Comparative evaluation of dexmedetomidine, ketamine & their combination for epidural analgesia in orthopedic surgeries of the lower limb.

ABSTRACT

Background : Epidural anesthesia is a perioperative pain control treatment that has a variety of applications in anaesthesiology. It could be used as as a primary anaesthetic, although it's most usually utilised as an adjuvant for management of pain. It could be a one-time shot or a continuous infusion for a long-drawn therapeutic intervention. Apart from the potential for significant analgesia, its use minimises the need for other anaesthetics and analgesics, lowering the risk of adverse effects. It has also been proven to lower the level of cortisol, to facilitate the resumption of bowel function, reduce the risk of Pulmonary embolism and deep vein thrombosis in the post-operative phase, while minimizing the duration of institutional stays.

Aim: Comparison and Evaluation of the effect of the drugs dexmedetomidine , ketamine & them together as a combination in addition to bupivacaine, as an adjuvant for intermittent epidural top ups for lower limb orthopaedic surgeries .

Study design : Prospective observational study

Place and duration of study : The study will be conducted over a period of 2 years and 6 months in the department of anaesthesiology, Jawaharlal Nehru medical college and Acharya vinoba bhave rural hospital, wardha.

Methodology: Our prospective, comparitive observational study included 90 patients randomly assigned into 3 sets of 30 each, one was administered dexmedetomidine epidurally, one was given ketamine and one was given their combination epidurally.[1] The quality and duration of analgesia provided by all 3 groups were then compared to find out which of them provides better and prolonged pain relief. Along with analgesia, the other parameters assessed were hemodynamic response, sedation and any other side effects.

Expected results: We're attempting to establish the hypothesis that the combination of both the drugs is better than dexmedetomidine or ketamine administered individually. It has been proved in various researches that epidural ketamine prolonged the duration of analgesia,[8] but it was less than epidural dexmedetomidine. We expect that the combination would decrease the postoperative rescue analgesics requirements and less hemodynamic alterations hence providing greater patient satisfaction as compared to the two drugs separately.

Keywords: dexmedetomidine, ketamine, combination, bupivacaine, epidural, spinal

INTRODUCTION

Epidural anesthesia is a perioperative pain control treatment that has a variety of applications in anaesthesiology. It could be used as as a primary anaesthetic, although it's most usually utilised as an adjuvant for management of pain. It could be a one-time shot or a continuous infusion for a long-drawn therapeutic intervention. Apart from the potential for significant analgesia, its use minimises the need for other anaesthetics and analgesics, lowering the risk of adverse effects. It has also been proven to lower the level of cortisol, to facilitate the resumption of bowel function, reduce the risk of Pulmonary embolism and deep vein thrombosis in the post-operative phase, while minimizing the duration of institutional stays.

This study compares dexmedetomidine, ketamine, and its combination in patients undergoing lower-limb orthopaedic surgery under spinal epidural anaesthesia, as an adjunct to bupivacaine for epidural analgesia. [12] The study aims at finding out which of them is better as an analgesic and sedative with lesser hemodynamic alterations and lesser side effects.

One of the very selective 2-adrenergic agonist includes **dexmedetomidine**. It has a α2:α1 selection ratio of 1620:1. Dexmedetomidine elicits sedation by increasing the activity of inhibitory gamma-aminobutyric acid (GABA) neurons in the ventrolateral preoptic nucleus and lowering noradrenergic neuron activity in the locus ceruleus in the brain stem.

The liver metabolises dexmedetomidine mostly through glucuronidation (34%) and oxidation via CYP2A6 and other Cytochrome P450 enzymes. It should therefore be used with caution in those who have liver dysfunction.

Ninety-five percent or more of dexmedetomidine that has been metabolised is eliminated in the urine.

The anaesthetic, analgesic, and psychotomimetic actions of **ketamine** are brought on by antagonistic activity at the NMDA receptor. By reducing central sensitization in dorsal horn neurons due to NMDA receptor antagonism, ketamine prevents the transmission of pain signals from the spinal cord. Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPA receptors) are activated in the brain as a result of acute NMDA receptor blockage, which affects neurotransmission in the limbic system and mediates the antidepressant effects of NMDA receptor antagonists.

The Use of SubAnesthetic Intravenous Ketamine using Dexmedetomidine as an adjuvant in the Mana gement of Acute Pain from CRPS was investigated. They came to the conclusion that the combined impact of ketamine and dexmedetomidine provides effective symptom alleviation while reducing the total amount of ketamine administered. The combination reduced undesirable adverse effects and ba nished the requirement for intensive care unit admission due to anaesthetic doses of ketamine. **[4]**
.

This study was to assess how adding tiny doses of ketamine to a multimodel postoperative patient controlled epidural analgesia regimen affected the outcome. They found that adding minor doses of ketamine to a multimodel PCEA regimen improves analgesia while lowering morphine consumption [2].

A study to assess the efficacy of ketamine and dexmedetomidine combined versus dexmedetomidine alone for awake fiberoptic nasotracheal intubation. They observed that in awake fiberoptic nasotracheal intubation, the combination offered superior hemodynamic stability and sedation than dexmedetomidine alone [5].

This research was to evaluate the perioperative hemodynamics, analgesia & the recovery profile postoperatively in patients undergoing spine surgery who received ketamine versus fentanyl infusion. They came to the conclusion that low-dose ketamine infusion is more effective than fentanyl in managing postoperative pain following spine surgery because it maintains intraoperative hemodynamic stability and provides good postoperative analgesia. It lowers the risk of problems associated with opioid infusion therapy [3].

The goal was to compare intraoperative hemodynamic changes and evaluate whether the research drugs ketamine and Dexmedetomidine were efficacious for day care hysteroscopic surgeries.
They arrived to the conclusion that Dexmedetomidine could be the optimal anaesthetic agent for day-care hysteroscopic surgeries(Jayashree Sen, Bitan Sen in 2019).

For the regulation of shivering during spinal anaesthesia, authors assessed dexmedetomidine, ketamine, and a dexmedetomidine–ketamine combination. Dexmedetomidine is superior to ketamine

and the combination in preventing shivering, according to the researchers(Sherif S. A. Rehim, Ghada M. Aboalfadl, Alaa M. Abdelatif in 2019).

RESEARCH QUESTION

Which among the chosen study drugs [dexmedetomidine, ketamine or their combination] is better and more effective analgesic?

Rationale : There have been various studies about dexmedetomidine and ketamine. Both have different properties and effects on our system and we wanted to see how they fare when administered as a combination. We also wanted to see whether this combination proves to be better than any of the individual drugs, hence the objective of the assessment.

AIM

Comparison and Evaluation of the effect of the drugs dexmedetomidine , ketamine & them together as a combination in addition to bupivacaine, as an adjuvant for intermittent epidural top ups in lower limb orthopaedic surgeries

Primary objective

Assessment of dexmedetomidine , ketamine and its combination as analgesics in orthopaedic procedures involving the lower limbs.

Secondary objective

To compare the following parameters in both the groups
1. haemodynamic changes
2. sedation
3. side effects if any

METHODOLOGY

PROPOSED RESEARCH DESIGN

The research will commence once it has received approval from the ethical and screening committees at the Jawaharlal Nehru Medical College, DMIMS (DU), Acharya Vinoba Bhave Rural Hospital (AVBRH), Datta Meghe Institute of Medical Sciences, Sawangi, meghe, and Wardha.
All patients will be handed with a consent form to be duly signed after proper and thorough understanding of the patient, prior to the surgery.

DESIGN OF STUDY:

The study will be conducted over a period of 2 years and 6 months
Study Facility: Department of Anaesthesiology, JNMC & AVBRH
Research methodology : Prospective observational study
Population undergoing study : Adult patients, aged 18 to 60

PARTICIPANTS:

INCLUSION CRITERIA :

- Patients of ASA grade I and II awaiting lower - extremity orthopaedic surgery. Males and females alike
- Age group 18yrs - 60yrs

EXCLUSION CRITERIA :

- Patient unwillingness to take part in the research
- ketamine and dexmedetomidine are both known allergens.
- ASA grades III and IV
- Significant ECG changes
- Any type of hepatic or renal dysfunction
- Any serious cardiac or respiratory dysfunctions
- Any abnormality in prothrombin time (PT) or activated partial thromboplastin time(aPTT)
- Coagulopathy, whether congenital or acquired
- History of any Previous thromboembolic disease/episode
- Any malignant disease
- Infection of Local site

- **SAMPLE SIZE CALCULATION**
-
- $n = \frac{2 * SD^2 * [Z\alpha_{12} + Z_\beta]^2}{d^2}$
- n = size of sample
- SD = Standard deviation derived from previous study
- d = mean value differences in one study
-
- we expect a difference of around 61.1
-
- $Z\alpha_{12} = Z(0.05/2) = Z \times 0.025 = 1.96$ [from table]
- $Z_\beta = Zx0.20 = 0.824$ [Z table] at power of 80
- $n = \frac{3x [63.04]^2 \times [2.8]^2}{[61.1]^2}$
-
- $= \frac{3x\ 3974.04x7.84}{3733.2}$
- $= \frac{93469.4}{3733.3} = 25.03$
-
- The study will involve 90 patients who meet all of the study's inclusion and exclusion criteria.
-
- Patients for the study will be randomly allocated to one of three study groups
  □ Group D_x (n=30): Inj. dexmedetomidine
- □ Group K_t (n=30): Inj. ketamine
- □ Group DK (n=30): Inj. dexmedetomidine + Inj. ketamine

All patients will require a pre-anaesthetic checkup the day before surgery. Basic patient data, medical history and history of presenting complaints, general and systemic examination, and basic blood and lab tests will be recorded. Patients will be briefed about the study's objectives, as well as its benefits and drawbacks. Each patient willing to be a part of the study will be provided with a form of informed written consent to be duly signed by them. They will be required to fast for at least 8 hours before to surgery.

INTRAOPERATIVE

ECG, pulse oximeter, and NIBP would be used for standard monitoring. Before beginning the case, the following baseline variables shall be documented:
Pulse rate
Rate of respiration
Non-invasive blood pressure monitoring
SpO2

An 18 G IV cannula will be used for peripheral intravenous cannulation, simultaneously all patients will be pre-loaded with 10ml/kg of Ringer Lactate / normal saline.
All patients will be administered spinal and epidural anaesthesia.

TECHNIQUE

The medial approach includes the needle to be introduced into the spaces in between the vertebral spinous processes. [7]
After the target site has been identified, lidocaine one percent is to be injected into the epidermis and adjacent tissues to alleviate the pain produced during the epidural needle insertion.
The epidural needle should be advanced with the stylet *in situ* and the bevel pointed cephalad in position once local anaesthesia has been established; this will aid in the proper positioning of the epidural catheter. For the intent of accessing the epidural space, the epidural needle should pierce through the epidermis, subcutaneous tissue, supraspinous, and interspinous ligaments. When inside, remove the stylet, connect the needle to the LOR [Loss of Resistance] syringe (It can be filled with air, saline, or a combination of the two). The needle should be advanced while exerting pressure to the plunger. A loss of resistance is evident when the ligamentum flavum is penetrated; which corresponds to the epidural space. Five to ten ml of normal-saline can be administered to widen the epidural space, presumably mitigating any chances of injury to the vessel.
The needle shall be advanced 1 cm lateral to the spinal interspace in paramedian approach. For medial route, local anaesthetic must be allocated as specified for the medial technique. After that, the epidural needle should be inserted into the paraspinal tissues. Because of its orientation, the needle would not pass through neither supraspinous nor interspinous ligaments. When the needle feels engaged in the ligamentum flavum, it must be brought to a halt. After that, the LOR syringe should fastened, and then epidural space should be established as stated for the median approach.
The epidural catheter should be guided through the needle using either the midline or paramedian approach once the LOR syringe has been withdrawn. The epidural catheter should be inserted to 20 cm in length. The epidural needle is then extracted, with careful attention paid to the depth of the epidural space indicated by the epidural needle's markings. The epidural catheter is then retracted slowly, with the goal of leaving the tip in the epidural space for upto 5 to 6 cm; this is done by multiplying the depth of the epidural space by 5 to 6. The resulting number is the retraction level for the epidural catheter. A 2 cm syringe can be used to carefully aspirate as well as rule out CSF leakage after the catheter is in its final position.
Spinal anaesthesia will be delivered in the L3-L4 intervertebral space using a 25gauge spinal needle with the required dosage of 0.5 percent Bupivacaine heavy. The patient will be placed in supine position. There will be no adjuvant employed for spinal anaesthesia. The patients will be divided into either of the 3 groups:

1. **Group D_x** : Patient will receive dexmedetomidine in a dose of 0.5 µg/kg diluted into 5ml sterile water epidurally at the time of induction and after 2 hours they'll receive bupivacaine 0.125% with adjuvant dexmedetomidine 1 µg/ml epidurally.
2. **Group K_t** : Patient will receive ketamine in dose of 0.5 mg/kg diluted into 5ml sterile water epidurally at the time of induction and after 2 hours they'll receive bupivacaine 0.125% with adjuvant ketamine 0.5 mg/ml epidurally.[8]
3. **Group KD** : Patient will receive bolus dose of ketamine in a dose of 0.3 mg/kg & dexmedetomidine in a dose of 0.1 µg/kg at the time of induction and after 2 hours they'll receive bupivacaine 0.125% along with dexmedetomedine 1 µg/ml + ketamine 0.5 mg/ml

The following parameters will be recorded thereafter:

- Level of sedation

- Hemodynamic parameters
- VAS score for postoperative pain assessment
- Time for first epidural top-up of rescue analgesia
- The number of rescue analgesia top-ups necessary in the next 24 hours
- Adverse effects (if noted)

Sensory block will be evaluated every 2 minutes using the pin prick method using a blunt-tipped needle until surgical anaesthesia is obtained at dermatome level T10.
Intraoperatively; haemodynamic changes, sedation (Ramsay Sedation score 1-6), and pain score(VAS 0-10) will be monitored at 2, 5, 10, 15 and 30 minutes, followed by 1 hour, 3 hours, 6 hours, 12 hours, and 24 hours postoperatively. When pain persists with a VAS of 4 or above, patients will be given Inj. Bupivacaine (0.125 percent) 1.5 ml/segment as a rescue analgesic. The entire amount of rescue analgesic necessary, as well as any adverse consequences, will be recorded. The epidural catheter will be withdrawn 24 hours following surgery.

INTRA-OPERATIVE EVALUATION

1. Duration of analgesia
2. Hemodynamics
3. Modified Ramsay Sedation Scale for sedation scoring
4. Side effects intraoperatively

POST-OPERATIVE EVALUATION

1. VAS score for postoperative pain assessment
2. Time for first epidural top-up of rescue analgesic
3. Number of rescue analgesics required
4. Hemodynamics monitoring
5. Sedation score using Modified Ramsay Sedation Score

EXPECTED OUTCOME

Dexmedetomidine and ketamine are both potent analgesics, although they have different properties. Dexmedetomidine, for example, induces bradycardia and hypotension in the body,[9] whereas ketamine causes hypertension and tachycardia.[11] We're attempting to prove that combining the two drugs is preferable to administering dexmedetomidine[6] or ketamine individually. Epidural ketamine prolongs analgesia for a shorter period of time than epidural dexmedetomidine, according to several experiments. Malti J Pandya et al had concluded in their study that in patients undergoing lower extremity orthopaedic surgery, continuous epidural infusion
with dexmedetomidine and ketamine successfully
lowered the need for postoperative rescue analgesics and offered good patient satisfaction. [13]
We anticipate that when these drugs are given together, they will complement each other and limit the requirement for postoperative rescue analgesics while generating fewer hemodynamic changes, yielding to higher patient satisfaction than if they were given separately.[10]

One major drawback of the current study is the exact dose equivalence of ketamine and dexmedetom idine as administered in epidural anaesthesia.
The results are also influenced by the patient's assessment and experience of pain, as well as their communication regarding pain analysis, which might make it difficult to analyse the factors. The use of ideal scales and scores is thus utilised as a reference to make it easier for patients to communicate their opinions about the drugs used and to ensure that the study is as accurate as possible.

Conclusion

Conclusion will be drawn after completion of the study.

Ethical Approval And Consent

The research will commence once it has received approval from the ethical and screening committees at the Jawaharlal Nehru Medical College, DMIMS (DU), Acharya Vinoba Bhave Rural Hospital (AVBRH), Datta Meghe Institute of Medical Sciences, Sawangi, meghe, and Wardha.
All patients will be handed with a consent form to be duly signed after proper and thorough understanding of the patient, prior to the surgery.

COMPETING INTERESTS DISCLAIMER:

Authors have declared that they have no known competing financial interests OR non-financial interests OR personal relationships that could have appeared to influence the work reported in this paper.

AUTHOR'S CONTRIBUTION

Deeksha Mishra has designed and written the case report with the expertise of Dr. Vivek chakole who has helped with the literature search and manuscript preparation and formation of the final edit of manuscript and review.

REFERENCES

1. Stoelting K. Pharmacology and physiology in Anesthesia practice. Anesthesiology textbook 4th edition (Lippincott Williams & Wilkins); Ch-15, Antihypertensive drugs: 344-345, Ch-3, opioid agonists and antagonists

2. Mamta Sethi, Nitin Sethi, Pradeep Jain, Jayashree Sood: Role of epidural ketamine for postoperative analgesia after upper abdominal surgery, 2011;55:141-5

3. Hatem A. Attalla, Rabab M. Habeeb, Asmaa I. Elzwedy: Intravenous infusion of ketamine versus fentanyl for postoperative analgesia in spine surgeries, 31:1206–1212

4. Sharanya Nama, Daniel R. Meenan and William T. Fritz : The Use of Sub-Anesthetic Intravenous Ketamine and Adjuvant Dexmedetomidine when Treating Acute Pain from CRPS, 13:365-368

5. Sunil Kumar Sinha, Bandi Joshiraj, Lalita Chaudhary, Nitin Hayaran, Manpreet Kaur, Aruna Jain : A comparison of dexmedetomidine plus ketamine combination with dexmedetomidine alone for awake fiberoptic nasotracheal intubation: A randomized controlled study. 10.4103/0970-9185.142846

6. Karhade SS, Acharya SA, Harnagale K. Comparative analysis of epidural bupivacaine versus bupivacaine with dexmedetomidine for vaginal hysterectomy. *Anesth, Essays Res*. 2015;9(3):310–313.

7.Morgan and mikhail's. Clinical anesthesiology. In: Clinical anesthesiology, fifth Edition (McGraw Hill Education), chapter 45. Spinal, Epidural & Caudal Blocks ;. p. 937–974.

8.Sethi M, Sethi N, Jain P, Sood J. Role of epidural ketamine for postoperative analgesia after upper abdominal surgery. *Indian J Anesth*. 2011;55(2):141–145.

9.Paula, Saraiva PF. Synergistic effect between dexmedetomidine and 0.75% ropivacaine in epidural anesthesia. *Rev Assoc Med Bras*. 2008;54:110–115.

10.Soliman R, Eltaweel M. Comparative study of dexmedetomidine and fentanyl as an adjuvant to epidural bupivacaine for postoperative pain relief in adult patients undergoing total knee replacement: a randomized study. *J Anesthesiol Clin Sci*. 2016;5:1–1.

11.Xue X, Lv Y, Zhao Y, Leng Y, Zhang Y. Efficacy of prophylactic epidural ketamine for reducing shivering in patients undergoing cae- sarean section with combined spinal-epidural anesthesia. *Biomedical Reports*. 2018;8(5):485–490.

12.Babu S, Kumar VA. A comparative study in the post-operative spine surgeries: epidural ropivacaine with dexmedetomidine and ropivacaine with clonidine for post-operative analgesia. *Indian J Anaesth*. 2013;57(4):371–376.

13. Malti J Pandya, Ayush Shah : Comparative evaluation of dexmedetomidine and ketamine for epidural analgesia in lower limb orthopedic surgeries, 2020;7(1):166-171.