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A Comparative Evaluation of Postoperative Analgesia with intrathecal co-administration of combination of Ketamine-Midazolam and Ketamine-Dexmedetomidine in abdominal hysterectomies with bupivacaine.

Anaesthesiology

KEYWORDS: Postoperative analgesia, intrathecal ketamine-midazolam, dexmedetomidine, abdominal hysterectomy.

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ABSTRACT

Background : This study was undertaken to observe and compare primarily, postoperative analgesia with intrathecal ketamine-midazolam and intrathecal ketamine-dexmedetomidine using hyperbaric bupivacaine for spinal anaesthesia and secondarily the onset and duration of sensory and motor block, hemodynamic effect and level of sedation.

Method and Material : Patients were randomly assigned to one of the three groups, using a "slips of paper in a box" technique consisting 30 patients in each group.

Group C (Control)- Patients receiving intrathecal spinal anaesthesia with 0.5% hyperbaric bupivacaine (3ml) + normal saline (0.5%).

Group M- Patients receiving intrathecal spinal anaesthesia with 0.5% hyperbaric bupivacaine (3ml) + 5mg ketamine (preservative free) (0.1ml)+ 1 mg midazolam (preservative free)(0.2 ml).

Group D – Patients receiving intrathecal spinal anaesthesia with 0.5% hyperbaric bupivacaine (3ml) + 5 mg ketamine (preservative free)(0.1ml) + 5µg dexmedetomidine(0.05ml) similar volumes were taken with insulin syringe and total solution was made 3.5ml by adding normal saline.

Result : Onset of sensory and motor block was faster with both intrathecal ketamine-midazolam and ketamine-dexmedetomidine in comparison to control group but fastest onset was seen with intrathecal ketamine-dexmedetomidine. Maximum prolongation of duration of sensory block and motor block was seen with intrathecal bupivacaine with ketamine-dexmedetomidine. Total number of rescue analgesic required in 24 hours postoperatively was less with both the drug combinations but least with intrathecal ketamine-dexmedetomidine (Group D).

Conclusion : Intrathecal dexmedetomidine with ketamine caused prolongation of postoperative analgesia and reduced requirement of rescue analgesic in postoperative period.

Introduction : Lower abdominal surgeries can be performed safely under neuraxial (spinal or epidural) block, general anaesthesia or their combination but neuraxial blockade is the preferred mode of anaesthesia. Spinal anaesthesia is a form of regional anaesthesia involving injection of a local anaesthetic into the cerebrospinal fluid of the patient's subarachnoid space to anaesthetize the spinal nerve roots running through it.

Since the patient remains fully conscious, monitoring of patients is easier with less incidence of postoperative nausea and vomiting so less chances of aspiration in comparison to general anaesthesia. Early mobilizationafter spinal anaesthesia reduces thromboembolic phenomenon and hospital stay time.

Spinal anaesthesia is not devoid of complications. Apart from the risk of theoretically introducing infection to the central nervous system, difficulty in finding the space it being a blind procedure in bony abnormalities and old age and psychologically unfit in same patients, its limited duration of action makes it unsuitable to maintain adequate postoperative analgesia. There are some serious complications associated with spinal anaesthesia like hypotension, bradycardia, prolonged motor block, high spinal and total spinal anaesthesia.

Hyperbaric preparation of local anaesthetics is mostly used to limit cephaladspread(Luck JF et al. 2008)[1]. Bupivacaine is the most commonly used drug, although lignocaine, tetracaine, procaine, ropivacaine, levobupivacaine and cinchocaine are also used (Lambert D. et al 1987)[2].

In recent years, use of intrathecal adjuvants has gained popularity with the aim of prolonging the duration of block, better success rate, patient satisfaction, decreased resource utilization compared with general anaesthesia and faster recovery. Adequate pain management is essential to facilitate rehabilitation and accelerate functional recovery, enabling patient to return to their normal activity more quickly. The quality of the spinal anaesthesia has been reported to be improved by the addition of opioids (such as morphine, fentanyl and sufentanil) and other drugs such as dexmedetomidine, clonidine[3], neostigmine[4], ketamine and midazolam but no drug inhibiting nociception is without associated adverse effects. Postoperative neurological sequelae have been reported with ketamine with preservative but these are not associated with preservative free ketamine[5].

This study aimed to observe and compare primarily postoperative analgesia with intrathecal ketamine-midazolam and intrathecal ketamine- dexmedetomidine with hyperbaric bupivacaine for spinal anaesthesia and secondarily the onset and duration of sensory and motor block, hemodynamic effect and level of sedation.

Methods and Material : After approval from ethical committee of the institute, the study was conducted at S.R.N. Hospital (associated to M.L.N. Medical College, Allahabad) over a period of one year. This prospective study was conducted on 90 adult patients of ASA physical status 1 & 2 aged 40-60 yrs scheduled for elective total abdominal hysterectomies. Patients were explained the purpose of the study along with the procedure and thereafter a valid, informed and written consent was taken from all the patients undergoing study.

Patients were randomly assigned to one of the three groups, using a "slips of paper in a box" technique consisting 30 patients in each group.

Group C (Control) - Patients receiving intrathecal spinal anaesthesia with 0.5% hyperbaric bupivacaine (3ml) + normal saline (0.5%).

Group M - Patients receiving intrathecal spinal anaesthesia with 0.5% hyperbaric bupivacaine (3ml) + 5mg ketamine (preservative free) (0.1ml)+ 1 mg midazolam (preservative free)(0.2 ml).

Group D – Patients receiving intrathecal spinal anaesthesia with 0.5% hyperbaric bupivacaine (3ml) + 5 mg ketamine (preservative free)(0.1ml) + 5µg dexmedetomidine (0.05ml) similar volumes were taken with insulin syringe and total solution was made 3.5ml by adding normal saline.

All 30 patients in each group underwent surgery under spinal anaesthesia and no patient was given any sedation or general anaesthesia. Following parameters were assessed –

1. Onset of sensory block – It was determined by the time from administration of spinal anaesthetic solution to loss of pin prick sensation to T10 dermatome. (checked every 30 seconds from administration of spinal anaesthetic drug till 15 minutes)

2. Onset of motor block – It was determined by the time from administration of spinal anaesthetic solution to motor block uptoBromage score 3 (checked every 30 seconds from administration of spinal drug till 15 minutes.

3. Duration of sensory block – was defined by the time taken by sensory block to regress upto S1 dermatome (was assessed by pin prick method every 15 minutes following intrathecal injection.

4. Duration of motor block – was defined by the time by motor block to recover uptoBromage score 0 (was assessed every 15 minutes following intrathecal injections).

5. Duration of analgesia (time from completion of administration of spinal block to first requirement of analgesic supplement (VAS 7).

6. Total number of doses of analgesic supplement in 24 hrs postoperatively.

7. Sedation score – it was evaluated at 5, 30, 60, 90 and 120 minutes after spinal block using Ramsay Sedation Scale as mentioned below –

1	Anxious, agitated or restless or both
2	Cooperative, oriented and tranquil
3	Responding to commands only
4	Brisk response to light glabellar tap or loud auditory stimulus
5	Sluggish response to light glabellar tap or loud auditory stimulus
6	No response to light glabellar tap

Maximum sedation score was noted.

1. Heart rate, non invasive blood pressure (mean arterial pressure) and peripheral oxygen saturation was measured at 1, 5, 15, 30, 45, 65, 90 and 120 minutes.
2. Complications if any during intraoperative or postoperative phase noted and properly taken care of.

Observation :

Table – 1

Comparison and Analysis of baseline vital parameters

Hemodynamic parameters	Group C (n=30)	Group M (n=30)	Group D (n=30)	P value (ANOVA)
Pulse rate (mean± SD)	75.87±10.97	76.57±10.41	76.57±10.38	0.968
Range	54-100	59-96	58-97	
MAP (mm Hg) (mean± SD)	93.87±5.19	93.57±5.57	94.27±4.65	0.870
Range	82-104	82-103	86-103	

Table – 2

Comparison of duration for surgery in three groups

Duration (min)	Group C (n=30)	Group M (n=30)	Group D (n=30)	P value (ANOVA)
Mean±SD	72±9.15	73.17±10.13	74.17±10.18	0.694
Range	60-90	60-90	60-90	

Table – 3

Comparison of onset time for sensory and motor block in three groups

Onset time (min)	Group C	Group M	Group D
Sensory block Mean±SD	6.03±0.81	4.56±0.69	4.17±0.55
Motor block Mean±SD	7.27±0.73	5.53±0.81	5.07±0.57

Table – 4

Comparison of Duration of Analgesia in three groups

Duration (min)	Group C (n=30)	Group M (n=30)	Group D (n=30)
Mean±SD	288±47.66	465.67±48.12	664.67±60.61
Range	210-420	360-540	540-750

Table – 5

Analysis of Duration of Analgesia in three groups

Comparison	Duration of Analgesia	
	T	P value
M Vs C	14.37	<0.05
D Vs C	26.76	<0.05
D Vs M	14.08	<0.05

Table – 6

Comparison of Total no. of Rescue Analgesic in 24 hrs in three groups

	Group C (n=30)	Group M (n=30)	Group D (n=30)
No. of inj. Mean±SD	2.97±0.56	2.37±0.56	2.07±0.52
Range	2-4	1-3	1-3

Result : Demographic data were comparable in respect to age, weight, baseline vital parameters and duration of surgery (Table 1). All the parametric data of three groups were analyzed using student t- test and one way ANOVA. Onset of sensory and motor block was earlier with both intrathecal ketamine-midazolam and (4.56±0.69 vs 6.03±0.81) ketamine –dexmedetomidine in comparison to control groups (4.17±0.55 vs 6.03+0.81) but fastest onset was seen with intrathecal ketamine-dexmedetomidine (4.17±0.55)(Table 3). Addition of ketamine-midazolam or ketamine-dexmedetomidine to intrathecal bupivacaine caused prolongation of duration of sensory block and postoperative analgesic (Table 2) but maximum prolongation was seen with intrathecal bupivacaine with ketamine-dexmedetomidine. Duration of analgesia was longer in both group M (ketamine – midazolam) 465.67±48.12 min Vs 288±47.66 min and group D (ketamine – dexmedetomidine) 664.67±60.61 min Vs 288±47.66 min in comparison to control group (Table 4). Group D had longer duration of motor block than group M (664.67±60.61 Vs 465.67±48.12 min (Table 4,5). Total number of rescue analgesics required in 24 hrs postoperatively was less with intrathecal ketamine-dexmedetomidine (Table 6). None of the patients in any group showed significant sedation or hemodynamic changes (Table 1) and thee no statistically significant difference in maximum sedation in three groups (P>0.5).

Discussion : Spinal anaesthesia is the choice for lower abdominal and lower limb surgeries. Duration of analgesia with spinal anaesthesia has been reported to be improved by addition of options and other drugs as dexmedetomidine, clonidine, neostigmine, ketamine, midazolam. **Murali Krishna et al**[6] compared low dose of intrathecal ketamine and midazolam with bupivacaine and found prolonged analgesia and less hemodynamic instability. We also found that intrathecal ketamine (5mg)-midazolam (1mg) caused prolongation of duration of postoperative analgesia (465.67±48.12 min vs 288±47.66 min) and it was statistically significant (P value<0.05). **Guansty S. et al**[7] concluded that addition of $S^{(+)}$ketamine intrathecally to spinal plain ropivacaine (0.75%) led to rapid onset of both sensory and motor blockade and enhanced the segmental spread of spinal block without prolonging the duration of spinal analgesia in our study intrathecal ketamine with bupivacaine was

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associated with earlier onset of sensory and motor block and prolonged duration of sensory and motor block all these results were statistically significant. In addition we found prolongation of analgesia with intrathecal ketamine-midazolam.

Shadangi B K et al[8] compared the addition of preservative free midazolam to bupivacaine intrathecally and found prolonged postoperative analgesia without increasing block. In our study we also found that intrathecal midazolam prolonged postoperative analgesia and it was statistically significant.

Nanjegowda N et al (2011)[9] found that addition of preservative free midazolam 2 mg to intrathecal 0.5% hyperbaric bupivacaine prolonged the duration of analgesia without any adverse effect. In our study we also observed that intrathecal midazolam caused prolongation of duration of postoperative analgesia without any adverse effects. **Mahmoud M. mustafa et al**[10] found that dexmedetomidine had a dose dependent effect on the onset and regression of sensory and motor block when used as an adjuvant to bupivacaine in spinal anaesthesia , in our study we also found that addition of dexmedetomidine (5µg) to intrathecal bupivacaine caused earlier onset of sensory and motor block and delayed recovery from sensory and motor block without causing any hemodynamic instability.

Watiya Ramadan Mahdy et al (2011)[11] found that dexmedetomidine was an attractive adjuvant to spinal bupivacaine in caesarean section giving good quality of spinal anaesthesia with minimal side effects and no adverse effect on babies. In our study we also found addition of dexmedetomidine (5µg) to intrathecal bupivacaine caused earliest onset of sensory and motor blocks. All these results were statistically significant.

Allah Shah et al (2012)[12] found that patient receiving ropivacaine –dexmedetomidine showed excellent hemodynamic stability and postoperative analgesia. In our study we also found that intrathecal dexmedetomidine caused prolongation of postoperative analgesia and less requirement of rescue analgesic in postoperative period.

It was concluded that addition of ketamine-dexmedetomidine to intrathecal bupivacaine caused earlier onset of sensory and motor block, prolongation of duration of sensory block, motor block, analgesia and less requirement of analgesics in postoperative period without increasing side effects or complications. Addition of ketamine-midazolam also showed all these advantages but less than that with ketamine-dexmedetomidine.

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