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Original Research Article

A comparative study of intrathecal nonopioid adjuvants to hyperbaric bupivacaine for spinal anaesthesia

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ABSTRACT

Background: Intrathecal drugs when used as adjuvant to spinal anaesthesia produce substantial anti-nociception and potentiate analgesia of bupivacaine. This study was planned to evaluate the effects of intrathecal non opioid drugs-clonidine, midazolam, neostigmine and magnesium sulphate on duration of analgesia, characteristics of SA and hemodynamic stability when added to 0.5% hyperbaric bupivacaine for spinal anaesthesia.
Methods: In this randomized, prospective, double blind study, 100 ASA physical status I and II adults patients posted for elective lower abdominal surgery were divided into 4 groups (n=25). Group BN received preservative free neostigmine 25µg, group BMG received Mgso4 50mg, group BC received clonidine 30µg and BM received midazolam 2mg with 15mg hyperbaric bupivacaine. Duration of postoperative analgesia, effect on onset and duration of sensory and motor block, incidence of side effects was noted. Continuous variables were compared using one way Analysis of Variance (ANOVA).
Results: The duration of postoperative analgesia was significantly prolonged in BM group 391.64 (132.98) minutes, followed by BN group 308.76 (127.40), BC group 296.60 (52.77) and BMG group 252.2 (86.76). The numbers of analgesic doses in 24 hours were significantly less in BM group. One patient required additional analgesia in BM group as against 40%, 36% and 64% in BN, BC, BMG group respectively. The duration of sensory block was significantly prolonged in group BM followed by group BC and BN.
Conclusions: Intrathecal midazolam provides superior analgesia without clinically relevant side effects. The onset of analgesia was rapid and duration prolonged with intrathecal midazolam followed by neostigmine and clonidine.

Keywords: Hyperbaric bupivacaine, Intrathecal magnesium sulphate, Intrathecal neostigmine, Intrathecal midazolam, Intrathecal clonidine, Lower abdominal surgery, Postoperative pain, Postoperative analgesia, Spinal anaesthesia

INTRODUCTION

Neuraxial blockade is the preferred mode of anaesthesia for lower abdominal and lower limb surgeries. It has rapid onset, superior analgesia, less failure rate and it is cost effective. It provides excellent pain relief as compared to intravenous or epidural route.[1] But the duration of block is short and it lacks postoperative analgesia. Use of intrathecal adjuvants has gained popularity with the aim to prolong postoperative analgesia, patient satisfaction and fast recovery. Neuraxial opioids though effective have worrisome respiratory depression, nausea, vomiting, urinary retention and pruritus that limit their use in ward.[2,3]

Currently researchers have focused on non-opioid spinal receptors that inhibit transmission of pain signals. Increased understanding of spinal processing of pain has led to development of specific drugs that inhibit pain transmission. Intrathecal (IT) neostigmine and magnesium sulphate both produce substantial anti-nociception without neurotoxicity, potentiate analgesia of bupivacaine and opioids as evident from animal and human studies.[3-5] Also

intrathecal (IT) midazolam and clonidine both produce a dose dependent anti-nociception when used alone or in combination with local anaesthetics.[6,7] They improve intra-operative analgesia, prolong duration of sensory and motor blockade along with sparing effect on post-operative analgesic consumption.[3,8,9] The incidence of side effects observed with intrathecal clonidine in earlier studies is reduced by lower doses of clonidine (<150µg).[10,11] Same is true for neostigmine. The ability of IT neostigmine to protect against SA induced hypotension and to increase gastrointestinal motility in the absence of respiratory depression are positive features that stimulated us to undertake this study.[3,12,13]

We compared the four non-opioid adjunct analgesic drugs to establish the superior additive for postoperative analgesia after neuraxial administration.

METHODS

It is a randomized, prospective, double blind; parallel group clinical trial. It was approved by institutional ethics committee and conducted in accordance with the principles laid down in the Declaration of Helsinki. Written informed consent was obtained from the participants. Hundred American society of anaesthesiologist grade I and II subjects of age between 20 and 65 years, of either gender presenting for lower abdominal surgery under spinal anaesthesia at tertiary health care centre were enrolled in the study. Patients were excluded if they have psychiatric disorder, chronic pain or any condition that precludes spinal anaesthesia or those taking antihypertensive medication and failure of spinal block with need for general anaesthesia. Premedication with oral diazepam 5mg administered at bed time, intravenous (IV) ranitidine 50mg and ondansetron 4mg given just before induction of anaesthesia. Intravenous access established with 18gauge cannula followed by preloading with 10ml/kg lactated ringers solution. Standard monitoring (ECG, non-invasive blood pressure, and pulse oxymeter) was used.

Hundred subjects were randomly assigned into one of the four treatment group using computer generated random numbers. The allocation sequence was concealed from the researcher enrolling and assessing the participants. The participant and data collector both were blinded to the test solution. Group BN received intrathecal neostigmine 25µg (Myostigmin 0.5mg/ml- Neon laboratories Ltd.), group BMG received $Mgso_4$ 50mg (Magneon 50% w/v, Neon laboratories Ltd.), group BC received clonidine 30µg (Clonidine hydrochloride-150µg/ml-Cloneon, Neon laboratories) and BM received midazolam 2mg (Midazolam hydrochloride-5mg/ml-Midosed, Neon laboratories) with 15mg hyperbaric bupivacaine. The test solutions were prepared in identical syringes by anaesthesiologist not involved in outcome measurement. All the study drugs were preservative free and total volume of drug injected was 3.5ml.

Spinal anaesthesia was carried out in lateral position at lumbar 3-4 inter space using 23 gauge disposable spinal needle. After clear and free flow of cerebrospinal fluid (CSF), one of the study solutions was administered intrathecally depending upon the group at the rate 0.2ml per second. The head end of the operating table was elevated by 10-20 degree.

Sensory block was assessed by loss of sensation to pin prick. Motor block assessed as inability to move lower limb. The level of sedation was recorded every 15 minutes intra operatively and post operatively for 6 hours by sedation score described by Chernik et al, no sedation (wide awake), mild sedation (sleeping comfortably), moderate sedation (deep sleep but arousable), Severe sedation (deep sleep not arousable).[6]

Supplemental oxygen via ventimask was given at 5liter/minute during procedure. Pulse rate, blood pressure and oxygen saturation (SPO_2) was recorded every 5 minutes for 15 minutes, then every 10 minutes till end of surgery and 2, 4, 6, 12, 24 hours postoperatively. IV fluids (crystalloids, colloids or blood) were administered for maintenance and according to surgical blood loss. Hypotension was defined as systolic BP <90mmHg or 20% fall in systolic BP from baseline value and treated with 250ml bolus IV fluids and IV mephenteramine 6 mg. Bradycardia was defined as pulse rate <60/min and treated with IV atropine sulphate 0.6mg. The pain score was recorded on 10cm visual analogue scale, 0= no pain, 10= Intolerable pain). Each patient received intramuscular diclofenac sodium 75mg immediately after shifting in ward. Further analgesic dose was administered on patient's demand. If pain persists (VAS>5), IV tramadol 1mg/kg was given.

All durations were calculated considering the time of spinal injection as time zero.

The primary outcome measure was duration of postoperative analgesia i.e. time from IT injection till demand for rescue analgesic or VAS>5. Pain score was recorded every two hours until first rescue analgesic dose. The total number of analgesic doses in 24 hours was recorded.

Data was collected regarding the onset of sensory block (Time taken from IT injection to loss of pinprick sensation bilaterally at L1, duration of sensory block (Time from IT injection to 2 segment regression), onset of motor block (Time from IT injection to disappearance of leg movements) duration of motor block (Time from IT injection till reappearance of leg movements), Side effects like hypotension, bradycardia, sedation, nausea, vomiting, respiratory depression (SPO_2<90%) shivering, itching, drowsiness, headache bowel/bladder dysfunction, neurological deficit were recorded as and when they occur. IV metoclopramide 10mg was given as rescue antiemetic. Each subject was observed for 24 hours, 48 hours and 7

days after surgery. The recruitment stopped after enrolling 25 participants in each group.

The sample size of 25 subjects per group was necessary for detecting clinically significant difference of 67 minutes in duration of analgesia assuming a power of 80% and a significance level of 5% using GraphPad StatMate 2.00 software. The data was analysed using one way ANOVA with Tukey HSD post-hoc test [MedCalc Version 17.6-MedCalc software bvba (BE), Belgium]. Catagorical data was analysed by Chi square test with Yates correction using OpenEpi version 3.01 (www.openepi.com).

RESULTS

Total data from 100 subjects (25 in each group) were analysed by original assigned group of investigators. There was no dropout, refusal or any departure from initial study protocol. The groups of patients were comparable with respect to age, sex and duration of surgery (Table 1). The surgical procedures performed were herniorrhaphy, abdominal hysterectomy, appendectomy, vaginal hysterectomy and Frayer's prostatectomy. There was no significant difference in onset of sensory and motor block and the time required to achieve maximum cephalic spread of sensory level. The duration of sensory block was significantly prolonged in group BM followed by group BC and BN. After intergroup comparison, the difference was significant among the groups except group BMG and BN. The duration of motor block was significantly prolonged in BC groups (p=0.0023). The difference in group BC and BMG (p=0.0203) as well as between BC and BN (p=0.0049) was statistically significant (Table 2).

Table 1: Demographic characteristics and duration of surgery in study groups.

Variable	Group BM	Group BC	Group BMG	Group BN	P Value
			(n=25)		
Age (Years)	40.40 (15.45)	44.92 (11.61)	39.40 (8.36)	41.36 (7.03)	0.32
Gender (M:F)	19:6	21:4	20:5	21:4	0.72
Duration of surgery (min)	59.08 (20.64)	65.36 (21.09)	62.12 (23.07)	68.16 (24.32)	0.50

Group BM- intrathecal hyperbaric bupivacaine 15mg + midazolam 2mg.
Group BC - intrathecal hyperbaric bupivacaine15mg + clonidine 30µg.
Group BMG - intrathecal hyperbaric bupivacaine15mg + MgSO4 50mg.
Group BN -intrathecal hyperbaric bupivacaine15mg + neostigmine 25µg.
Data expressed as mean (SD) and analysed by One Way Analysis of Variance,
p<0.05- Significant

Table 2: Effect on characteristics of spinal blockade in study groups.

Variable	Group BM	Group BC	Group BMG	Group BN	P Value
			(n=25)		
Onset of sensory block (min)	1.84 (0.98)	2.44 (3.87)	1.69 (0.82)	2.02 (1.08)	0.62
Two segment regression (min)	210.84 (68.44)	169.28 (63.69)	74.56 (17.07)	84.36 (26.08)	0.00
Onset of motor block (min)	2.08 (0.8)	2.30 (0.45)	1.82 (1.05)	1.98 (1.43)	0.39
Duration of motor block (min)	293.80 (108.69)	322.92 (135.00)	239.6 (75.17)	226.28 (64.08)	0.0023

Group BM- intrathecal hyperbaric bupivacaine 15mg + midazolam 2mg.
Group BC - intrathecal hyperbaric bupivacaine15mg + clonidine 30µg.
Group BMG - intrathecal hyperbaric bupivacaine15mg + Mgso4 50mg.
Group BN -intrathecal hyperbaric bupivacaine15mg + neostigmine 25µg.
Data expressed as mean (SD) and analysed by One Way Analysis of Variance,
p<0.05-significant

The mean duration of analgesia was significantly longer in Group BM (391.64 ±132.98 min). The difference between group BM and BC, BM and BMG, BM and BN was statistically significant (p value 0.01, 0.0001, 0.032 respectively) (Table 3). The diclofenac requirement is comparable in all four groups. Additional analgesic requirement significantly less in BM group compared to other three groups. The difference between BC and BMG group was also significant (p =0.0044) (Table 3). The total number of analgesic doses required was significantly less in group BM followed by group BC and BN. After intergroup comparison, the difference was significant among the groups except group BMG and BN. The pain score was comparable at 2 hours in all the four groups. The inter group comparison at 6 hours the difference between BM and BC (p=0.00), BC and BMG (p=0.0001), BC and BN (p=0.0005) was significant (Table 3).

Table 4 describes the incidence of adverse effects in study groups. Significant bradycardia was observed in BC and BN group (p<0.05). Hypotension was noted in BC, BMG and BN groups (p<0.05). Sedation was significantly high in BMG group (p=0.0048).

Table 3: Effect on duration postoperative analgesia and analgesic requirement in study groups/ analgesia characteristics in studied groups.

Variable		Group BM	Group BC	Group BMG	Group BN	P Value
		(n=25)				
Duration of analgesia (min)		391.64 (132.98)	296.60 (52.77)	252.2 (86.76)	308.76 (127.40)	0.0001
No. of analgesic doses		2.04 (1.01)	2.76 (0.87)	3.64 (0.75)	3.48 (0.58)	0.000
Diclofenac requirement (mg)		153.00 (76.48)	177.00 (36.74)	150 (30.61)	156 (20.76)	0.1618
No. of patients demanding Additional analgesia †		0 (0%)	9 (36%)	16 (64%)	10 (40%)	0.006
Pain score (VRS)	2 Hours	0	0	0	0	
	4 Hours	1.53(1.58)	3.12 (9.92)	5.1 (2.17)	3.70 (2.71)	0.129
	6 Hours	3.12(1.71)	6.28 (1.45)	3.80 (2.17)	4.00 (2.39)	0.000

Group BM- intrathecal hyperbaric bupivacaine 15mg + midazolam 2mg, Group BC - intrathecal hyperbaric bupivacaine15mg + clonidine 30µg, Group BMG - intrathecal hyperbaric bupivacaine15mg + $MgSO_4$ 50mg, Group BN -intrathecal hyperbaric bupivacaine15mg + neostigmine 25µg, Data expressed as mean (SD) and analysed by One Way Analysis of Variance, p<0.05-significant, Dunn's multiple comparisons tests-*Group N and Group C (p<0.05), **-Group N and Group C (p<0.01), ***-Group N and Group C (p<0.001)
† Data analysed using Chi square test, P<0.05- Significant

Table 4: Incidence of adverse effects in study groups.

Variable	Group BM	Group BC	Group BMG	Group BN	P Value
	(n=25)				
Bradycardia	00 (0%)	09 (36%)	3 (12%)	6 (24%)	S*
Hypotension	04 (16%)	12 (44%)	16 (64%)	12 (48%)	S**
Sedation	01 (4%)	05 (20%)	14 (56%)	05 (20%)	S***
Vomiting during surgery	01 (4%)	04 (16%)	01 (4%)	08 (32%)	S#
PONV	07 (28%)	07 (28%)	10 (40%)	10 (40%)	NS
Neurological symptoms	01 (4%)	01 (4%)	01 (4%)	01 (4%)	NS
Shivering	03 (12%)	04 (16%)	04 (16%)	04 (16%)	NS

PONV- Postoperative nausea and vomiting,
Group BM- intrathecal hyperbaric bupivacaine 15mg+midazolam 2mg,
Group BC - intrathecal hyperbaric bupivacaine15mg+clonidine 30µg,
Group BMG - intrathecal hyperbaric bupivacaine 15mg+ $MgSO_4$ 50mg,
Group BN - intrathecal hyperbaric bupivacaine 15mg + neostigmine 25µg,
Values are number (%) analyzed by Chi square test, Data expressed as No. of patients (%) and analyzed by Chi square test P<0.05- Significant, S*- Significant-Group BM Vs BC, BM Vs BN, BC Vs BMG, S**- Significant-Group BM Vs BC, BM Vs BN, BMG Vs BN, S***- Significant-Group BMG Vs BC, BMG Vs BN, BMG Vs BM, S#- Significant-Group BMG Vs BN, BM Vs BN, NS - Not Significant

Intra operative vomiting was high in BN group compared to BM and BMG group. The four groups were comparable for incidence of PONV, shivering and neurological symptoms.

DISCUSSION

Effective treatment of pain represents an important component of postoperative recovery. It serves to blunt autonomic, somatic, and endocrine reflexes with a resultant potential decrease in perioperative morbidity.[14,15] Our study confirms the analgesic efficacy of intrathecal (IT) midazolam, neostigmine and low dose clonidine when added to hyperbaric bupivacaine for spinal anaesthesia.

We observed better quality of analgesia with IT midazolam compared to other three drugs. The postoperative analgesia was maintained for longer period with less pain score and less analgesic consumption. Additional analgesia was required in only one patient in this group. The cumulative analgesic requirement was indicated by the total number of analgesic doses required during first 24 h after surgery. It was lowest in Midazolam group. The analgesic consumption was not significantly reduced with $MgSO_4$. Neither the spread nor the potency of spinal bupivacaine was affected by these additives.[15-18] Our findings of analgesia characteristics are in accordance with the pharmacokinetic profile of neostigmine and $MgSO_4$.[18-21] Also our results correspond to previously reported data in different studies when IT midazolam or clonidine was compared with placebo.[11-14]

The pain score in the recovery room was reduced to a significant degree by all our drugs. The midazolam group had the lowest pain score followed by $MgSO_4$ and neostigmine. The placebo group was not included for ethical reasons.

We administered first dose of diclofenac 75mg to all the patients immediately after shifting in ward for ethical reasons as per the standard protocol of our hospital. Further analgesic was administered on demand. This might be the reason for insignificant difference in amount of diclofenac requirement. But the effectiveness of

midazolam was indicated by lower pain score in this group.

Several investigators have shown that intrathecal midazolam produces a dose dependent anti-nociception sufficient to produce anaesthesia for abdominal surgery.[22] Patient do not require opioid analgesic when subjected to painful somatic stimulus like leg surgery.[23] It is also effective in relieving chronic mechanical low back pain as well as pain due to metastatic bone tumours.[22] Sympathetic nervous system function remains intact after intrathecal midazolam.[23-25] This sparing effect on sympathetic nervous system may explain lesser degree of hypotension and bradycardia in midazolam group in our study.

Three possible mechanisms are suggested for the anti-nociceptive action of midazolam. First the benzodiazepine/GABA-A receptor complex mediated analgesia as they are abundantly present in lamina II of dorsal horn of spinal cord.[26,27] It also causes release of endogenous opioid acting at spinal delta receptors as naltrinadole, a delta receptor opioid antagonist suppresses its analgesic effect.[28] Thirdly it inhibits adenosine uptake or enhance adenosine release.[25] The use of IT midazolam in humans is reported in at least 18 peer reviewed reports in about 797 patients since 1986. It is shown to be free of neurotoxicity or other side effects up to 2mg dose and in continuous infusion up to 6mg/day for long period in man.[3,24,29,30]

The postoperative analgesia of intrathecal neostigmine, a cholinesterase inhibitor was first reported by Hood DD et al, in 1995, the effectiveness being comparable to morphine.[21] Spinal administration of neostigmine produces analgesia in a novel manner. It inhibits breakdown of endogenous neurotransmitter acetylcholine (Ach) that has intrinsic analgesic properties.[3,15,18,31] The concentration of acetylcholine in CSF increases with painful stimulus and remains at a plateau for 4-6 hours.[12,19-21] The degree of analgesia depends upon the amount of tonic release of acetylcholine in CNS.[16,32] It is likely that CSF neostigmine concentration even after lowest dose were adequate to significantly inhibit cholinesterase in CSF.[5,13,19] The dose of intrathecal neostigmine required in postoperative patients is much smaller than that required in volunteers.[18] There is amplification of postoperative analgesia of intrathecal neostigmine by postoperative pain. Intrathecal neostigmine causes clear anti-nociception in first two postoperative days but fails to do so five days after surgery.[33] High density of muscarinic cholinergic receptor binding sites have been demonstrated in substantia gelatinosa and in lamina III and V of dorsal grey matter of spinal cord.[32,33] Both M1 and M2 receptor subtypes are demonstrated in superficial dorsal horn.[33] Spinal neostigmine apparently activates descending pain inhibitory systems that relay on a spinal cholinergic interneuron probably exacerbating a cholinergic tonus that is already activated during the acute postoperative pain.[18,32,33] Intrathecal neostigmine was found to be extremely efficient for alleviating somatic pain.[32] Analgesic effect also reflects blocking of sympathetic ganglion through nicotinic receptors or a direct antispasmodic effect on the viscera through muscarinic receptors.[32] The preliminary dose response studies suggest that analgesic effect was dose independent.[20] Smaller dose neostigmine ≥50µg in volunteers and ≥10µg in surgical patients could enhance sensory anaesthesia with few side effects when added to bupivacaine.[3,16,18] A smaller dose may have the same efficacy with less adverse effects. Intrathecal neostigmine with 25-50µg dose produces dose independent reduction in postoperative rescue analgesic consumption.[3,12] Neostigmine induced increase in gut motility might be beneficial in reducing postoperative ileus.[13]

Clonidine a selective alpha-2 adrenergic agonist produces analgesia by sympatholysis at peripheral level, decreased catecholamine release in the brain and suppression of tumour necrosis alpha in plasma during perioperative period. Spinal clonidine produces dose dependent analgesia along with hypotension, bradycardia and sedation.[3,11,34] Most of the studies using 37.5 to 50µg reported significant hypotension and bradycardia.[10,11] A 30µg dose provides maximum benefits and minimum side effects.[11] It also directly decreased mean arterial pressure by inhibition of preganglionic sympathetic neurons in spinal cord.[3,35] We observed some amount of bradycardia (36%) and hypotension (44%) with even low dose clonidine and sedation in 20% subjects.

Magnesium sulphate reveals anti-nociceptive effect in animal and human pain models; it has potential to prevent central sensitization from peripheral nociceptive stimuli. Painful stimulus release glutamate and aspartate neurotransmitters which binds to the NMDA receptors. Activation of these receptors leads to calcium entry into the cell that initiate a series of central sensitization such as wind-up and long term potentiation in spinal cord. This NMDA signaling is important in determining the duration and intensity of postoperative pain.[36-38] Magnesium blocks the calcium influx into the cell i.e. natural physiological calcium antagonism and non-competitively antagonises the N-methyl-D-aspartate (NMDA) receptors. Mg^{++} is a neuro -protectant protecting cerebellar neurons against glutamate toxicity and spinal cord from ischemic injury during aortic cross clamping.[39-41] Selective NMDA receptor antagonists are not available for clinical pain management. However several compounds like magnesium sulphate and ketamine approved for use in humans for other indications have significant NMDA receptor blocking properties. The dose of $Mgso_4$ was based on data from previous human studies and rat models of postoperative pain.[4,17,42,43] Further dose response studies are required to determine whether large doses of intrathecal $MgSO_4$ can produce better potentiation of analgesia and reduction in analgesic requirement.[17,44] It is possible that effects of magnesium sulphate on NMDA receptor complex are weaker or they do not play an important role in maintenance of postoperative pain.[39] But

the super additive interaction of magnesium sulphate and ketamine is also reported.[41]

In present study mild sedation was observed in 56% subjects with $MgSO_4$, the patients were sleeping comfortably. The incidence was similar to that reported previously. The incidence of PONV was reduce by both IT clonidine and midazolam from reported 45% to 28% in both the groups.

Nausea and vomiting due to neostigmine is dose dependent, smaller dose can produce analgesia without nausea.[6,15,16,18] Eisenach et al ascribed the vomiting to the effect of neostigmine on brain.[13] The rostral spread to brainstem may contribute to the severity of adverse effects (bradycardia, nausea and vomiting, urinary retention, motor weakness, etc). The side effects occur 30-60 minutes after injection. To minimize the cephalad spread, injection of neostigmine in hyperbaric solution and maintaining head up position is recommended.[13,19,21,31] The hyperbaric solution produced analgesia limited to lower limbs without producing nausea and vomiting.[15] Similarly in our study the risk of nausea and vomiting could be minimized by using neostigmine with hyperbaric bupivacaine and maintaining head up position. Neither midazolam nor clonidine was associated with bowel/bladder dysfunction or neurological deficit until discharge. We did not observe any other central cholinergic effects of neostigmine like hallucination, agitation, mydriasis, nystagmus, pruritus, increased sweating or salivation. Long term neurological signs and symptoms could not be detected as the study period was short and difficulty in establishing neurotoxicity on clinical grounds. Also the study is not adequately powered to comment conclusively on neurotoxicity. Further trial using larger sample size is recommended.

Clinical Implications

Although it is not registered for this purpose, intrathecal midazolam is used along with local anaesthetic for SA and postoperative analgesia in many institutions in India. These effects are valuable in prolonged surgeries. There is no serious side effect, technical challenge or unpredictable pharmacological risk.

CONCLUSION

From this study, we can conclude that gentamicin is more nephrotoxic and causes greater fall in creatinine clearance although the dose of gentamicin administered is much lower compared to amikacin. Further, the nephrotoxicity is accentuated by increasing age factor in both groups but variation in gender was seen among them. Gentamicin causes significantly higher degree of nephrotoxicity in male compared to female. Addition of intrathecal midazolam, neostigmine and clonidine to hyperbaric bupivacaine prolong spinal sensory block and postoperative analgesia. Analgesia with clonidine is minor and short lived associated with some bradycardia. Intrathecal midazolam provides superior analgesia without clinically relevant side effects.

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