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EVALUATION OF ANALGESIC EFFICACY AND SAFETY OF EPIDURAL MAGNESIUM SULPHATE, DEXMEDETOMIDINE AND KETAMINE AS ADJUVANTS TO BUPIVACAINE FOR INTRA OPERATIVE ANALGESIA IN EXPLORATORY LAPAROTOMY

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ABSTRACT

Background- Postoperative pain relief has always been a cause of concern for patients undergoing exploratory laparotomy. Epidual infusions of local anaesthetics are from times being used for the same. Various additives added to it may supplement the analgesic potency of local anesthetics. Studies to find the ideal additive have always been on the go. **Objectives-** This study aimed at evaluating intraoperative analgesia after lumbar epidural ketamine, magnesium sulphate or dexmedetomidine associated to 0.25% bupivacaine for exploratory laparotomy. **Method-** A randomized study was done. The patients undergoing elective exploratory laprotomy were divided into three groups (Group A, Group B, and Group C).

Group A –patients who were to receive magnesium sulphate (n=20)

Group B- patients who were to receive dexmedetomidine (n=20)

Group C-- patients who were to receive ketamine(n=20)

Isoflurane concentration and intraoperative analgesia(using clinical signs) was recorded.

Results- Our study has observed decreased systemic systolic pressure in 60% of Ketamine, 25% of Clonidine and 30% of Dexmedetomidine group patients; heart rate was decreased in 15% of Ketamine and 10% of Dexmedetomidine group patients. **Conclusion-** The above results help us to conclude that epidural ketamine, dexmedetomidine and magnesium sulphate decrease the requirement of fentanyl and isoflurane inspired concentration in the intraoperative period of exploratory laprotomies.

KEYWORDS – exploratory laparotomy ;epidural; intraoperative analgesia; isoflurane; safety.

INTRODUCTION

N-methyl-D-aspartate (NMDA) receptor antagonists may prevent or block Central Nervous System hypersensitivity.[1] Hence there has been an inclination to study the involvement of excitatory aminoacids, especially their post-synaptic actions on spinal cord via NMDA receptors.[2] In low doses, ketamine also tends to decrease nociception by blocking these receptors' channels.[1,2]

Activation of alpha2-adrenergic receptors triggers an intense analgesic response by involving supra-spinal and spinal receptors, including the activation of post-synaptic noradrenergic descending pathways receptors, cholinergic neurons, and nitric oxide and encephalin release.[3]

Recent studies have shown that α2-adrenergic agonists also play an important role in pain modulation by inhibiting nervous conduction of A_ and C fibers.[4] Alpha2-adrenergic agonists have also shown to decrease the need for halogenated anesthetics during intraoperative period. With the development of super-selective drugs, such as dexmedetomidine, this decrease may be approximately 95% when the inhalational agent is halothane.[5]

The addition of magnesium to epidurally administered bupivacaine in patients undergoing elective cesarean section with combined spinal‑epidural anesthesia helped to improve the quality of postoperative analgesia.[6]

To our knowledge no study has been conducted to evaluate the analgesic efficacy of magnesium sulphate added epidurally in exploratory laprotomies.

This study aimed at evaluating intraoperative analgesia afterlumbar epidural ketamine, magnesium sulphate or dexmedetomidine associated to 0.25% bupivacaine for exploratory laprotomy.

METHODS

Institutional Ethical Committee approval was taken. 60 patients with American Society of Anesthesiologists (ASA) status I-III between 20 and 60 years admitted for elective exploratory laprotomy were enrolled for the study. Sealed envelope method was used for randomization The patients undergoing elective exploratory laprotomy were divided into three groups (Group A, Group B, and Group C).

Group A –patients who were to receive magnesium sulphate 50mg in 1 ml 0.9% NS as adjuvant with 10ml 0.25% bupivacaine (n=20)

Group B- patients who were to receive dexmedetomidine 2ug/kg in 0.9% NS as adjuvant with 10 ml 0.25% bupivacaine(n=20)

Group C-- patients who were to receive ketamine0.5mg/kg as adjuvant with 10ml 0.25% bupivacaine(n=20)

Exclusion criteria

- Patients with ASA score of IV or more,
- body mass index >30 kg/m2,
- hypersensitivity to drugs in the study
- severe renal, hepatic, or neurologic disease
- those using opioid or systemic analgesic preoperatively

During the preanaesthetic checkup, patients were instructed about pain evaluation using visual analog scale (VAS) of 0-10 cm (0 cm = no pain and 10 cm = the worst pain).

In the operation theatre,a 16 G cannula was secured and ringer lactate was started on flow.ECG monitoring,non invasive blood pressure monitoring and pulse oximetry was started. After recording the vitals, Epidural catheter (20G) was inserted through 18G Tuohy needle at L3 L4 /L2 L3 intervertebral space in lateral decubitus position.

The epidural space was identified using loss of resistance technique. Epidural catheter was inserted and fixed at 9 - 10 cm inside the space. A test dose of 3 ml of 1.5% lidocaine with epinephrine 1:200,000 was given to rule out intravascular or intrathecal placement of the catheter. Catheter was covered with a sterile transparent dressing.

Patient was induced with fentanyl 2ug/kg and propofol 1.5-2.5mg/kg. After induction, neuromuscular blockade was achieved with vecuronium 0.2mg/kg.Patients were then intubated with 7-8 endotracheal tube.Anaesthesia was maintained with isoflurane. Controlled ventilation was achieved with low flow anesthesia system to allow inspired gases humidification and warming. Tidal volume was 8 to 10 mL.kg-1 and respiratory rate was enough to maintain PETCO2 between 30 and 35 mmHg.

Epidural was activated right after patient positioning according to the allocated groups. All patients received the same volume of drug combinations in the epidural space at the rate of 1mL/sec.

Blood pressure, heart rate, peripheral hemoglobin saturation (SpO2), expired CO2 (PETCO2) and inspired isoflurane concentration were recorded after epidural anesthesia and tracheal intubation, and then every 15 minutes until the end of surgery when patients were referred to the Post-Anesthetic Recovery Unit (PACU). Analgesia was evaluated by clinical signs. Inhalational agent inspired concentration was evaluated by inspired and expired gas analysis.

Increases in heart rate and/or systemic systolic pressure above pre-blockade levels were treated with bolus intravenous fentanyl (50 µg). Systemic systolic pressure decrease below 30% of pre-blockade levels or below 90 mmHg was corrected with intravenous sympathomimetic amine primarily mephenteramine 6mg. Significant decrease in heart rate below 50 beat/min promoting low output was treated with intravenous muscarinic antagonist atropine 0.6mg.

Analysis of Variance with Scheffé's proof was used for demographics data; Student's *t* test was used for statistical analysis of surgery duration; Fisher Exact test was used for systemic systolic pressure and heart rate variations; Analysis of Variance with Tukey's method was used for isoflurane inspired concentrations in ketamine, magnesium sulphate and dexmedetomidine groups; $p < 0.05$ was considered significant.

RESULTS

There were no significant statistical differences in patients weight and age according to Analysis of Variance with Scheffé's proof (Table I).There were also no significant statistical differences in surgery duration among groups according to Student's *t* test (Table II)

Table I - Demographics Data (Mean ± SD).

Groups/ Number of Patients	Age (years)	Weight (kg)
Ketamine (n = 20)	37.8+-9.8	64.6+-6.6
Magnesium sulphate(n=20)	38.1 ± 9.1	67.1 ± 10.5
Dexmedetomidine(n=20)	41.8 ± 8.4	68.3 ± 10.2

Without statistical significance, Scheffé's proof, $p > 0.05$

Table II - Surgery Duration (Mean ± SD).

Groups / Number of Patients	Duration (minutes)
Ketamine (n = 20)	120 ± 36
Magnesium sulphate(n=20)	112 ± 51
Dexmedetomidine(n=20	132 ± 50

Without statistical significance, Student's *t* test, p > 0.05

All patients receiving ketamine, magnesium sulphate or dexmedetomidine had decreased heart rate and systemic blood pressure as a consequence of NMDA receptors block by ketamine, or of pre-synaptic self-inhibitory feedback mechanism of α2 -adrenergic receptors by dexmedetomidine, and of epidural block by bupivacaine. There was no need for intraoperative analgesic supplimentation.

Fentanyl doses were those used during anesthetic induction and varied from 100 µg to 200 µg.

There has been mean isoflurane inspired concentration decrease of 0.65vol% in the Ketamine group, 0.87vol% in the magnesium sulphate group and of 0.83 vol% in the Dexmedetomidine group. According to ANOVA with Tukey'smethod, there has been statistically significant difference in inhalational agent inspired concentrations for the Ketamine group as compared to magnesium sulphate and Dexmedetomidine groups.

There has been systemic systolic blood pressure decrease below 30% of pre-blockade levels or below 90 mmHg in 12 patients in Ketamine group, 5 in magnesium sulphate group and 6 in Dexmedetomidine group patients. According to Fisher Exact test, there has been statistically significant difference in the Ketamine group as compared to other 2 groups. Marked heart rate decrease below 50 beat.min-1, has promoted low output in one ketamine (40 beat.min-1) and two Dexmedetomidine group patients (30 beat.min-1). There were no statistically significant differences among groups according to Fisher Exact test.

Table III - Drug Effects on Systemic Systolic Pressure (SSP) and Heart Rate (HR).

Groups/Number of patients	↓SSP	↓HR
Ketamine(n=20)	12	1
Magnesium sulphate (n=20)	5	0
Dexmedetomidine (n=20)	6	2

DISCUSSION

Inpatients undergoing abdominal procedures under general anesthesia and receiving fentanyl and isoflurane in constant minimum alveolar concentration of 0.5%, in them low ketamine doses have promoted decreased intraoperative opioid consumption.[7]

A human trial with clonidine as sole analgesic agent in abdominal surgeries with initial 2 µg.kg-1 (Group 1), 4 µg.kg-1 (Group 2) and 8 µg.kg-1 (Group 3) epidural doses, followed by 0.5 µg.kg-1.h-1 (Group 1), 1 µg.kg-1.h-1 (Group 2) and 2 µg.kg-1.h-1 (Group 3) continuous infusion until 12 postoperative hours has observed that intra and postoperative analgesia have been dose-dependent.[8]

A prospective, randomized and double-blind study with caudal S(+) ketamine associated to clonidine and combined with general anesthesia with sevoflurane for pediatric inguinal hernia correction has observed excellent intraoperative analgesia with minor side effects.[9]

A human study with epidural ketamine for thoracotomies has observed significant decrease in the need for intraoperative fentanyl as compared to the group receiving saline.[10]

Epidural ketamine or fentanyl associated to bupivacaine and combined to general anesthesia has evaluated intraoperative cardiovascular effects on patients submitted to total gastrectomy. Both fentanyl and ketamine associated to bupivacaine have promoted satisfactory intraoperative analgesia, however fentanyl has increased the incidence of systemic systolic pressure decrease. There were no statistical differences in heart rate between fentanyl and Ketamine groups.[11]

A multicenter human study has shown that the association of epidural and general anesthesia has decreased systemic systolic response in 31% of patients and has decreased heart rate in 12.7% of patients; patients receiving epidural clonidine had a higher incidence of heart rate decrease.[12]

Our study has observed decreased systemic systolic pressure in 60% of Ketamine, 25% of Clonidine and 30% of Dexmedetomidine group patients; heart rate was decreased in 15% of Ketamine and 10% of Dexmedetomidine group patients.

The above results help us to conclude that epidural ketamine,dexmedetomidine and magnesium sulphate decrease the requirement of fentanyl and isoflurane inspired concentration in the intraoperative period of exploratory laprotomies.

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