of a tertiary hospital.

Duration of the Study

This study was conducted for over 20 weeks.

Research Team Members

The following were the research team members with their respective roles and responsibilities:

Principal investigator - supervised all aspects of the study including the development of the concept of the study, writing of the protocol, submission of the protocol to the Institutional Review Board approval, direction of the recruitment of participants, manages the informed consent process, and supervising the data collection, preparation of summaries, final data analysis, interpretation, and presentation.

Anesthesia residents:

Anesthesiologist A - a member of the team of anesthesiologists assigned for the elective cases for the day. His sole responsibility was the preparation of the sterile solution to be given to the patient. He labelled these with unique codes. Furthermore, he has the sole knowledge with regards to the composition of the solution (either it contains clonidine adjuvant or the control plain normal saline solution). He was also responsible for the distribution of these solutions.

Anesthesiologist B - another member of the team of anesthesiologists assigned for the elective cases for the day. His responsibilities were the following: inserted the epidural catheter, administered the prepared solution, assessed the level of the motor and sensory block, timed the onset of action of levobupivacaine epidural anesthesia, and monitored the patient during the operation.

It was made sure that the anesthesiologist who prepared the solution was different from the anesthesiologist who performed the lumbar puncture/ epidural catheter insertion and administered the prepared solution.

Instrument and Intervention

Group A received 15 ml 0.5% levobupivacaine mixed with 30-µg clonidine (0.2 ml), and group B received 15 ml 0.5% levobupivacaine mixed with 0.2ml 0.9% plain normal saline solution by epidural route. Both preparations were placed in a 20 ml syringe. The prepared solution was given as a bolus to the patient at a rate of 1ml/second and with 1- minute pause for every 5 ml delivered to observe for any

untoward signs and symptoms. The anesthesiologist who administered the prepared solution was blinded. Everything else was kept constant in both groups.

Procedure

COVID 19 PROTOCOLS

This study strictly adhered to the COVID 19 protocols provided by the Infection Prevention and Control Unit of the "Tertiary Level Hospital". Minimum recommended personal protective equipment for low risk transmission surgery were followed. For the anesthesiologist, this included a fit tested N95 mask and goggles. Patients were asked to wear surgical facemask at all times during the surgical procedure.

PREINDUCTION

The patient from the ward was brought to the exchange area of the operating room. He was then transferred to the operating room's transport stretcher. At the exchange area, a review of patient's history and physical examination were done. The patient was given sedative/anxiolytic and was transferred to the main operating theater where the patient was assigned.

Once transferred to the main operating theater, the patient was moved from the transport stretcher to the operating table. The patient was hooked to oxygen via nasal cannula at 3 liters per minute. Then was attached to American Society of Anesthesiologist Standard monitors such as: non-invasive blood pressure monitor, cardiac monitor, pulse oximeter, and temperature probe. Baseline vital signs were determined.

Prior to induction of anesthesia, the patient was hydrated with plain lactated ringer's solution at a rate of 10 ml per kilogram. Once hydration has been done, he was positioned for the insertion of the epidural catheter.

It was made sure that the levobupivacaine solution to be given to the patient was already prepared before the induction process. The patients were randomly assigned to either group A or group B. Group A received 15 ml 0.5% levobupivacaine mixed with 30 µg clonidine (0.2ml), and group B received 15 ml 0.5% levobupivacaine mixed with 0.2ml 0.9% plain normal saline.

INDUCTION

The patient was positioned for lumbar puncture insertion: lateral decubitus or sitting position. The lumbar puncture area was cleaned with povidone-iodine solution and infiltrated with 2% lidocaine. Lumbar puncture was done using Tuohy needle gauge 18. Epidural space was identified using lost of resistance to air technique. About 4 centimeters of epidural catheter was left in the epidural space. Proper placement of the catheter at the epidural space was verified using a test dose of 3ml, 1.5% lidocaine with epinephrine 0.2mg (1:200,000). After insertion, the patient was then placed in supine position and dermatomal mapping was done. Once the desired dermatomal level was attained, the patient was positioned optimized for the surgical procedure.

Procedure/Maneuvers:

The patient either received the prepared solution containing 15 ml levobupivacaine 0.5% Isobaric mixed with 30 μg (0.2ml) clonidine which were given simultaneously or 0.2 ml plain normal saline which was also given simultaneously. The solution was placed in a 20 cc syringe labeled with a code composed of four characters, which was a combination of numbers and letters. The code was generated using random code generator software.

This was followed by the assessment of the onset of epidural anesthesia using the Bromage and pinprick testing. Bromage scoring is

a grading system based on the patient's ability to move their lower extremities and signifies the intensity of the anesthetic block. The Bromage scoring system is as follows: grade I - unable to move feet or knees, grade II- able to move feet only, grade III-just able to move knees, IV- full flexion of feet and knees. The anesthesiologist administering the solution was blinded. Once the block was considered adequate: inability to feel pinprick at T10 dermatomal level and attainment of Bromage score of I, the surgery was allowed to commence.

The following data were collected: the time taken for onset of epidural anesthesia which was sensory block at T10 and Bromage I; the highest dermatomal level of sensory analgesia; the time to two segment regressions. All recorded in minutes.

A Casio digital HS-70W-1D timer was used in this study and the same model was used in all patients during data collection.

Intraoperative monitoring

Vital signs were monitored every minute for 15 minutes and every 5 minutes thereafter until the surgery ended. Any untoward side effects such as: hypotension, bradycardia, and respiratory depression were closely monitored. Emergency medications were made available at all times. Regression of sensory bock was assessed using pinprick test. Once sensory block regressed to T12, top up with 5ml (0.5% isobaric) levobupivacaine was done.

At the end of the surgery, the patient was transferred to the post anesthesia care unit and was kept attached to non invasive blood pressure monitor, cardiac monitor, pulse oximeter, and temperature probe. Vital signs were monitored every 15 minutes until the patient was suitable for transout.

Post Operative Care

An anesthesiologist assessed the patient prior to transfer back to the ward. The Bromage scoring and Aldrete Scoring were used in determining the patient's readiness for transfer out of the post anesthesia care unit.

Aldrete Scoring

Activity
2 Able to move spontaneously on command four extremities
1 Able to move voluntarilty or on command two extrenities
0 Unable to move any extremities

Respiration
2 Able to deep breath and cough freely
1 Dyspnea, shallow or limited breathing
0 Apneic

Circulation
2 BP +20mmHg of presedation level
1 BP+ 20-50mmHg of presedation level
0 BP + 50 mmHg of presedation level

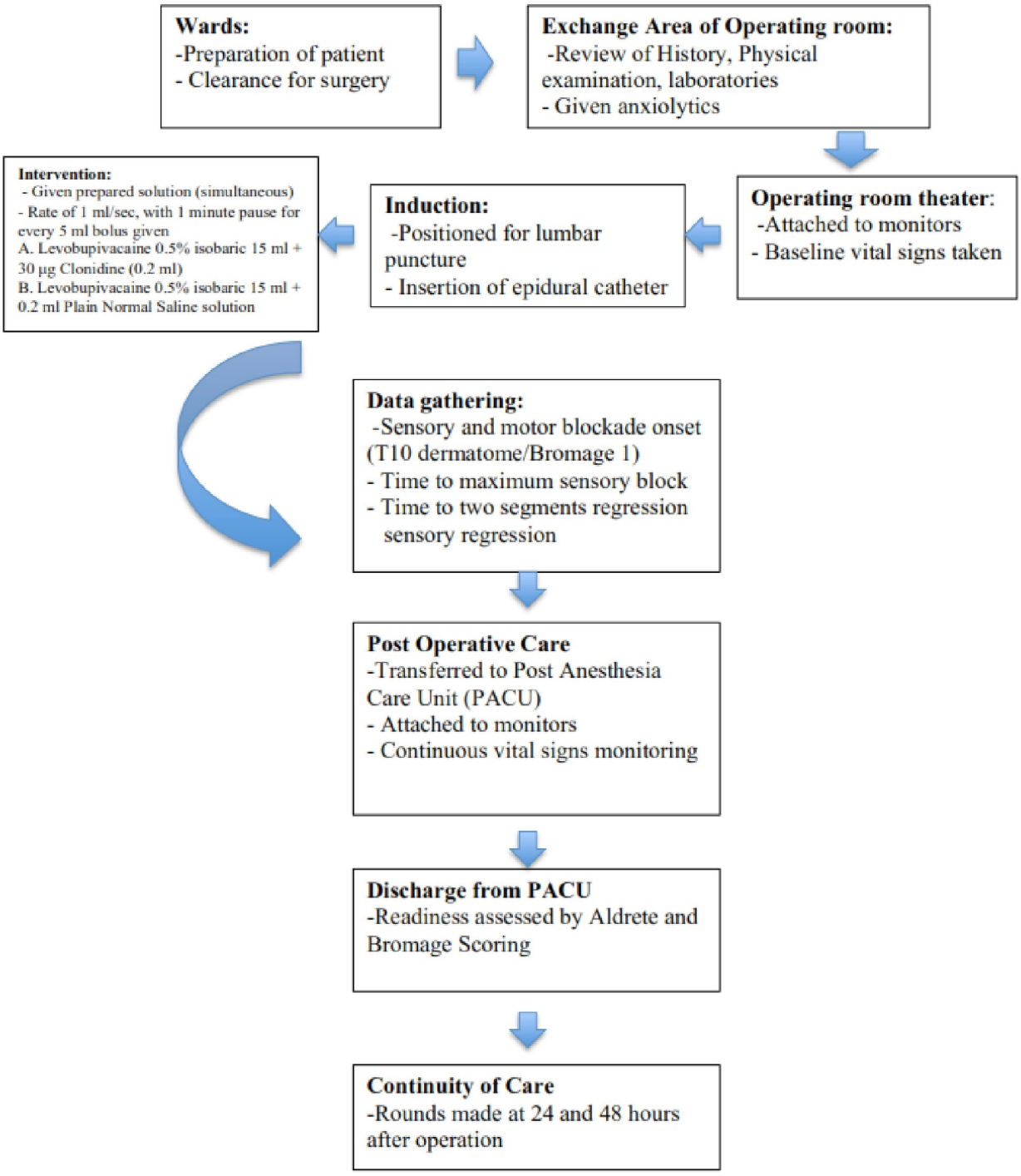
Consciousness
2 Fully awake
1 Arousable on calling
0 Not responding

Skin color
2 Normal
1 Pale, dusky, blotchy, jaundiced, other
0 Cyanotic

Bromage (Assessment of Intensity of Block)
I- Complete - Unable to move feet or knees
II- Almost complete - Able to move feet only
III- Partial - Just able to move knees
IV-None - Full flexion of Knees and Feet

The patient was discharged from the Post Anesthesia Care Unit when Aldrete score was at least 8 and a Bromage score of IV. Rounds were done to the patient 24 and 48 hours after the operation.

Procedure Flow Chart



Ethical Consideration

Ethical issues concerning research participants were mainly privacy, anonymity, voluntary and informed consent. The privacy of information obtained from the participants as well as their anonymity were respected. The participants voluntarily participated and at no one time coerced. The anonymity of the participants was adhered to as no personal information, such as names, were collected. However, it is not only the researcher who had the knowledge of the participant's information but also the entire research team. The researcher assured that all collected data from this research project was kept in a metal box with a lock. Such metal box was kept inside the storage room in the office of the Department of Anesthesia. Information and data in electronic form were kept in a password-protected personal computer in the department's desktop. All data was kept for five (5) years and disposed by shredding for printed documents and deletion of electronic copies from the computer. No one but the researcher had the access to it. This approach was considered once approved and supported by the Western Visayas Medical Center Research Ethics Committee.

Data Analysis Procedure

SPSS software was used to analyze all the data gathered. Descriptive analysis was used in the subject's characteristic. The parametric test of difference used in the data analysis was justified by Shapiro-Wilkman test of normality. The data that were obtained were processed using statistical mean, standard deviation, and T-test for independent sample and effect size and hypothesis was tested at 5% significance level.

Results

The present investigation determined the effect of clonidine as an adjuvant to levobupivacaine anesthesia on the onset of sensory and motor blockade and if there is a significant difference on the onset of action sensory and motor blockade between the experimental and control groups among 36 patients scheduled for elective orthopedic surgery under epidural anesthesia at a tertiary hospital using double-blind randomized controlled trial research design. Data obtained were all analyzed at 5% significance level using the independent t-test since the data distribution was observed to be normally distributed as revealed by Shapiro-Wilk test of normality for the experimental group (p =.405) and control group (p = .408)

Effect of Clonidine Adjuvant and Control on the Onset of Levobupivacaine Anesthesia in Experimental and Control Groups

Groups	N	Mean	SD
Clonidine	18	5.62	1.14
Control	18	11.33	1.22

Table 1 *shows the average time of onset of levobupivacaine anesthesia in experimental and control groups among 36 patients scheduled for elective orthopedic surgery under epidural anesthesia at a tertiary hospital*

The descriptive data in table 1 shows the average onset time of levobupivacaine anesthesia in two groups of patients scheduled for elective orthopedic surgery under epidural anesthesia. The experimental group received 15 mL of 0.5% levobupivacaine (Isobaric) with 0.2 mL (30 µg) clonidine as adjuvant while the control group received 15 mL of 0.5% levobupivacaine (Isobaric) with 0.2 mL of 0.9% plain normal saline solution as control. The introduction of 15 mL of 0.5% levobupivacaine among patients in both experimental and control groups has taken effect but the 15 mL of 0.5% levobupivacaine with clonidine as adjuvant showed faster onset time (M = 5.62, SD = 1.14) than the 15 mL of 0.5% levobupivacaine with 0.2 mL of 0.9% saline solution as control (M = 11.33, SD = 1.22).

Independent t-Test Result for the Difference in the Mean Onset Time Between the Experimental and Control Groups

	N	t	*p*
Clonidine	36	14.51	.000
Control Group	18	11.33	1.22

Table 2 *shows the difference in the average onset time of levobupivacaine anesthesia between experimental and control groups, p<0.05.*

Table 2 reveals the difference in the average onset time of levobupivacaine anesthesia between experimental and control groups. The *t*-test for the independent samples generated a p-value less than 0.05, hence, statistically, there is a significant difference in the onset time between the experimental and control groups, *t (33.86)* = 14.51, *p*= .000 with an effect size of 4. This suggests that clonidine as an adjuvant hastens the onset time of the 15 mL of 0.5% levobupivacaine anesthesia as compared to the 15 mL of 0.5% levobupivacaine anesthesia with the 0.9% plain normal saline solution as a control.

Effect of Clonidine Adjuvant and Control on the highest sensory block, time of maximum sensory block, two segment regression, and regression to T12 of Levobupivacaine Anesthesia in Experimental and Control Groups

	Highest dermatomal level (Thoracic)	Mean Time to maximum sensory block (Minutes)	Mean Time to two segment regression (Minutes)	Mean Time to sensory regression to T12 (Minutes)
Clonidine group	6	10	176.67	0
Control group	7	17.05	60	60

Table 3 shows the highest dermatomal level and the average times of: maximum sensory block, two segment regression, and sensory regression to T12 of levobupivacaine anesthesia in experimental and control groups among 36patients scheduled for elective orthopedic surgery under epidural anesthesia at a tertiary level hospital.

Based on this table it can be seen that that clonidine and control group both reached a higher than desired dermatomal level (T10) at T6 and T7 respectively. Furthermore, the time to maximum sensory block was also faster in the Clonidine group. The mean time to two segments regression of the Clonidine group was also longer at 176.67 minutes compared with the control group which was at 60 minutes.

Side Effects Experienced

	Bradycardia (%)	Shivering (%)	Sedation (%)	Hypotension (%)
Clonidine	33.3	11	33.3	0
Control	0	33.3	0	0

Table 4 shows the side effects experienced of patients in the clonidine group vs control group

It can be seen on this table that the most common side effect of clonidine are bradycardia and sedation (assessed by the Ramsay Agitation and Sedation Scale) both at 33.3% and this was followed by shivering at 11%. None of the participants experienced hypotension. However, shivering has a higher incidence in the control group.

Discussion

Onset of Action of Levobupivacaine

Levobupivacaine is the S enantiomer of the widely used Bupvacaine. It has a safer pharmacologic profile with less cardiac and neurotoxic effects. It is considered as long acting with dose-dependent duration of anesthesia. For a 15 ml 0.5% solution, the onset of sensory block is noted at 8-30 minutes. The maximum cephalad

spread is at T7-T8 dermatomal level and duration of analgesia at 4-6 hours.[9]

In this study the mean onset time of levobupivacaine was noted to be 11.33 minutes. The result of this study was faster compared to a study done by Casati, et al.[10] were the onset of action of levobupivacaine, bupivacaine and ropivacaine were compared. Results showed that for a 15 ml of 0.5% levobupivacaine, the onset of sensory block was at 31 +/- 16 minutes, while for 0.5% bupivacaine and 0.5% ropivacaine were at 25 +/- 19 minutes and 30+/- 24 minutes, respectively.

In another comparative study done by Koch, et al,[11] 0.5% bupivacaine and 0.75% ropivacaine, and 0.5% levobupivacaine showed clinically significant equivalent profiles. However, the levobupivacaine group showed more frequent top ups.

CLONIDINE PROPERTIES AS ADJUVANT

The addition of adjunctive agents (epinephrine, opioids or clonidine) to levobupivacaine in epidural anesthesia and analgesia may increase the duration and quality of analgesia, and decrease the volume of local anesthesia.[12]

Clonidine is part of the Philippine National Drug Formulary, hence widely available. It was first used in epidural block in the year 1984.[13] It is a mixed agonist that stimulates α1, α2 and imidazoline receptors while it has agonistic effects on α2 receptor.[14] It stimulates α2 adrenergic inhibitory neurons in the medullary center decreasing the sympathetic outflow from central nervous system to peripheral tissue, and the decrease in the sympathetic outflow causes decrease in blood pressure, heart rate and cardiac output. On spinal cord the activation of postganglionic α2 receptors in the substantia gelatinosa produces analgesia. Neuraxial placement of clonidine inhibits the spinal substance P release and the nociceptive neuron firing produced by noxious stimulation. The sedative and anxiolytic effects may be mediated by the postsynaptic α2a subtype adrenoreceptors located in the locus coeruleus.[15]

In this study, the side effects noted with Clonidine were both sedation and bradycardia (20% decrease in the baseline cardiac rate) both recorded at 33.3%. Hypotension was not noted in both groups.

In addition, clonidine also potentiates sensory and motor blockade of epidural and peripheral nerve block administered local anesthetics. Different reasons have been given. First, clonidine has intrinsic ability to block conduction in C and Aδ fibers and will intensify conduction block of local anesthetics. Second, clonidine may cause local vasoconstriction and thus impair vascular removal of epidural local anesthetics, and lastly it has been shown that any analgesic, whether neuraxial or systemic, will augment peripheral or spinal blockade. Clonidine also enhances neuraxial opioids, with epidural clonidine and fentanyl interacting in an additive manner.[16]

After epidural administration, clonidine is rapidly and extensively absorbed into the cerebrospinal fluid, the concentration peaking at 30-60 minutes after injection. It produces peak concentration in arterial blood within 10 minutes and venous blood within 30-45 minutes.[17]

The potentiating effect of clonidine was demonstrated in this study; the clonidine group's highest sensory block was at T6 while that of the control group was at T7. Mean time to maximum sensory block was also faster in the clonidine group 10 minutes while 17.05 minutes in the control group.

Clonidine's Effect on Duration of action

The result of this study showed that there was a longer decrease in two segments dermatomal regression of sensory block in the clonidine group when compared with the control group. The mean time to two-segment dermatomal regression in the clonidine group was 176.7 minutes compared to the 60 minutes in the control group.

Several studies support these findings. In a study done by Arumugan, et al,[19] clonidine tt a dose of 2 µg/kg prolonged the duration of epidural analgesia. Pain scale was assessed using the visual analog scale, and result showed that clonidine group had lower pain scale than the control group. The same result was supported by a study done by Prasad, et al[17] the use of 150 µg of clonidine using the epidural route showed a prolonged duration of analgesia as compared to the control group at 299 min vs 152 minutes, respectively. Arumugan, et al[19]

Several studies support these findings. In a study done by Arumugan, et al,[19] clonidine tt a dose of 2 µg/kg prolonged the duration of epidural analgesia. Pain scale was assessed using the visual analog scale, and result showed that clonidine group had lower pain scale than the control group. The same result was supported by a study done by Prasad, et al[17] the use of 150 µg of clonidine using the epidural route showed a prolonged duration of analgesia as compared to the control group at 299 min vs 152 minutes, respectively. Arumugan, et al[19] compared Levobupivacaine 0.5% at 1.5 mg/kg vs Levobupivacaine 0.5% at 1.5mg/kg with clonidine at 2 µg/kg. Results showed that the duration of anesthesia in levobupivacaine group and Levobupivacaine plus clonidine group was 173.5±12.7min and 234.5±16.1mins (CI-66.7-55.2). The difference in the total duration between the two groups was significantly higher in clonidine group (P-0.0001). This result is similar to a study done by Alves, et al,20 clonidine 300 micrograms was used as an adjuvant to 0.75% ropivacaine (150mg) and they found out that there was a significant prolongation in sensory and motor block duration (P<0.0001).

This slower regression of the Clonidine group can be explained the clonidine's ability to cause local vasoconstriction and thus slowing the vascular removal of local anesthetics leading to a prolonged duration of action of the local anesthetic.[8] Slower regression of local anesthetic would imply a less frequent "top up" or addition of local anesthetic, hence lowering the chances of local anesthetic systemic toxicity, and on the economic side a lower cost of operation for the patient.

In this study, no "top up" was done on any patients belonging to the clonidine group until the end of the surgical procedure because the sensory analgesia did not regress to T12 dermatome. Thus, the minimal volume utilization of the local anesthetic.

Clonidine's Effect On Onset of Action

The dosage of Clonidine based on the patient's weight as adjuvant on epidural anesthesia has been studied. In a study done by Gupta, et al,[18] clonidine was used an adjuvant to bupivacaine epidural anesthesia at a dose of 1 µg /kg among patients undergoing total knee replacement surgery, and compared with the control group, the result of their study showed that the clonidine group had faster onset of sensory and motor blockade at 8.23 and 10.26 minutes respectively when compared with the control group, where the onset of sensory and motor blockade was noted at 11.4 minutes and 13.4 minutes, respectively.

This study also showed that there was a statistically significant difference in mean arterial

pressure between the clonidine and control group with the clonidine group having a lower mean arterial pressure. However there were no significant differences in oxygen saturation, respiratory rate and sedation score between the two groups.

In another study done by Arumugan, et al,[19], the dose of clonidine was at 2 µg/kg. The onset of sensory blockade was at 7.8 minutes, while the motor blockade was 10.9 minutes.

A fixed dose of Clonidine regardless of the patient's weight was also investigated. The result of the study done by Prasad, et al26, the use of 150 µg of clonidine showed faster onset of action when added as adjuvant. Hazarika, et al,[21] did a study using 100 µg clonidine as an adjuvant to 20 ml of 0.5% levobupivacaine anesthesia. This study showed that the onset of sensory blockade and motor block was at 12 minutes versus the control group which was at 26 minutes.

In these studies the onset time of clonidine as an adjuvant to levobupivacaine epidural anesthesia was statistically significant when compared to levobupivacaine alone regardless of the dose given.

In this study, a lower dose of Clonidine was used at 30 µg. It was able to hasten the onset of action of the epidural anesthesia, prolonging its duration of action with minimal side effects comparable to other studies with higher fixed dose and patient's weight-based dosages.

Clonidine versus dexmedetomidine

Clonidine was compared with the newer alpha 2 adrenergic agonist dexmedetomidine. Results showed that both adjuvants have the ability to hasten the onset and prolong the duration of action of levobupivacaine epidural anesthesia. In a study done by Hazarika, et. al,[21] patients received epidural levobupivacaine 0.5% 20 ml with 100 μg clonidine as an adjuvant. The result showed that the onset of sensory blockade was at 12 minutes, while the onset of motor block was at 26 minutes. This was compared with dexmedetomidine, at a dose of 50 μg added to levobupivacaine 0.5% 20 ml. The result showed that dexmedetomidine had a faster onset of sensory and motor blockade compared with clonidine. The result of this study is further supported by another study done by Bajwa, et al,[22] where clonidine at 2 μg/kg was compared with dexmedetomidine at 1.5 μg/kg, dexmedetomidine showed a faster onset of action compared with clonidine. This faster in onset of action of dexmedetomidine is attributed to its greater affinity to alpha 2 receptor.

However, there was higher incidence of nausea, dry mouth, and sedation in the dexmedetomidine group. In terms of cost, dexmedetomidine is significantly more expensive at 2100 PHP per vial compared with clonidine at 104 pesos per ampoule.

Summary, Conclusion, and Recommendations

Summary

The present investigation determined the effect of clonidine as an adjuvant to the onset of action of levobupivacaine epidural anesthesia and if there is a significant difference on the onset of sensory and motor blockade between the experimental and control groups among 36 patients scheduled for elective lower limb orthopedic surgery under epidural anesthesia in a tertiary level hospital using double-blind randomized controlled trial research design. Results showed that the experimental group that has received 15 mL of 0.5% levobupivacaine (Isobaric) with 0.2 mL (30 µg) clonidine as an adjuvant has a faster onset time than the group that received 15 mL of 0.5% levobupivacaine (Isobaric) with 0.2 mL of 0.9%

plain normal saline solution. Furthermore, there is a significant statistical difference in the onset time of levobupivacaine anesthesia between experimental and control groups.

Conclusion

The present investigation proved that clonidine as an adjuvant leads to a significant faster onset time of 15 mL of 0.5% levobupivacaine epidural anesthesia than without an adjuvant. This can allow early commencement of surgery and more patients can be served due faster turnover time at the operating room.

Recommendations

Based on the aforementioned findings, the following recommendations are hereby advanced:

1. Clonidine may be used as an adjuvant for faster onset of action of 15 mL of 0.5% levobupivacaine epidural anesthesia for patients undergoing elective lower limb orthopedic surgery.
2. Clonidine's use as an adjuvant may be investigated in other surgical cases such as those involving the lower abdomen.
3. Other local anesthetic agent such as Ropivacaine and Bupivacaine may be explored
4. Adjuvants other than clonidine may also be investigated such as dexmedetomidine and epinephrine

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