A Comparative Evaluation of the Anaesthetic Properties of Bupivacaine Hydrochloride and Ketamine Hydrochloride with Dextrose Given Intrathecally for Inguinal Hernia Repair - A Prospective Observational Study in a Tertiary Care Centre, South Kerala

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ABSTRACT

BACKGROUND

Spinal Anaesthesia is the most commonly used form of anaesthesia for surgeries below the level of umbilicus. Bupivacaine is the drug of choice for subarachnoid block. Spinal anaesthesia with bupivacaine is associated with many side effects and complications especially in patients with multiple co-morbid conditions. In our study we compared the anaesthetic effectiveness of 3.5 ml hyperbaric bupivacaine with a mixture of 100 mg ketamine and 0.1 mg adrenaline, the solution is made hyperbaric by adding 1.4 ml of 5 % dextrose given intrathecally. The objective of our study was to compare the anaesthetic properties and clinical effectiveness of intrathecally administered ketamine with bupivacaine for inguinal hernia repair.

METHODS

This prospective observational study was conducted on fifty American society of Anaesthesiologists (ASA) 1 and 2 patients in the age group of 25 – 60 years posted for elective inguinal hernia repair from December 2004 to December 2005. They were allocated in to two groups. Group 1 (Bupivacine group) and Group 2 (Ketamine group). Bupivacaine group (group 1) received 3.5 ml of bupivacaine heavy and ketamine group (group 2) received preservative free ketamine 100 mg with 0.1 mg adrenalin 1/1000 solution in 1.4 ml of 5 % dextrose to make it heavy. Anaesthetic properties, side effects and complications of both groups were compared intraoperatively.

RESULTS

The onset of action of ketamine (1.58 minutes) was faster than bupivacaine (3.31 minutes) which is statistically significant. Duration of blockade was longer in bupivacaine group (sensory 227.92 and motor 203.08) compared to ketamine group (sensory 143.40 and motor 109.46). Ketamine group showed a greater level of haemodynamic stability than bupivacaine group.

CONCLUSIONS

Intrathecal ketamine produces optimal anaesthetic conditions for surgeries like inguinal hernia repair. Haemodynamic stability provided by intrathecal ketamine is beneficial in patients with multiple comorbidities.

KEYWORDS

Hyperbaric Bupivacaine, Ketamine in Hyperbaric Solution, Intrathecal Block, Inguinal Hernia Repair

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BACKGROUND

The objective of anaesthesia is to provide analgesia, relaxation with minimum physiological disturbances, rapid recovery, and avoidance of complications. Common modalities of anaesthesia techniques are general anaesthesia and regional anaesthesia. Among regional anaesthesia techniques, spinal anaesthesia is the commonest form of anaesthesia performed worldwide. Subarachnoid block is a safer alternative to general anaesthesia for surgical procedures below the level of umbilicus. Spinal anaesthesia has many advantages over general anaesthesia as it preserves physiological homeostasis better and the incidence of morbidity in the perioperative period is less.[1] It is more beneficial in obstetric anaesthesia. Most commonly used drug for spinal anaesthesia is bupivacaine hydrochloride heavy. It is a long acting amide group of local anaesthetic agent. Bupivacaine hydrochloride has slower onset of action and has disadvantages like hypotension, bradycardia, systemic toxicity, unpredictable level of analgesia and chance of total spinal anaesthesia.

Ketamine is a phencyclidine derivative commonly used as an intravenous induction agent. It non competitively blocks N-methyl D-aspartate (NMDA) receptor in the spinal cord when given intrathecally. Other than action on NMDA receptor it has minor actions on opioid receptors, voltage sensitive Ca channels and monoaminergic receptors which leads to anaesthetic and analgesic effect. In high dose, ketamine has local anaesthetic properties and postulated mechanism is inhibiting neuronal sodium channels. Ketamine has been proved to be having potent anaesthetic and analgesic effects when given intrathecal and epidural routes. Besides the potent analgesic effect, intrathecal ketamine has stimulatory property on cardiovascular and respiratory system. It is an advantage during spinal anaesthesia. Cardiovascular effects of ketamine are tachycardia, increase in blood pressure, increase in cardiac output etc. These effects are due to centrally mediated sympathetic response. The sensory and motor blockade produced by ketamine is faster than bupivacaine. Addition of adrenaline 0.1 mg & 5 % dextrose to ketamine improves the degree of motor blockade and prolong the duration of motor blockade.

Objective

The objective of our study was to compare the anaesthetic properties and clinical effectiveness of intrathecally administered ketamine hydrochloride heavy with bupivacaine hydrochloride heavy for inguinal hernia repair.

METHODS

The study was conducted as a prospective observational study in the Department of Anaesthesiology, Government Medical College, Thiruvananthapuram from December 2004 to December 2005 after obtaining approval from hospital ethical committee and written informed consent from 50 patients posted for elective inguinal hernia repair. Patients in the age group of 25 - 60 years with ASA physical status 1 & 2 were selected. Patients with contraindications for spinal anaesthesia like patient refusal, coagulation abnormalities, spinal deformities, severe stenotic valvular heart diseases, patients with seizure disorders and contraindications to ketamine like psychiatric illnesses were also excluded from the study. Bupivacaine group received 3.5 ml of hyperbaric bupivacaine (commercially available bupivacaine preparation is used). Ketamine group received 100 mg preservative free ketamine + 1.4 ml 5 % dextrose + 0.1 mg adrenaline. Total volume of group B is 3.5 ml. The drug was prepared aseptically just before the injection by an anaesthetist who was not part of the study. All patients were undergone a routine pre-anaesthetic check up and advised nil per oral from 10 pm on the previous night. Oral premedication with T. Diazepam 10 mg, T. Ranitidine 150 mg and T. Metoclopramide 10 mg were given at 10 pm day before surgery and 6 am on the day of surgery. All procedures of the study were explained to the patient on the preoperative visit and obtained an informed written consent in the regional language.

On the day of surgery after shifting the patient to the operation theatre an iv access was obtained with 18-G iv cannula and isotonic saline (0.9 % NS) 15 ml/kg was infused over 15 to 20 minutes. Baseline blood pressure, heart rate and SpO_2 in supine position were measured and recorded. Intra-operative monitors include non-invasive blood pressure, electrocardiogram and pulse oxymeter. Intravenous premedication was given with midazolam 0.02 mg/kg 5 minutes before lumbar puncture. Patient was positioned laterally keeping the affected side dependent. Lumbar puncture was attempted at L3- L4 space under strict aseptic precautions using 25-gauge Quincke needle. Drug was given slowly (0.1 ml/sec) after confirming clear flow of cerebrospinal fluid (CSF). Patient was made supine immediately after completion of injection.

Oxygen was supplemented through a simple facemask at the rate of 4L/minute. The parameters monitored after giving subarachnoid block were blood pressure (BP) and heart rate. A 20 % reduction in baseline BP was considered as hypotension.

Reduction in blood pressure or heart rate was managed with i.v. fluid boluses, vasopressors (ephedrine 6 mg i.v. bolus) and atropine. The sensory level was assessed with a 23-gauge blunt needle bilaterally along the midclavicular line. The onset of anaesthesia was assessed by loss of pin prick at T6 level and the Bromage score of ≥ 2. Latency of onset was noted.

Duration of anaesthesia was calculated till the time of loss of pin prick at T10 level and Bromage scale ≤ 2. Post-operatively, patients were monitored for 24 hours for the incidence of hypotension and bradycardia. Complications like nausea, vomiting, headache, shivering, respiratory depression, urinary retention and sedation were noted.

Statistical Analysis

For qualitative data percentages were calculated and the association between the variables was tested statistically

with the help of chi square test. Quantitative data assessed using student 't' test.

RESULTS

Fifty patients included in the study were divided into two groups. In the case of qualitative data percentages were calculated and the association between the variables were tested with chi square test. The quality of the mean values of two groups were tested by applying student 't' test.

Group	Bupivacaine	Ketamine	P Value
Age	43.12	42	0.6
Height	166.48	167.96	0.06
Weight	66.84	67.92	0.212

Table 1. Patient Characteristics

Group	Onset (minutes)		Duration (minutes)		Fall in MAP	Bradycardia ≤60 beats/ minutes
	Sensory	Motor	Sensory	Motor		
Bupivacaine	3.31	4.412	227.92	203.08	23.92	7
Ketamine	1.58	2.076	143.40	109.40	15.68	3
P value	0.000*	0.000*	0.000*	0.000*	0.000*	0.228

Table 2. Comparison of Anaesthetic Properties and Haemodynamic Variables

*indicates statistically significant difference at $P < 0.05$

In the bupivacaine group, mean onset time and duration of sensory blockade was 3.31 and 227.92 minutes and motor blockade was 4.412 and 203.08 minutes respectively. In the ketamine group, mean onset time and duration of sensory blockade was 1.58 and 143.40 minutes and motor blockade was 2.076 and 109.40 minutes respectively. The difference between the groups were statistically significant. There was a greater reduction in mean arterial pressure (MAP) in the bupivacaine group compared to ketamine group and the difference was significant statistically. There was no statistically significant difference in the incidence of bradycardia. Comparing the side effects none of the patients developed shivering in the ketamine group. Sedation and urinary retention in both groups were comparable.

DISCUSSION

Spinal anaesthesia is the most acceptable modality of anaesthesia especially for procedures below the level of umbilicus. It has advantages over general anaesthesia like simplicity of the procedure, no loss of consciousness, minimum physiological disturbances, reduces metabolic stress response to surgery, intense analgesia and muscle relaxation, decrease in intraoperative blood loss, decreased incidence of acid aspiration syndrome and decreased risk of arterial and venous thrombosis.[1] Additional advantages are can monitor the mental status of the patient and can be used safely in patients with advanced pulmonary disease without much respiratory compromise. Considering the cost also, spinal anaesthesia is cheaper than general anaesthesia.[2] It is superior to general anaesthesia in some situations like caesarean section where airway management and complications like acid aspiration syndrome are real concerns. Haemodynamic effects of spinal anaesthesia are mediated by autonomic denervation. This produces arterial and venous vasodilation which is maximum on the venous side as there are few smooth muscles in their walls and so retain no significant residual tone following acute sympathetic denervation. Heart rate is reduced in spinal anaesthesia due to blockade of pre-ganglionic cardiac accelerator fibers T1 to T4 and also due to significant decrease in right atrial pressure and pressure in the great veins as they enter the right atrium. Hypotension during spinal anaesthesia in normovolaemic patients is also due to decreased peripheral vascular resistance.[3] Cerebral blood flow remains unaffected after spinal anaesthesia in normal patients because cerebrovascular autoregulation is independent of sympathetic nervous system. Nociceptive stimuli arising from the operative site produces hormonal and metabolic responses which is better controlled with spinal anaesthesia to a degree not observed with general anaesthesia. One of the dreaded complications of spinal anaesthesia is cardiac arrest which can be prevented by very careful administration and strict and vigilant monitoring.[4]

Bupivacaine is a long acting amide group of local anaesthetic. It acts by reversible block of sodium ions through the sodium channel of neuronal tissue. Impulse transmission is prevented. There is marked depression of the rate of depolarisation that it fails to reach the threshold potential. As a result, an action potential is not propagated and autonomic, sensory and motor impulse transmission is interrupted leading to autonomic block, sensory block and motor paralysis. Lipid solubility, protein binding and pKa determines onset of action, duration and potency of a particular drug. Onset of action of local anaesthetics depends upon Pka of the drug. Local anaesthetics with PKa nearer to the physiological pH have rapid onset of action. This shows the amount of ionised and unionised form of drug present. The degree of ionisation also has an important influence on drug action because only the nonionized form readily crosses cell membrane. PKa of bupivacaine is 8.1, so only 19 % of unionized drug is available to penetrate the nerve sheath and membrane and thus the onset is delayed. Bupivacaine has a protein binding of 96 % and exerts prolonged action. Increased duration of action correlates with high plasma protein binding. Drug bounded to protein provide a depot for the maintenance of neural blockade. In our study, the onset time of bupivacaine was 3 to 4 minutes and the duration was 3 to 3.5 hours.[5,6,7] This was similar to the observation by James B Collins M D Juhee Song, PhD and Raman C Mahabir in 2013. Intrinsic vasodilator property is another factor determining potency and duration of action of local anaesthetics.

Local anaesthetics are well known for their toxicity. Mainly central nerve system and cardiovascular system are affected. Central nervous system toxicity of local anaesthetics causes initial excitation due to blockade of inhibitory pathways in the cerebral cortex which is followed by inhibition of facilitatory pathways resulting in generalised state of depression. Cardiovascular toxicity due to depression of rapid phase depolarization in Purkinje fibres and ventricular muscles. The rate of recovery from use of dependent block is slower in bupivacaine treated papillary

muscle. Bupivacaine hydrochloride exerts a dose dependent negative ionotropic action on myocardium. Bupivacaine is cardiotoxic and can cause cardiovascular collapse which is very difficult to resuscitate.[8,9]

Ketamine is structurally related to phencyclidine and it is mainly used as an intravenous induction agent especially for patients who are haemodynamically unstable. Other than anaesthetic property it has potent analgesic and bronchodilator effects. Ketamine exerts its action via non-competitive antagonism at phencyclidine (PCP) site of the NMDA receptor. It blocks Ca^{2+} pore of NMDA receptor.[10] Ketamine has interactions with calcium and sodium channels, dopamine receptors, cholinergic transmission, noradrenergic and serotoninergic uptake. It also has opioid like and antiinflammatory effects.[11] It can provide better surgical conditions, good analgesia and without cardiovascular complications.[12] Cardiovascular effects of ketamine when given intravenously are increase in heart rate, increase in blood pressure and increase in cardiac output. Peripheral arteriolar resistance increases with ketamine and in fact it is the only one intravenous induction agent with such a unique property. Systemic release of catecholamine, vagal nerve inhibition, norepinephrine reuptake inhibition in peripheral nerves and myocardium and norepinephrine release from sympathetic ganglia are all attributed after ketamine injection. Its effect on respiratory system is bronchial smooth muscle relaxation. Sympathomimetic effect and bronchodilator effects are very unique of ketamine. This effect is beneficial in asthmatic patients. Other conditions which benefit from ketamine induction are cardiac tamponade, restrictive pericarditis, heart disease with right to left shunt and patients who are susceptible for malignant hyperthermia. Ketamine has a PKa of 7.5, highly lipid soluble (5 – 10 times more than Thiopentone), 12 % protein bound and has 93 % bioavailability. Ketamine exerts anticholinergic effects on the NMDA receptors of spinal cord and inhibit acetyl choline release. The analgesic effect of ketamine when given intrathecally is postulated to be due to inhibition of dorsal horn neuronal activity. Ketamine by depressing impulse transmission in the medullary reticular formation blocks affective emotional components of nociception to higher brain centers from spinal cord. Cardiovascular effects of intrathecal ketamine are similar to intravenous ketamine. These effects are beneficial in some compromised individuals. Bronchial smooth muscle relaxation improves pulmonary compliance in patients with reactive airway disease and bronchospasm. Ketamine causes minimal respiratory depression. The onset of sensory blockade is faster in our study similar to the study done by Amar Parkash Kataria, Harjeeth Singh in 2018. Early onset of action observed in our study is explained partly by the effect of ketamine on blocking axonal conduction.[13,14,15,16] Prolongation of motor block is observed with addition of adrenaline which was not observed in our study may be due to the lower dose of adrenaline used in our study.[14,17] Sivatharshini and Sekharan conducted a study with 25 mg ketamine as an adjuvant with bupivacaine and observed that onset and duration of sensory block was earlier in group containing ketamine than bupivacaine alone.[18] The unique properties of ketamine is advantageous for anaesthetizing patients in resource limited areas like war fields. Bion in 1984 and S.K. Bansal et al. in 1994 published papers on administration of intrathecal ketamine for emergency war surgeries and found to be effective because of its cardiovascular stability and preserving spontaneous respiration. They have given 50 mg and 75 mg of ketamine made hyperbaric with dextrose and observed that mean onset time (76.08s) was faster and duration was 45 – 90 minutes. In our study the mean onset time was 1.5 and 2.076 minutes for sensory and motor block respectively. Duration of block is prolonged in our study compared to their study. This difference can be attributed due to the addition of adrenalin in our study.

Vasoconstrictors like epinephrine when used intrathecally in combination with local anaesthetics prolongs motor and sensory block. Epinephrine induced vasoconstriction reduced systemic uptake of local anaesthetics. Epinephrine mediated vasoconstrictor effect antagonises vasodilatory effect of local anaesthetics and it reduces the intraneural clearance of local anaesthetics. Epinephrine has action on α_1 and α_2 receptors in the spinal cord. Epinephrine act on the prejunctional and post junctional α_2 receptors in the dorsal horn of spinal cord. Presynaptic receptor activation leads to decreased neurotransmitter release and action on postjunctional receptors produces hyperpolarization and reduction in impulse transmission. Epinephrine in a dose of 0.1 to 0.6 mg when given intrathecally prolongs the motor and sensory block. In our study duration, motor and sensory block of ketamine group was less compared to bupivacaine group, can be attributed to low dose of adrenalin used.

When dextrose is added to a drug, the density of the drug increases. So, the baricity or specific gravity increases. Baricity determines the extent of spread of drugs given intrathecally, so that influences level of spinal block. Adding dextrose makes the spinal drug hyperbaric. Hyperbaric drug will have specific gravity more than cerebrospinal fluid. If isobaric or hypobaric drug preparation is used for spinal anaesthesia it has the disadvantage of not being able to control the subarachnoid spread of drug.

In our study, ketamine group was haemodynamically stable which was observed in a study by Hemanth et al. 2013.[12,18] Lower incidence of hypotension in the ketamine group may be due to the property of ketamine to release catecholamines.[19] There is no respiratory depression in the ketamine group in our study.[13] Bradycardia may occur if adrenaline is added intrathecally which can block the centrally mediated cardiovascular effects of ketamine there by unmasking direct cardiorespiratory action.[13] There was evidence that intrathecal ketamine does not cause neurotoxicity.[20] Our patients in ketamine group developed headache which was treated symptomatically with paracetamol. Khezri et al. performed a study in which central nervous system complications were not observed.[21] Similar observations were also obtained in a study by Hemanth et al. 2013.[22] Shivering was not observed in ketamine group in the post-operative period.[23] But incidence of nausea and vomiting was more in ketamine group. Preservative free ketamine is safe and effective when given intrathecally

especially in patients who cannot tolerate much haemodynamic changes and with respiratory problems.

CONCLUSIONS

We have done this study to evaluate the effectiveness of ketamine as a drug for spinal anaesthesia and compare the effects with bupivacaine. It was concluded from our study that ketamine hydrochloride in hyperbaric solution can be used intrathecally to produce optimal conditions to enable surgeries involving below the level of umbilicus like inguinal hernia repair without much haemodynamic changes and can be considered as an alternative drug to local anaesthetics for spinal anaesthesia.

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