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Study of Analysis Minimum Required with A fixed Concentration of Sufentanil during lower Limb Surgeries to Achieve Effective Anesthesia.

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Abstract
Objective: *The aim of the study, we wanted to compare the anesthetic efficacy of ropivacaine alone versus its combination with fixed dose sufentanil. We aimed to find the minimum required dose of ropivacaine when administered with a fixed concentration of sufentanil during lower limb surgeries to achieve effective anesthesia. We also attempted to find whether the combination in effective anesthetic dose produces any hemodynamic instability and/ or significant adverse effects during the surgery and in the immediate postoperative period.*
Methods: *This is a prospective study done with 70 patients clinical data reviewed of the first affiliated hospital of Anhui medical university of January 2015 to 2016 were identified and included for analysis who were scheduled for lower limb surgery under epidural anesthesia. Patients were divided into two groups based on the anesthetic agent that they were supposed to receive. We used up down sequence allocation method as the method for dose estimation as it is an efficient and widely used method to define dose-sparing properties and potency ratios of drugs and drug combinations. Using this method, we estimated the minimum dose of ropivacaine with a fixed dose of sufentanil which could produce effective anesthesia.*
Results: *Over all 70 patient's we analysis into 2 groups about male and female, on that study we found our result ropivacaine alone was ineffective for epidural anesthesia 8ml of 0.75% ropivacaine with 20 µg of sufentanil (2ml) in 10ml of normal saline, given in increasing volumes, starting from 4ml till effective anesthesia was achieved, was the most effective combination for epidural anesthesia*
Conclusion: *We also found our study that this effective fixed dose combination produced no side effects or hemodynamic instability during the surgery or in the immediate postoperative period. We concluded that this should be the standard dose for epidural anesthesia in lower limb surgeries.*
Keywords: *Epidural Anesthesia, Lower Limb Surgery, Ropivacaine, Sufentanil, Up Down Method*

I. Introduction

Epidural anesthesia is a relatively popular method of regional anesthesia, especially in lower limb surgeries, gaining greater acceptability in recent times due to the availability of newer safer drugs for its induction. There are a number of drugs and drug combinations being used for epidural anesthesia, ropivacaine, a local anesthetic, and sufentanil, a synthetic opioid, being among them. Ropivacaine alone, as well as the combination of ropivacaine and sufentanil is widely used for this purpose. Various doses of the agents have been tried and debate exists about their safety in effective dose.

Epidural anesthesia has a long history dating back to 1885, when Dr. James Leonard Corning first described the procedure.[1] The technique was studied in the coming years, and in 1947, Cuban anesthesiologist Manual Martinez Curbelo developed the technique of epidural catheterization,[2] which is the most popular form of epidural anesthesia now.

Epidural anesthesia is one of the most common techniques of regional anesthesia in the present day. It is a technique whereby a local anesthetic agent is injected into the epidural space of spinal cord. To achieve epidural analgesia or anesthesia, a larger dose of drug is typically necessary than with spinal analgesia or anesthesia. It is gaining in popularity for surgical procedures for which spinal anesthesia used to be the preferred choice not too long ago. Different studies have shown better patient outcomes for epidural or combined epidural approach when comparing spinal, epidural, and combined spinal epidural anesthesia. Results have varied depending on the type of surgery (urological/ orthopedic/ obstetric), but the general consensus is that epidural alone or its combination with spinal is more or at least equally effective than spinal anesthesia with remarkably fewer side effects.[3,4] Addressing just the cases of lower limb surgeries, epidural anesthesia is a reliable option. Once the epidural space is accessed, the subsequent anesthesia can later be converted into postoperative analgesia, which has been shown to produce positive effects on surgical outcome and functional rehabilitation after major knee surgeries as well as reduce the duration of rehabilitation.[5]

Various agents and combinations have been used in epidural anesthesia, usually consisting one local anesthetic with or without additional an opioid. While the presence of an epidural catheter helps in regulating the dose of the anesthetic agents, it is necessary to have a standard protocol with advised dosage of the drugs to be used in the procedure. With this study, we aim to shine a light on that matter using the local anesthetic Ropivacaine and the opioid Sufentanil for epidural anesthesia. Both the agents are relatively new and have not been studied on a large scale for when being administered epidurally for anesthetic purpose.

Study Aim

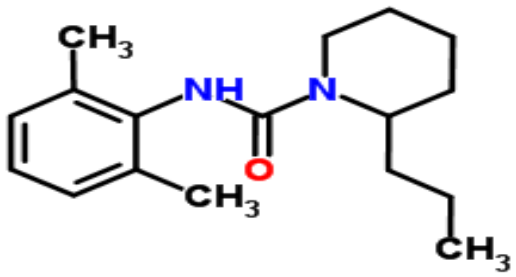
1) To find the minimum required dose of Ropivacaine alone for induction of epidural anesthesia in lower limb surgeries.
2) To find the minimum required dose of Ropivacaine when administered with a fixed concentration of Sufentanil during lower limb surgeries to achieve effective anesthesia.
3) To find whether the combination in effective anesthetic dose produces any hemodynamic instability and/ or significant adverse effects during the surgery.

Ropivacaine

Ropivacaine is a piperidine derivative long-acting amino amide local anesthetic agent, commercially sold as a white odorless powder. It was first clinically introduced in 1996 and is the first of its kind to be produced as a pure enantiomer. It produces effects similar to other local anesthetics via reversible inhibition of sodium ion influx in nerve fibers.

Structure

Fig 1. Molecular structure of Ropivacaine[6]



The piperidine chain can be seen in above figure with a propyl group attached to it. This addition is responsible for its decreased predisposition to be absorbed into the brain and heart. It may also be responsible for its decreased antibacterial capacity.

Ropivacaine is a structural derivative of Bupivacaine. Bupivacaine is notorious for its cardiotoxicity.[7,8] It is attributed to its predisposition to voltage gated sodium channels. Virtually all local anesthetics produce a similar profile of symptoms and signs related to that of the central nervous system, but the cardiotoxicity is difficult to demonstrate in most because it is not usually seen until the CNS toxicity is marked and well beyond the tolerable limits. The butyl group on the piperidine nitrogen atom of bupivacaine is replaced with a propyl group to form ropivacaine. This minor structural modification leads to a reduced hydrophobicity and the decreased ability to diffuse into the heart and brain. As a result, ropivacaine has lower systemic toxicity than bupivacaine. In addition, ropivacaine is manufactured as a pure S-enantiomer, instead of a racemic mixture as in bupivacaine. further lowering the cardiotoxic potential. Studies have successfully proven its relative safety over bupivacaine.[9]

Mechanism of Action

Ropivacaine causes reversible inhibition of sodium ion influx, and thereby blocks impulse conduction in nerve fibers.[10] There is accompanying dose-dependent inhibition of potassium channels.[11] Ropivacaine is less lipophilic than bupivacaine and thus has reduced capability to penetrate large myelinated motor fibers. As a result, it has selective action on the pain-transmitting A β and C nerves rather than Aβ fibers, which are involved in motor function.[12]

Pharmacokinetics

The route of administration and dose of ropivacaine determines its plasma concentration.[13] Vascularity of the site of administration and the circulatory status of the patient also affects its plasma concentration. In plasma, it binds to plasma α_1 acid glycoprotein to an extent of 94%. The total plasma concentration increases during continuous epidural infusion of ropivacaine, which is brought about by its decrease in protein binding and subsequent decrease in plasma clearance.[13,14] It rapidly, but temporarily binds to tissues at the site of injection, especially the nerve fibers. Ropivacaine crosses the placenta during epidural administration for anesthesia during labor,[15] but its level in fetal plasma is lower due to greater concentration of α_1 acid glycoprotein in maternal plasma. Ropivacaine is degraded in liver microsomes by the process of dealkylation and hydrolysis. The specific process is N-dealkylation to 2',6'-pipecoloxylidide by CYP3A4 and aromatic hydroxylation to 3'-hydroxy-ropivacaine by cytochrome P450 (CYP) 1A2.[16,17] Half-life of ropivacaine is 1.8 ± 0.7 h and 4.2 ± 1.0 h after intravenous and epidural administration, respectively. It is mainly excreted through the kidneys.

Cardiotoxicity and CNS toxicity

Ropivacaine is a relatively safer drug considering the fact that its cardiotoxic or CNS toxic potential is low following accidental intravascular injection.[18] Studies in animal models have shown that ropivacaine, as compared to bupivacaine, has far lower cardiotoxic potential.[19,20] Studies in human volunteers has confirmed these findings.

Drug Interactions

Since the toxic effects of these drugs are additive, ropivacaine should be used with caution in patients receiving other local anesthetics[12] or drugs structurally related to amide-type local anesthetics.**Error! Bookmark not defined.** There is a possibility of interactions with drugs metabolized by CYP1A2 via competitive inhibition such as theophylline and imipramine.[21]

Dosage

Table 1. Dosage recommendations for ropivacaine in adults and children

Indication in Adults	Concentration (%)	Volume	Dose
Surgical anesthesia			
Lumbar epidural (Caesarean section)	0.75	15-20 mL	113-150 mg
Lumbar epidural (Other surgery)	0.75	15-25 mL	113-188 mg
Thoracic (Single block for postoperative pain relief)	0.75	5-15 mL	38-113 mg
Intrathecal administration	0.5	3-4 mL	15-20 mg
Peripheral nerve block*	0.75	10-40 mL	75-300 mg
Field block†	0.75	1-30 mL	7.5-225 mg
Postoperative pain			
Lumbar epidural (Continuous infusion)	0.2	6-10 mL/h	12-20 mg/h
Thoracic epidural (Continuous infusion)	0.2	6-14 mL/h	12-28 mg/h
Peripheral nerve block (Continuous infusion)	0.2	5-10 mL/h	10-20 mg/h
Field block†	0.2	1-100 mL	2-200 mg
Intra-articular injection	0.75	20 mL	150 mg
Labor pain (Lumbar epidural)			
Bolus	0.2	10-20 mL	20-40 mg
Intermittent top-ups	0.2	10-15 mL‡	20-30 mg
Continuous infusion	0.2	6-14 mL/h	12-28 mg/h
In children			
Caudal epidural block (Below T12)§	0.2	1 mL/kg	2 mg/kg
Peripheral nerve block	0.5	0.6 mL/kg	3 mg/kg

*Major nerve block brachial plexus or sciatic nerve block; †Minor nerve block or infiltration
‡Minimum interval 30 minutes; §For bodyweight up to 25 kg.

Ropivacaine over Bupivacaine

Ropivacaine is a well-tolerated regional anesthetic. We have already established that it is a far safer drug over bupivacaine and is less likely to produce bupivacaine like CNS toxicity or cardiotoxicity. Moreover, lower incidence of motor block in ropivacaine recipients was accompanied by similar effective pain relief among treatment groups resulting in greater patient satisfaction.[22,23] Although it may be slightly less potent than bupivacaine when administered epidurally or intrathecally, equi-effective doses have been established. In spite

of the fact that ropivacaine is more expensive than bupivacaine, it is the preferred drug for regional anesthesia and management of post-operative pain.

Sufentanil

Sufentanil, first manufactured in 1974, is a synthetic μ-opioid receptor agonist. It is about 5 to 10 times more potent than its parent drug, fentanyl,[24] and 500 times as potent as morphine. This property makes sufentanil the drug of the highest analgesic potential among all clinical opioids applied. This property is mainly associated with the high solubility of sufentanil in fats and its easy penetration through the blood-brain barrier.[25]

Structure

Fig 2: Molecular structure of Sufentanil[26]

The piperidine ring in Sufentanil contains additional methoxy group and a thiofuran believed to be responsible for its markedly high analgesic property when compared with other opioids. Sufentanil is a fentanyl analog, structurally differing from fentanyl through the addition of a methoxy group on the piperidine ring and the replacement of the phenylethyl group by thiofuran. The addition of methoxy group on the piperidine ring is believed to reduce duration of action.[27]

Mechanism of action

Sufentanil, although structurally different from morphine, has the same mechanism of action. Sufentanil, as other opioids, acts through its interaction with the opiate receptors. The opiate receptors are coupled with G-protein receptors. They function as both positive and negative regulators of synaptic transmission via G-proteins that activate effector proteins. The exchange of GTP for GDP on the G-protein complex following the binding of sufentanil. The effector system in this complex is adenylate cyclase and cAMP located at the inner surface of the plasma membrane. Sufentanil decreases the intracellular cAMP by inhibiting adenylate cyclase. This results in the inhibition of the release of nociceptive neurotransmitters such as substance P, GABA, dopamine, acetylcholine and noradrenaline. The remaining subunits stimulate the mitogen-activated protein kinase (MAPK), which is thus involved in the activation of the post-inflammatory chain of eicosanoids.[25] Sufentanil also inhibits the release of enzymes like vasopressin, somatostatin, insulin and glucagon. Sufentanil's conversion into morphine is the likely cause for its analgesic activity. Sufentanil also opens the calcium-dependent inwardly rectifying potassium channels (OP1 receptor agonist). This further results in hyperpolarization and reduced neuronal excitability.

The overall result of this is inhibition of central and peripheral nervous conduction and release of neurotransmitters and substance P in the posterior horns of the spinal cord. The hyperpolarization affects the interneurons of the spinal cord and cerebral structures. The cerebral aqueduct, raphe nucleus and blue nucleus are affected in particular. These regions are rich in opioid receptors. The emotional reactions to the opioids used is due to the biogenic amines produced in this region. The differences in the reaction of receptor activation by opening only one ion channel and maintaining the other one closed depends on the type of a receptor and its location. Presynaptic and postsynaptic inhibition can be observed as well as possible effects on the GABAergic interneuron complex of CNS besides the spinal and supra-spinal effects of sufentanil[25]

Pharmacokinetics

Sufentanil is administered via intravenous or intrathecal route. Intranasal spray of sufentanil is also commercially available, however its use is controversial because of marked fluctuation in bioavailability (46-71%), burning sensation during administration, and incidences of thoracic rigidity (especially in children). A novel patient-controlled analgesia system, the sufentanilsublingual tablet system (SSTS), has been shown to be a promising prospect as an alternative to invasive (intravenous/ intrathecal) sufentanil. [28] The lipophilic nature of sufentanil aids in rapid and titrable absorption from the sublingual route. Sufentanil lacks active metabolites and

possesses a high therapeutic index in preclinical models (26,000 compared to 70 for morphine).[29] It has a rapid equilibration half-life between plasma and CNS (t½ke0 = 6 minutes compared to 2.8 hours for morphine).[30,31,] Sufentanil has rapid onset of action, and its quick release from the tissue storage sites allow for its quick recovery. The half-life of sufentanil is 162 minutes and its duration of action is 30-60 minutes.[32] The liver and small intestine are the major sites of metabolism and the rate is dependent on the circulation of the organ. Within the anesthetic dosage range, sufentanil has a more rapid recovery compared to equipotent fentanyl dosages.

Adverse Reactions

All opioids are notorious for the production of respiratory depression and skeletal muscle rigidity, particularly of the truncal muscles. Rigidity of chest muscles remains one of the most troubling side effects of sufentanil.[33,34] Hypotension, bradycardia, somnolence are the other commonly observed side effects. Bradycardia and chest rigidity has been attributed to fast administration of sufentanil or atropine prior to it[25].In all, sufentanil can be considered one of the safest opioids compared to the equieffective dosage of other opioids, even its predecessor fentanyl. Its ability to maintain hemodynamic stability during surgery better than other opioids and inhalation anesthetics has made it a popular drug for cardiosurgical 'fast track' and in pediatric patients with congenital heart defects.

Drug interactions

Tricyclic antidepressants, phenothiazines, Monoamine Oxidase Inhibitors, amphetamine and neostigmine potentiate sufentanil, either by competing for metabolism resulting in slower metabolism, or by interaction at central neurotransmitter level. These drugs are best avoided when sufentanil is used or is under consideration for use. These interactions stand true for not only sufentanil, but also for all other opioids.

Dosage

The recommended dose for induction of anesthesia in adults is 15-30 μg/kg.[35] In patients undergoing combined anesthesia with volatile agents and anesthetic infusions, the effective analgesic dose can be tenfold lower with the initial supply of the drug being 0.5-1.5 μg/kg and the total procedure dose being 2-3 μg/kg during medium to long surgery. Its recommended dose in neonates is 5-15 μg/kg and in children aged 3-12 years of age is 5-20 μg/kg. For subarachnoid administration, dose in the range of 2 μg-10 μg is used. The dose of sufentanil in the continuous epidural infusion ranges from 0.3 to 1 μg/kg/h with an aim to maintain a level of 0.2-0.4±0.2 ng mL in the target compartment. At present, sufentanil is the preferred drug in severely ill patients and when anesthesia is expected to be long. The standard dosing includes the induction bolus of 1 μg/kg and the maintenance dose of 1 μg/kg/h. It is combined with midazolam in premedication and isoflurane for maintenance which eliminates most of the unanticipated effects.

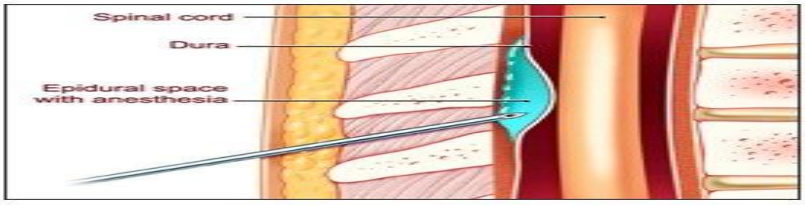
Sufentanil over other opioids

As already established, sufentanil is more potent, has fewer incidences of side effects, and assures greater hemodynamic stability than other opioids. Its greater potency also allows for less frequent refills during continuous infusions. It maintains hemodynamic stability during surgery better than other opioids as well as inhalational anesthetics.[36] Thus, by the virtue of being safer and more convenient, sufentanil has become the drug of choice over other opioids.

Epidural Anesthesia

Anatomy Epidural space is a potential space within the bony cavity of the spinal canal and outside the dural sac. The cephalad part of the spinal epidural space begins at the level of foramen magnum, where the periosteal and spinal layers of dura fuse together. The caudal part extends to the sacro-coccygeal membrane. The anterior portion of the epidural space is formed by the posterior longitudinal ligament, which covers the posterior part of the vertebral body and the intervertebral disk. Posteriorly, the epidural space is formed by the anterior lateral surface of the vertebral lamina and the ligamentum flavum. Laterally, the epidural space is formed by the pedicles of the vertebrae and the intervertebral foramen. The ligamentum flavum is used as the key landmark for identification of the epidural space. It differs from spinal route because the drug is not administered into the cerebro-spinal fluid (CSF). The epidural space does not contain CSF, rather it is present between the dura and the arachnoid mater.

Fig 3. Anatomy of epidural space in context to epidural analgesia[37]



The epidural space, as seen in the above figure, lies superiorly to the subarachnoid space when the patient is in prone position. The epidural catheter is placed in this space.

Both the thoracic and the lumbar epidural space as well as sacral epidural space have been used for epidural anesthesia. A meta-analysis was done in 1988 comparing the effects of thoracic and lumbar approaches to the epidural space for opioids alone. The study failed to demonstrate any significant improvement in analgesia when the thoracic approach was used.[38] However, a majority of anesthetists prefer the thoracic approach because of significantly lesser incidences of lower limb motor blockade. This phenomenon, however, occurs less frequently when ropivacaine is used as the local anesthetic in combination. Along with opioids and local anesthetics, a number of agents have been used as adjuvants to improve the efficacy of epidural analgesia. These include ketamine, midazolam, clonidine and adrenaline. Addition of all these have shown to have greater pain relief.[39,40] Clonidine, though, caused significant hypotension.

Regional (Epidural) Anesthesia and General Anesthesia

Regional anesthesia may have favorable outcome effects compared with general anesthesia by effectively blocking the afferent inputs, providing initial postoperative analgesia, reducing endocrine metabolic responses, and providing sympathetic blockade with reduced bleeding and less risk of thromboembolic complications. Randomized studies have supported the use of regional anesthesia with fewer postoperative pulmonary and thromboembolic complications.

The benefits of epidural anesthesia over general anesthesia includes reduced stress response of surgery, less intraoperative blood loss, fewer thromboembolic events, fewer postoperative pulmonary complications, earlier return of gastrointestinal function, earlier ambulation, earlier hospital discharge and less perioperative mortality along with the fact that it is cheaper. Studies have favored spinal or epidural analgesia over general anesthesia in appropriate cases. This is probably explained by the positive physiological effects of the provided afferent blockade with better initial pain relief, a reduced endocrine metabolic response, and sympathetic blockade with less blood loss and increased leg blood flow, all resulting in reduced cardiopulmonary and thromboembolic morbidity.

The onset of analgesia is slower with epidural analgesia or anesthesia than with spinal analgesia or anesthesia. An epidural injection may be performed anywhere along the vertebral column (cervical, thoracic, lumbar, or sacral), while spinal injections are typically performed below the second lumbar vertebral body to avoid piercing and consequently damaging the spinal cord. It is easier to achieve segmental analgesia or anesthesia using the epidural route than using the spinal route. An indwelling catheter is more commonly placed in the setting of epidural analgesia or anesthesia than with spinal analgesia or anesthesia.

Several studies have shown that, when compared with general anesthesia, epidural anesthesia has lower risk of pneumonia, improved recovery of gastrointestinal function, reduced mortality after major surgery and also reduced length of stay in hospital.[41.42]Especially in lower limb surgery epidural has good analgesic effect, lower risk of thrombosis and also unique advantages of complications such as inflammatory reaction. Moreover, in lower limb surgery, the sympathetic blockade associated with subarachnoid and epidural anesthesia decreases circulating catecholamine levels and improves lower-extremity blood flow, with the potential to decrease the incidence of deep vein thrombosis and prevent lower-extremity arterial bypass thrombosis[43.] In addition, improved intraoperative and postoperative hemodynamic stability may be achieved with regional anesthesia,[44] potentially leading to decreased cardiac complications[45] Finally, the lack of airway instrumentation may lead to improved postoperative pulmonary function.

However, epidural anesthesia entails several adverse effects such as hypotension, and also possesses high risk of failed epidural anesthetic block. Moreover, the onset time is relatively slow, the block may sometimes be patchy, asymmetrical or limited in extent, and visceral pain can be observed in up to 50% of patients. Recent studies have shown that low dose of epidural (intrathecal) local anesthetic could reduce the drawbacks entailed by epidural anesthesia.[46]

Epidural Anesthesia and Spinal Anesthesia

Epidural anesthesia has the advantages of widespread use, familiar technique, indwelling catheter top up doses, modification and extension of block, and absence of post rural puncture headache as compared to spinal anesthesia. Several studies on spinal anesthesia suggest more disadvantages as non-top-up facilities to

prolong or optimize the block unless a subarachnoid catheter is inserted and these micro-catheters are vulnerable, difficult to insert, expensive as well as being implicated in cauda equina damage.

Epidural analgesia has been demonstrated to have several benefits after surgery, including: effective analgesia without the need for systemic opioids. Injecting medication into the epidural space is primarily performed for analgesia. This may be performed using a number of different techniques and for a variety of reasons. Additionally, some of the side-effects of epidural analgesia may be beneficial in some circumstances (e.g. vasodilation may be beneficial if the subject has peripheral vascular disease). When a catheter is placed into the epidural space a continuous infusion can be maintained for several days, if needed.

Studies have proven the advantages of epidural anesthesia when used in the proper setting. The chances of postoperative respiratory depression and infection has been found to be minimal.[47] In addition, the risk of postoperative myocardial infarction is also much lower than when compared to other forms of anesthesia.[48,49] The surgical stress on the patient is reduced.[48,50] The is no gastric irritation caused by the sympathetic activity of intestine to increasing the intestinal motility when epidural anesthesia is used.[48,51] However, in a randomized controlled trial, Rigg et al found no survival benefit for high-risk individuals except these advantages.[52]

Drugs for Epidural Anesthesia

Ropivacaine has become the most popular local anesthetic for epidural anesthesia. It has been combined with various adjuvants. One study found that addition of dexmedetomidine, an alpha-2 agonist, to ropivacaine in epidural anesthesia had a faster onset and longer duration of sensory and motor blockade, and had acceptable sedation and hemodynamic stability and minimal dose requirement.[53] Another 2016 study[54] found similar outcome, where this combination was compared with ropivacaine- clonidine combination. Episodes of hypoxemia, which can be problematic during longer surgeries, were found to be absent using this combination. Roelants et al did a comparative study between clonidine and sufentanil with ropivacaine in 195 patients to find the better combination for epidural analgesia in patients in labor.[55] Both groups were found to have similar need for rescue doses, with the only difference being higher incidences of nausea in the sufentanil group. Even when considering ropivacaine alone, its comparison with levobupivacaine showed that it had shorter onset of action[56] and longer duration of action. Similar result was found when comparing ropivacaine with bupivacaine. The study done to evaluate 0.75% ropivacaine as a local anesthetic in terms of duration and quality of epidural anesthesia for lower extremity surgeries and compare these effects with 0.5% bupivacaine found that there were no significant differences in the block parameters but ropivacaine was associated with relatively longer duration of postoperative analgesia.[57] Yurtlu et al added articaine to ropivacaine and found that the combination of 2% articaine and 0.75% ropivacaine for epidural anesthesia in a cesarean section was preferable over epidural 0.75% ropivacaine alone.[58] Kulkarni et al[59] found that the use of 0.37% ropivacaine was safer than 0.25% bupivacaine for Cervical epidural anesthesia for radical mastectomy.

It provided good surgical anesthesia with lesser degree of motor blockade and adverse respiratory effects. Sixty elderly consented patients of either sex with American Society of Anesthesiologist (ASA) II and III, scheduled for elective hemiarthroplasty were randomized into two Groups of 30 patients to receive epidural study solution of 15 mL of 0.75% Ropivacaine or 0.5% Bupivacaine with 1 mL fentanyl (50 μg) by Rastogi et al.[60] They concluded that epidural 0.75% Ropivacaine with fentanyl showed better clinical profile as compared to 0.5% Bupivacaine with fentanyl for hemiarthroplasty in elderly patients. Ulker et al[61] compared spinal, low-dose spinal and epidural anesthesia with ropivacaine plus fentanyl for transurethral surgical procedures. They concluded that all three anesthetic techniques could be used safely and were appropriate for transurethral surgical procedures. However, low-dose spinal anesthesia with ropivacaine plus fentanyl was more preferable in transurethral surgery because an adequate sensorial level could be attained with less motor blockade. A study of admixture of clonidine and fentanyl to ropivacaine in epidural anesthesia for lower abdominal surgery in 60 patients was done with the aim to evaluate and compare clonidine-ropivacaine combination with fentanyl-ropivacaine in epidural anesthesia and also to find out whether addition of clonidine can reduce the dose of fentanyl in epidural anesthesia.[62] The study found that the analgesic properties of the clonidine and fentanyl when used as adjuvant to ropivacaine in epidural anesthesia are almost comparable and both can be used in combination at lower dosages without impairing the pharmacodynamic profile of the drugs as well as with a significant reduction in side effects.

Optimal dose of Ropivacaine in combination with fixed dose Sufentanil

Dosage studies for ropivacaine have been done alone as well as in conjunction with sufentanil for epidural administration for anesthesia. Guler et al[63] compared of 3 doses of ropivacaine for epidural anesthesia in transurethral surgery in the Department of Anesthesiology, Medical Faculty of Erciyes University, Turkey in 81 patients. The divided the patients into 3 groups, Group I (n=27) received 15 ml (102.5mg) of 0.75% solution, group II (n=27) received 10 ml (75 mg) of 0.75% solution, and group III (n=27) received 10 ml (50mg) 0.5% ropivacaine. The quality of the blocks and the hemodynamic changes were compared. They found that motor block was significantly less in group III than in groups I and II. The sensory block level was T6 or more in 55%

of patients in group I, 35% in group II, and 21% in group III. The duration of sensory block was less, and the time to achieve the T10 level was greater in group III. Hypotension and bradycardia were more frequent in group I. They were able to conclude that effective anesthesia with few side effects was obtained with low dose (50mg) ropivacaine. Gan et al[64] injected 15 ml epidural ropivacaine in 30 men and 30 women to determine the median dose required to impair a straight leg raise test (SLRT), starting at a concentration of 0.425%, increasing the concentration by 0.025% after an ineffective injection and decreasing the concentration by 0.025% after an effective injection. The median (95% CI) concentration of ropivacaine that prevented straight-leg raise within 30 min of injection was found to be 0.43% (0.41-0.45%) in men, and 0.40% (0.39-0.41%) in women ($p = 0.001$). A study on the effect of thoracic epidural anesthesia with different concentrations of ropivacaine on arterial oxygenation during one-lung ventilation (OLV) was done in Fudan University Cancer Hospital, Shanghai.[65] 120 patients scheduled for lung surgery were randomly divided into four groups to epidurally receive saline (Group S), 0.25% (Group R0.25), 0.50% (Group R0.50), and 0.75% (Group R0.75) ropivacaine intraoperatively. Ropivacaine was administered intraoperatively at a dose of 6-8 ml of first bolus + 5 ml/h infusion. Pao2 was significantly lower in Group R0.75 compared with that in Group S and Group R0.25 in 10 and 20 minutes after administration. They concluded that a decrease in oxygenation during OLV occurred only at the highest dose of epidural local anesthetic and not at lower doses and that higher doses of epidural medication required less propofol and more vasopressors. Xiao et al performed a randomized, double-blinded, dose-ranging study to find the dose-response of intrathecal ropivacaine when co-administered with sufentanil for cesarean delivery under combined spinal-epidural anesthesia in seventy-five patients with scarred uterus. The patients received 6, 8, 10, 12, or 14 mg intrathecal hyperbaric ropivacaine with 5 μg sufentanil.

The ED50 and ED95 of intrathecal hyperbaric ropivacaine along with 5 μg sufentanil was calculated to be 8.28 mg and 12.24 mg, respectively. A prospective randomized double-blind dose-response study was done with 58 elderly patients with American Society of Anesthesiologists physical status I-II who were scheduled for TURP surgery under epidural anesthesia. The study aimed to examine the sparing effect of sufentanil on the median effective concentration of epidural ropivacaine in elderly patients undergoing elective transurethral resection of prostate (TURP). The found that the administration of 5 μg of epidural sufentanil caused a 37% reduction in the EC_{50} of epidural ropivacaine. The patients had been divided into two groups. The first group received 15 mL of ropivacaine (group R) and the second group received ropivacaine plus 5 μg of sufentanil (group RS). The concentration of ropivacaine was determined by Dixon's up-and-down sequential allocation. The first participant received 0.3% of ropivacaine in both groups and subsequent concentrations were determined by the response of the previous patient in the same group. The EC_{50} of ropivacaine during TURP surgery was 0.186% in group R, and 0.136% in group RS ($p<0.01$).

II. Materals And Methods

2.1 Data Collection

The subjects for this study were patients of both the sexes, who were scheduled to undergo lower limb surgery under epidural anesthesia in Anhui Medical University from June 2015-July 2016, after obtaining approval from the local ethics committee and written informed consent from all the patients. A total of 70 cases that underwent a variety of lower limb surgical procedures in this duration were considered.

The patients were divided into two groups. The first group, Group A, was only administered ropivacaine while Group B was given a combination of ropivacaine and sufentanil. The dose of sufentanil in Group B was kept a constant while different doses of ropivacaine was used which was determined for each patient by up down method.

Cases were considered independent of the operative diagnosis. The surgical procedures were, including but not limited to, endo-venous laser ablation surgery for great saphenous varicose vein, ACL reconstruction, Hip replacement, Achilles tendon repair, Hemiarthroplasty, Plating or intra medullary fixation, Tension Band Wiring or K-wire fixation.

2.2 Inclusion and Exclusion Criteria

Inclusion or exclusion of the patients for the study was pre-determined by the following criteria.

Inclusion criteria:

1. ASA I (No organic pathology or patients in whom the pathological process is localized and does not cause any systemic disturbance or abnormality.

Examples: This includes patients suffering with fractures unless shock, blood loss, emboli or systemic signs of injury are present in an individual who would otherwise fall in Class 1. It includes congenital deformities unless they are causing systemic disturbance. Infections that are localized and do not cause fever, many osseous deformities, and uncomplicated hernias are included. Any type of operation may fall in this class since only the patient's physical condition is considered.) and

2. ASA II (A moderate but definite systemic disturbance, caused either by the condition that is to be treated or

surgical intervention or which is caused by other existing pathological processes, forms this group.
Examples: Mild diabetes. Functional capacity I or IIa. Psychotic patients unable to care for themselves. Mild acidosis. Anemia moderate. Septic or acute pharyngitis. Chronic sinusitis with postnasal discharge. Acute sinusitis. Minor or superficial infections that cause a systemic reaction. (If there is no systemic reaction, fever, malaise, leukocytosis, etc., aid in classifying.) Nontoxic adenoma of thyroid that causes partial respiratory obstruction. Mild thyrotoxicosis. Acute osteomyelitis (early). Chronic osteomyelitis. Pulmonary tuberculosis with involvement of pulmonary tissue insufficient to embarrass activity and without other symptoms.).

Age groups (14-65 years).

Exclusion criteria
1. Significant coexisting cardiopulmonary disorders.
2. Presence of diseases predisposing to altered sensation like uncontrolled diabetes mellitus.
3. Uncontrolled hypertension.
4. Any contraindication to regional anesthesia.
5. History of anaphylaxis to local anesthetics.
6. Allergic to the drugs to be used (ropivacaine, sufentanil).
7. Patients with spine deformities.

2.3 Pre-operative preparation

Routine pre-operative investigations were done in all the patients. These included chest x-ray, complete blood count (CBC), liver function test (LFT), renal function test (RFT), electrocardiogram (ECG) and serology. Prophylactic antibiotics were started to diminish the chance of infection. Additional investigations were done in relevant cases pertaining to their co-existing morbidities.

2.4 Up and Down Method

The up and down method (UDM) is the most widely used method for finding out the optimum dose of a given anesthetic or an anesthetic combination. We used the UDM model proposed by Dixon and Mood [79]. The dose of the anesthetic agent in Group B was determined by this method. According to this method, the dose level for the second patient was determined by the response of the first patient. Assuming the dose administered to the first patient was *x*, if the first patient has a positive response (affective anesthesia in this case), the dose administered in the second patient was next lower dose (x-1). If the first patient has a negative response, the dose administered in the second patient was next higher dose (x+1). Successive patients were assigned a dose in the same way, i.e. by adjusting according to the response of the previous patient. At the lowest and highest hypothesized dose, adjustments were made accordingly to keep all the doses with the range.

The first dose for anesthesia was chosen arbitrarily as Inj. Ropivacaine 9 ml plus inj. Sufentanil 2ml (20ug), mixed in 9 ml of normal saline, total volume of combination being 20ml, given in divided doses starting with a 4ml dose, followed by an 8 ml dose. Further doses of the anesthetic mixture could be added after 5 minutes if satisfactory anesthetic affect was not achieved.

The other fixed dose combinations of the agents were Inj. Ropivacaine 7 ml and Inj. Sufentanil 2ml (20ug) with 11 ml normal saline, and Inj. Ropivacaine 8 ml and inj. Sufentanil 2ml (20ug) with 10 ml normal saline.

2.5 Procedure

Once the patient was brought into the operating room, all the arrangements for the epidural anesthesia were done according to the protocol. An intravenous catheter was inserted into a large peripheral arm vein and 500 ml Lactated Ringer's solution was administered before administration of epidural anesthesia. Continuous pulse oximetry (SpO2), electrocardiogram (ECG) and Non-invasive arterial pressure (NIBP) were monitored. Under all aseptic conditions, patients then underwent epidural anesthesia.

Using the method of loss of resistance to air, an 18-G Tuohy needle was inserted into the epidural space. Epidural catheter was then threaded into the epidural space and fixed. Oxygen was given at 2 L/min via nasal cannula during the operation. A test dose of 2ml of 1% lidocaine was not used. The effects of first initial infusion dose was observed after a minute which included sensory block, proper placement of epidural cannula and systemic effects like cardio-pulmonary suppression.

2.6 Evaluation Criteria

The definition of a positive response was specified as satisfactory anesthetic affect after 20 minutes of administration of the first dose of the anesthetic combination. Satisfactory anesthetic affect was defined by scores of 3 each in the Hollmen scale and Bromage scale.

Sensory level to pinprick was assessed by the Hollmen scale:
0 = ability to appreciate a pinprick as sharp
1 = ability to appreciate a pinprick as less sharp
2 = inability to appreciate a pinprick as sharp (analgesia)
3 = inability to appreciate a pin touching (anesthesia).
Note: The level of sensory block was assessed bilaterally along the mid clavicular line by the loss of pinprick sensation with the help of a 17 G needle.

Motor block in the lower limbs was determined by the Bromage Scale:
0 = ability to lift extended leg at hip
1 = ability to flex knee but not lift extended leg
2 = ability to move foot only
3 = inability to move foot.

Subjective pain was assessed with a 10-cm linear visual analogue scale (VAS). If adequate analgesia (VAS ≤30 mm) was not achieved, another dose of 8ml was infused. Subsequently, intraoperative VAS was assessed every 5 minutes, until the end of surgery and a bolus of 5ml was infused whenever needed. The total amount of drug needed to achieve adequate analgesia, duration of anesthetic effect post-surgery, the level of sensory block, severity of pain and recovery time were assessed. Moreover, side effects such as hypotension, bradycardia, respiratory depression, nausea, vomiting, shivering, and pruritus during surgery were also recorded. NIBP, heart rate and SpO2 were measured automatically at 2 min intervals from the start of anesthesia for 10 minutes, and then at 5-min intervals until the end of surgery.

The severity of pain at rest and movement, the amount of opioid analgesics administered, and patients' satisfaction with their postoperative pain management were all assessed.

Anesthesia was determined to be a failure if affective anesthesia was not achieved after 20 minutes of administration of the complete 20ml of the combination.

2.7 Equipment and other operational requirements
Equipment:
(1) IV cannula and IV fluids,
(2) Sterile epidural stray,
(3) Epidural 18 gauge Tuohy needle,
(4) Epidural catheter 20G polyamide closed end.
(5) Loss of resistance syringe.

Anesthetic Drugs:
(1) Inj. Ropivacaine 0.75% amp,
(**2)** Inj. Bupivacaine 0.75%, 0.375, 0.5% vials,
(3) Inj. Sufentanil 20 microgram.

Emergency drugs:
(1) Inj. Adrenaline,
(2) Inj. Atropine,
(3) inj. Ephedrine
(4) Inj. Dopamine.

Resuscitation equipment:
(1) Oxygen cylinder,
(2) AMBU bag,
(3) Laryngoscope,
(4) Endotracheal tube of different sizes,
(5) Suction apparatus.

Monitoring equipment:
(1) ECG,
(2) NIBP,
(3) Pulse oximeter.

2.8 Statistical Analysis
The software SPSS version 7 was used for statistical analysis purpose.

III. Results

Out of the 70 patients enrolled, 5 were excluded because of failure to access the epidural space for anesthesia, and 3 were excluded because of blockage of the epidural catheter before anesthesia could be achieved. So, a total of 62 patients undergoing lower limb surgery were successfully administered either Ropivacaine alone, or Ropivacaine and Sufentanil via the epidural route. Group A, which received only ropivacaine, consisted 20 patients and Group B, which was given a combination of ropivacaine and sufentanil, had 42 patients.

Group A consisted of 10 males and 10 female patients, adding up to a total of 20. The age of the patients ranged from 22 years to 61 years. The mean age was 40.1 years.

Out of the 42 patients in Group B, 30 were male and 12 were female. The age of the patients ranged from 21 years to 62 years of age. The mean age was 48.5 years. The patients underwent different surgical procedures with different times of surgery. The shortest surgical procedure lasted 53 minutes while the longest lasted 86 minutes. The mean duration of surgery was 66.8 minutes.

Table 2. Preoperative Demographics

Parameter	Group A	Group B
Male: Female	10: 10	30: 12
Mean Age (SD)	40.1 (11.8)	45.8 (12.4)
Mean Height (SD)	165 (6.1)	165.7 (6.4)
Mean Weight (SD)	66.2 (7.3)	65.7 (10.5)

SD= Standard Deviation

Age in years; Height in centimeters; Weight in kilograms.

Table 1 shows the preoperative demographics of the patients in the 2 groups. The number of males and females in Group A was same while the males outnumbered the females by almost 3 times in Group B. The patients belonged to a varied age group. The mean height was 165 centimeters in Group A and 165.7 centimeters in Group B, and the mean weight was 66.2 kilograms in Group A and 67.5 kilograms in Group B.

Patients in Group A were administered ropivacaine in a normal saline solution. 10ml of 0.75% ropivacaine was mixed with 10ml of normal saline. After epidural access was obtained, 4ml of the solution was injected into the epidural space. After 5 minutes, a second dose of 8ml of the solution was added. Further doses were added after 5 minutes if satisfactory anesthesia was not achieved. Of the 20 patients in Group A, none could be successfully anesthetized even after administration of the full 20ml of the anesthetic solution. The patients remained hemodynamically stable throughout the process and none showed any adverse reaction to the drug.

Side effects of the drug combination like nausea, vomiting, respiratory depression, hypo-tension was expected but none of the participating 42 patients in Group B developed any of the above mention side effects. Vitals were monitored throughout the duration of surgery to look for spikes of hemodynamic instability but none of the patients developed significant hypotension, hypertension, tachycardia, bradycardia or respiratory depression. All the surgeries were uneventful and all the patients had made a full recovery from anesthesia by the time of their transfer from the postoperative ward.

Table 3. Intraoperative Parameters

Parameter	Group A	Group B
Mean Systolic BP (SD)	137.7 (16.1)	137.4 (11.6)
Mean Diastolic BP (SD)	77.4 (8.5)	78.0 (8.7)
Mean Pulse (SD)	72.0 (6.7)	72.3 (7.1)
Mean Respiratory Rate (SD)	18.2 (1.1)	18.1 (2.2)

BP= Blood Pressure; SD= Standard Deviation

BP in mmHg; Pulse in beats per minute; Respiratory Rate per minute.

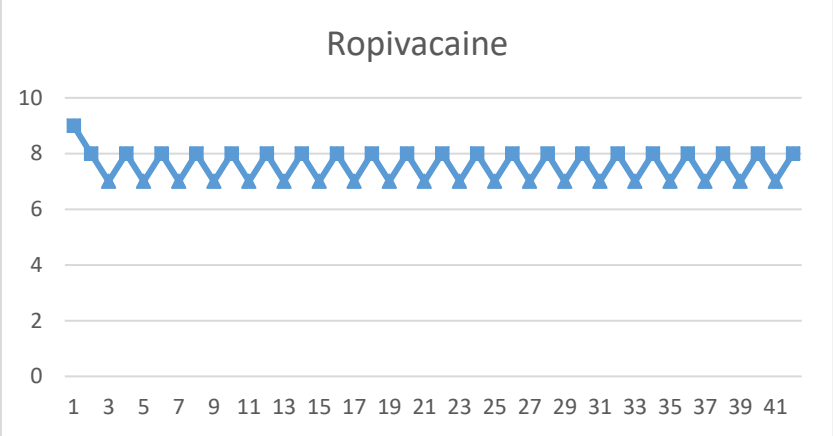
Table 2 shows the Intraoperative Parameters of all the patients. The mean systolic BP was 137.4 mmHg and the mean diastolic BP was 78 mmHg. The mean pulse rate was 72.3 beats per minute and the mean respiratory rate was 18.1 per minute.

In Group B, the first patient was administered 4ml of the mixture of Inj. Ropivacaine 9 ml and Inj. Sufentanil 2ml (20ug), mixed in 9 ml of normal saline, followed by 8ml of the same preparation. The anesthesia was successful with the patient not requiring any additional doses. The next patient was administered with the preparation of 8 ml ropivacaine with 2ml sufentanil in 10 ml NS. Anesthesia was successful at the end of 20 minutes in this case as well. Preparation with 7ml ropivacaine, 2 ml sufentanil and 11 ml NS was used next.

Despite using the full 20 ml of the drug combination, satisfactory anesthesia could not be achieved and thus a different form of anesthesia has to be administered at the end of the 20 minutes.

As per the up down allocation sequence method, the next patient received the 8ml ropivacaine preparation. Successful anesthesia could be achieved in this patient. The dose was reduced back to 7ml in the next patient resulting in unsuccessful anesthesia. The same steps were carried out for all the 42 patients. All the patient receiving the dose of 8ml could be successfully anesthetized while anesthesia in all the patients receiving 7ml ropivacaine failed. We plotted the dose given to all the patients in a line graph which is shown below.

Figure 4. Ropivacaine Dose-Response in combination with Sufentanil



In figure 4, we can see the dose response of ropivacaine plotted in a line graph. X-axis denotes the successive patient number and the Y-axis denotes the dose of ropivacaine in ml. The successful doses are denoted by a square and the unsuccessful doses by a triangle. As it is evident from the above graph, all the patients who received 8ml or more of ropivacaine could be successfully anesthetized while anesthesia was not possible in those receiving 7ml ropivacaine.

A total of 22 patients could be successfully anesthetized at the end of the study. We take a look at some of their anesthesia parameters in the following table.

Table 4. Anesthesia Parameters of the successfully anesthetized patients

Parameter	**Value**
Mean Duration of Surgery (SD)	66.8 (9.1)
Mean Time of Anesthesia (SD)	83.9 (11.1)
Highest Level of Block Achieved	T8
Mean time to T11 block (SD)	10.7 (1.8)
Mean time to Highest Level of Block (SD)	19.1 (1.7)

Duration of Surgery in minutes, Duration of Anesthesia in minutes, Time to T11 block in minutes, Time to Highest Level of Block in minutes.

Table 4 shows that the mean duration that the surgeries lasted was 66.8 minutes and the mean duration that the anesthetic affect lasted was 83.9 minutes. The highest level of block that could be achieved in any of the patients was T8. The mean time duration to achieve the highest level of block was 19.1 minutes. T11 was the desired level of block and the mean duration to achieve T11 block was 10.7 minutes.

We wanted to compare the vital parameters of the patients receiving different doses of ropivacaine in this study, so we separated the patients into three groups receiving different doses of the drug for this purpose and calculated their vital parameters separately.

Table 5. Vital Status of patients receiving different doses of ropivacaine

Parameter	**9ml**	**8ml**	**7ml**
Mean Systolic BP (SD)	151 (NA)	142.2 (10.9)	131.7 (9.9)
Mean Diastolic BP (SD)	78 (NA)	80.7 (8.5)	75.2 (8.5)
Mean Pulse (SD)	72 (NA)	72.5 (7.8)	72.1 (6.7)
Mean Respiratory Rate (SD)	18 (NA)	17.4 (2.0)	18.9 (2.2)

BP= Blood Pressure; SD= Standard Deviation; NA= Not Applicable

BP in mmHg; Pulse in beats per minute; Respiratory Rate per minute.

Table 5 shows the comparative vital status of the patients receiving 9ml, 8ml and 7ml of ropivacaine. Only one patient received 9ml ropivacaine (so no Standard Deviation). 21 patients were administered the combination

containing 8ml ropivacaine in all and the number of patients who received 7ml ropivacaine combination was 20. It is important to note here that not all patients in the 8ml group needed the full dose of anesthetic preparation and the administered volume ranged from 12ml of the preparation, to full 20ml of the preparation. As we can see from the above table, all the groups had acceptable vitals during the period of anesthesia. Although the blood pressure (both systolic and diastolic) were higher in the 8ml group than in the 7ml group, it was still in the normal acceptable range. None in either of the groups developed bradycardia (mean pulse was 72, 72.5 and 72.1 in the three groups). Similarly, respiratory depression was also not seen with patients able to maintain respiratory rate in the normal physiological range in all three groups.

IV. Discussion

Up–down sequential allocation is an efficient and widely used method to define dose-sparing properties and potency ratios of drugs and drug combinations. [80] Since this is done in a true clinical setting, real-life recommendations can be made from the results of such study.

We chose 20µg of Sufentanil as the fixed dose of the co-anesthetic agent for a varying dose of ropivacaine. The choice of the dose of sufentanil was based on the maximum dose of the drug commonly used in combination in our hospital setting. One full vial of 0.75ml ropivacaine (10ml) i.e. 75 mg was designated to be the maximum dose of ropivacaine to be used in the combination. 10ml, 9ml, 8ml or 7ml of the solution was to be used. The use of low doses of the agent was an attempt to minimize the side effects. We randomly started with a 9ml ropivacaine combination. It was found to be a successful dose and subsequent doses were selected according to the up down allocation method.

Ropivacaine alone or Combination

Ropivacaine alone as well as its combination with sufentanil have been for epidural anesthesia in lower limb surgeries. In our study of 62 patients, none of the patients who received only ropivacaine as the anesthetic agent could be successfully anesthetized. The patients in Group A were administered up to 10 ml of 0.75% Ropivacaine via epidural route. But anesthesia was deemed a failure in 100% of cases in this group. Of the 42 patients in Group B, who received a combination of fixed dose Sufentanil and a varying dose of Ropivacaine, 22 could be successfully anesthetized with a high enough dose of Ropivacaine in the combination. Based on this observation, the combination of Ropivacaine and Sufentanil was found to be superior than Ropivacaine alone for epidural anesthesia.

Optimum Dose

In Group A, since none of the patients could be successfully anesthetized, even the maximum administered dose (10ml of 0.75% Ropivacaine) was deemed to be an insufficient dose for epidural anesthesia.For the patients in Group B, a 9ml combination of ropivacaine had to be used once, 8ml combination 21 times, and 7ml combination 20 times. The 9ml and 8ml ropivacaine combinations were successful in producing adequate anesthesia in all the instances while the 7ml ropivacaine combination failed every single time. On the basis of this observation, the most effective fixed dose combination of ropivacaine and sufentanil was found to be that of 8ml of 0.75% ropivacaine and 20µg of sufentanil.

Hemodynamic Stability

All the patients in the study, irrespective of the doses of the anesthetic combination they received, were hemodynamically stable during the intraoperative and immediate postoperative period. All their vital parameters including their blood pressure, pulse rate and respiratory rate remained in the normal range during the period of observation. It is important to note that none of the patients selected for the study had serious comorbidities that could potentially complicate the procedure. None had uncontrolled hypertension or significant peripheral neuropathy.

Side Effects

We were prepared for the potential side effects of both the drugs in combination even though a lower dose of both the drugs was used. None of the patients developed the common side effects like nausea and vomiting despite the fact that we did not use any prophylactic anti-emetics. Similarly, other expected side effects like hypotension and respiratory depression were also not observed in any of the patients. The effective dose of the combination for anesthesia was devoid of any side effects.

Conclusion

On the basis of our observation of the anesthetic effects and the side effects of the singe agent 0.75% ropivacaine, and 0.75% ropivacaine and 20µg sufentanil combination for epidural anesthesia in lower limb surgery, we can conclude that a combination dose of 8ml of 0.75% ropivacaine, 2ml (20µg) sufentanil, and

10ml normal saline administered via epidural catheter with the initial dose being 4 ml of the combination followed by 8ml of the combination after 5 minutes of the administration of the initial dose is the most effective fixed dose combination of the agents for epidural anesthesia in lower limb surgery. We can also conclude that this fixed dose combination is devoid of any side effects. Ropivacaine alone is not an effective anesthetic agent in the dose that was used for this study. The combination of the two anesthetic agents is superior to the single agent.

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