International Journal of Research in Medical Sciences
Dubey R et al. Int J Res Med Sci. 2017 Mar;5(3):863-870
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012
DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20170626

Original Research Article

A comparative study on post-operative analgesic effect by intrathecal midazolam and neostigmine with control group

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Received: 26 January 2017
Revised: 13 February 2017
Accepted: 13 February 2017

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ABSTRACT

Background: Pain happens to be the most common suffering during postoperative period, which is not generally effectively treated. There is good evidence in literature that addition of midazolam to spinal bupivacaine improved postoperative analgesia when compared to spinal bupivacaine alone. Neostigmine represents a novel approach to providing analgesia. Recent studies showed that intrathecal administration of various doses of neostigmine produces analgesia without neurotoxicity. The present study was undertaken to evaluate analgesic effects of intrathecal Midazolam and neostigmine.
Methods: The present study was carried out in the department of anaesthesiology, CCM medical college, Durg Chhattisgarh, India during study period August 2015 to July 2016. The study comprised of 60 patients undergoing surgery of lower abdomen below umbilicus (T10) and lower limbs. Patients of age Group between 20-60 years of age of either sex of ASA group I and II were included in the study. Pre-anesthetic evaluation was done prior to surgery. The patients were randomly divided into 3 groups of 20 patients each. Data was compiled in MS excel and checked for its completeness and correctness, then it was analyzed.
Results: Mean age in Group I was 39.3+1.5 years. in Group II was 37.8±11.7 years, in Group III was 42.2±13.7 years. In group I maximum 14 patients (70%) had analgesia of less than 4 hours. Mean duration of analgesia was 3.73±0.87 hours. In group II maximum 18 patients (90%) had analgesia 4-8 hours. The mean duration of analgesia was 6.34±1.28 hours. In group III 10 patients (50%) had analgesia of 4-8 hours and 10 patients (50%) had analgesia of 8-12 hours. The mean duration was 8.35±1.36. The difference in VAS score in group in group I and group III is significant. There was no statistically significant change in systolic blood pressure, diastolic blood pressure, Pulse rate & respiratory rate attributable to intrathecal Midazolam and neostigmine.
Conclusions: Addition of preservative free midazolam to inteathecal bupivacaine prolongs duration of effective analgesia as compared to bupivacaine alone without any side effects. Addition of preservative free neostigmine to intrathecal bupivacaine prolongs duration of effective analgesia and sensory and motor block without any significant side effects.

Keywords: Midazolam, Neostigmine, Pain, Post operation

INTRODUCTION

Pain happens to be the most common suffering during postoperative period, which is not generally effectively treated. The aim of postoperative pain treatment is to provide subjective comfort in addition to inhibiting trauma induced nociceptive impulses to blunt autonomic and somatic reflex response to pain and subsequently to enhance restoration of function by allowing the patients to breath, cough and move more easily. The real art of

medicine lies in the treatment of pain. Thus, an increasing number of patients have become more medically sophisticated and more likely to request specific modes of treatment. In recent year, the use of intrathecal /epidural drugs has been wide spread. Intrathecal morphine is considered to 'Gold standard' Decades of morphine use therapeutically and non-therapeutically have demonstrated sometimes poor benefit/risk ratio of this drug and thus led to search for new drugs. Recent research has focused on non-opioid spinal receptor that inhibit the transmission the pain signals. There is ample evidence to show that α_2 noradrenergic receptors, NMDA receptors, γ-aminobutyric acid (GABAA) receptors and muscarinic (M1 and M2) receptors atc. are involved in nociceptive mechanisms.[1,2]

Benzodiazepine receptors are present thouroughout the nervous system including spinal cord. Benzodiazepines affect the transmission of nociceptive impulses at the spinal cord by modulating GABAA receptors (Serrao et al. Of the clinically available benzodiazepine only midazolam is water soluble and its tissue irritability is not significant. Since early 1980's intrathecal has been shown to produce antinociceptive effects in animals and humans (C.S. Goodchild). There is good evidence in literature that addition of midazolam to spinal bupivacaine improved postoperative analgesia when compared to spinal bupivacaine alone. Neostigmine represents a novel approach to providing analgesia. Auto radiographic studies have demonstrated muscarinic (M1 and M 2 receptors) in dorsal horn i.e. lamina II and III of spinal cord (Seybold et al,). Neostigmine inhibit breakdown of endogenous spinal neurotransmitter acetylcholine, which has been shown to cause analgesia. Recent animal and human studies showed that intrathecal administration of various doses of neostigmine produces analgesia without neurotoxicity.[3-7] The present study was undertaken to evaluate analgesic effects of intrathecal Midazolam and neostigmine.

METHODS

The present study was carried out in the department of anaesthesiology, CCM Medical College, Durg Chhattisgarh, India during study period August 2015 to July 2016. The study comprised of 60 patients undergoing surgery of lower abdomen below umbilicus (T10) and lower limbs. Patients of age Group between 20-60 years of age of either sex of ASA group I and II were included in the study.

Exclusion criteria

- Patients refusal
- Patients having haemorrhagic disorders
- Any sepsis at the site of lumbar puncture or any spinal deformity
- Severe hypotensive or hypertensive states
- Patients with raised intracranial tension, chouronic headache and chouronic backache
- Known hypersensitivity to local anaesthetic drug
- Patients having systemic diseases like neurological, cardiac, respiratory, renal, hepatic or endocrinal.

Pre-anesthetic evaluation was done prior to surgery. Thorough physical and systemic examination was performed to rule out any disorder the cardiovascular, respiratory, renal, hepatic endocrinal and neurological systems.

The routine investigation done like Hb, TLC, DLC, blood sugar, blood urea, urine biochemical and microscopic examination, serum creatinine, serum bilirubin, ECG chest X-ray and other specific investigation if required per their relevance. The patients were randomly divided into 3 groups of 20 patients each.

Table 1: Drug received in different groups.

Group	Drug received
I	[Control group] Patients received only inj. Bupivacaine 15 mg intrathecally.
II	Patients received inj. Bupivacaine 15 mg with inj. Midazolom 2 mg intrathecally.
III	Patients received inj. Bupivacaine 15 mg with inj. Neostigmine Methyl Sulphate 100 µg intrathecally.

All the patients were informed about visual analogue scale preoperatively. Autoclaved spinal set and anaesthetic drugs were arranged as appropriate. All the study drugs used intrathecally were preservative free. Before starting anesthesia, all relevant things were kept ready for any emergency during the intraoperative period.

The technique was explained to every patient. A written consent was obtained priorly. All patients received oral Alprazolam 0.25 mg night before surgery. After shifting the patient on operating table preoperative vital parameters were recorded. 20G IV canula was secured. All patients were given 1000 ml of compound sodium lactate solution as a circulatory preload followed by an infusion of 6-10 ml/Kg/hour. Monitors were attached before performing procedure

Patient was positioned in lateral or sitting position as per patient's comfort on operation table. Under all aseptic precautions lumbar puncture was done with 26G quinckes spinal needle at L3-L4 inter vertebral space by using a midline technique. When the free flow of cerebrospinal fluid occurred, syringe containing the injection drug was attached to spinal needle hub tightly; a volume of cerebrospinal fluid aspirated and then the study solution was injected at a slow rate (0.25 ml/s). Immediately after injection, the patients were placed supine; a pillow was kept under shoulder and eyes of patient covered. Time of injection was noted. Other supportive management was also done during the procedures if needed.

Following observations were recorded

- Time of onset of sensory anaesthesia
- Time of onset of motor block
- Level of sensory block
- Duration of surgery
- Duration of motor block
- Duration of sensory block
- Assessment of pain relief
- Duration of absolute analgesia
- Duration of effective analgesia
- Vital parameters
- Any adverse effects

The assessment of results of both groups was done per the following parameter

- Duration of absolute and effective analgesia
- Degree of analgesia (in terms of onset and trends of VAS till rescue analgesia)
- Effects of spinal anesthesia (in terms of onset and duration of sensory and motor block and complication intra operatively)
- Vigilant monitoring was done to notice any deviation from base line values of pulse rate, respiratory rate and blood pressure (both systolic and diastolic) and Spo2 level.
- Incidence of complications.

The results were analysed by unpaired 't' test and p value.

$$t=\frac{\overline{X_1}-\overline{X_2}}{SE}$$

$(\overline{X_1})$ = Mean of firs set of observation

$(\overline{X_2})$ = Mean of second set of observation

SE = Standard Error

If p value is <0.05 then difference between the two set of observation will be considered significant; if p value is <0.001 then it is considered as highly significant; if p value is >0.05 then it is considered as non-significant.

RESULTS

Table 2 shows age wise distribution of cases. Mean age in Group I was 39.3±1.5 yrs. in Group II was 37.8±11.7 yrs, in Group III was 42.2±13.7 yrs.

Table 2: Age wise distribution of patients.

Age	Group I	Group II	Group III
Mean± SD	39.3±1.5	37.8±11.7	42.2±13.7

Table 3 shows onset of sensory block. Slowest onset time (from 0-1 min) was noted in 1 case (5%) in group I, 3 cases (15%) in group II and 2 case (10%) in group III. Longest onset time (7-8 min) was noted in 1 case (5%) in group I. Patients receiving study drugs (group II and III) has significantly rapid onset of sensory block as compared to control group (p<0.05).

Table 3: Onset of sensory block.

Onset time	Group I	Group II	Group III
Mean±SD	4.02±1.23	2.15±1.12	2.02±0.76
Significance test between group		I and II	I and III
t value		4.259	4.877
p value		<0.05	<0.05

Table 4: Onset of motor block.

Onset time	Group I	Group II	Group III
Mean±SD	5.07±1.32	3.03±1.09	2.72±0.89
Significance Test between group		I and II	I and III
t value		4.797	5.925
p value		<0.05	<0.05

The patients of group II and III had significantly rapid onset of motor block as compared to group I. (p<0.05) (Table 4).

Table 5: Duration of motor block.

Onset time (in time)	Group I		Group II		Group III	
	No	%	No	%	No	%
90-120	3	15%	1	5%	0	0%
120-150	5	25%	2	10%	0	0%
150-180	2	10%	3	15%	0	0%
180-210	4	20%	10	50%	0	0%
210-240	2	10%	2	10%	2	10%
240-270	1	5%	1	5%	5	25%
270-300	3	15%	1	5%	12	60%
>300	0	05%	0	0%	1	5%
Mean±SD	190.5±57.2		191.5±35.3		372.5±27.6	
Significance test between group			I and II		I and III	
t value			0.061		5.620	
p value			>0.05		<0.05	

The mean duration of motor block in group I was 190.5±57.2 min (3.17±0.95 hours), in group II was 191.5±35.3 min (3.19±0.95 hours) and in group III was 372.5±27.6 min (4.54±0.46 hours). In group III maximum 12 patients (60%) had motor black between 4.5 to 5 hours (270-300 min). Patients receiving intrathecalnoestigmine had significantly prolonged motor block (Table 5).

In group I, mean duration of sensory block was 208.8±58.0 min. In group II mean duration of sensory block was 231.3±38.0 min which was significantly prolong. Maximum 8 patients (40%) had sensory block 210-240 min (p<0.05). In group III mean duration of

sensory block was 280.5±28.6 min which was significantly prolong. maximum 8 patients (40%) had sensory block 270- 300 min (p<0.05) (Table 6).

Table 6: Duration of sensory block.

Duration (in min)	Group I		Group II		Group III	
	No	%	No	%	No	%
90-120	0	0%	0	0%	0	0%
120-150	5	25%	1	5%	0	0%
150-180	3	15%	1	5%	0	0%
180-210	4	20%	3	15%	1	5%
210-240	4	20%	8	40%	1	5%
240-270	1	5%	4	20%	5	25%
270-300	1	5%	3	15%	8	40%
>300	2	10%	0	0%	5	25%
Mean±SD	208.8±58.0		231.3±38.0		280.5±28.6	
Significance test between group			I and II		I and III	
t value			2.458		4.835	
p value			>0.05		<0.05	

Table shows duration of absolute analgesia which was calculated from the time of spinal to the first complaint of pain. In group I maximum 14 patients (70%) had analgesia of less than 4 hours. Mean duration of analgesia was 3.73±0.87 hours. In group II maximum 18 patients (90%) had analgesia 4-8 hours. The mean duration of analgesia was 6.34±1.28 hours. In group III 10 patients (50%) had analgesia of 4-8 hours and 10 patients (50%) had analgesia of 8-12 hours. The mean duration was 8.35±1.36 (Table 7).

Table 8 shows distribution of patients per the duration of effective analgesia which was calculated from the time of spinal to first rescue of analgesia. In group I maximum 11 patients (55%) had analgesia less than 4 hours, mean duration was 3.91±0.88 hours. In group II maximum 15 patients (75%) had analgesia of 4-8 hours. The mean duration of effective analgesia was 7.21±1.31 hours. In group III maximum 16 patients (80%) had analgesia of 8-12 hours. The mean duration of analgesia was 9.78±1.43 hours.

Table 7: Duration of absolute analgesia.

Duration (in hours.)	Group I		Group II		Group III	
	No	%	No	%	No	%
0-4	14	70%	0	0%	0	0%
4-8	6	25%	18	90%	10	50%
8-12	0	0%	2	10%	10	50%
12-16	0	0%	0	0%	0	0%
16-20	0	0%	0	0%	0	0%
20-24	0	0%	0	0%	0	0%
>24	0	0%	0	0%	0q	0%
Mean±SD	3.73±0.87		6.34±1.28		8.35±1.36	
Significance test between group			I and II		I and III	
t value			7.312		12.449	
p value			<0.001		<0.001	

Table 8: Duration of effective analgesia.

Duration (in hours.)	Group I		Group II		Group III	
	No	%	No	%	No	%
0-4	11	55%	0	0%	0	0%
4-8	9	45%	15	75%	3	15%
8-12	0	0%	5	25%	16	80%
12-16	0	0%	0	0%	1	5%
16-20	0	0%	0	0%	0	0%
20-24	0	0%	0	0%	0	0%
>24	0	0%	0	0%	0	0%
Mean±SD	3.91±0.88		7.21±1.31		9.78±1.43	
Significance test between group			I and II		I and III	
t value			9.055		15.103	
p value			<0.001		<0.001	

Table 9: VAS score.

Mean Vas score	Group I	Group II	Group III
At Ist complaint of pain	7.62±2.12	5.51±2.24	3.12±0.92
At Ist rescue of analgesia	8.46±2.31	6.79±2.12	5.25±1.12
Over all 24 hours	6.95±4.52	5.62±3.78	3.58±2.12
Significance test between group		**I and II**	**I and III**
t value		2.021	4.014
p value		>0.05	<0.05

Table 9 shows VAS score at 1st complaint of pain at 1st rescue of analgesia and over all 24 hours mean VAS score. In group II mean VAS score at 1st complaint of pain was 5.51±2.24 and at 1st rescue of analgesia is 6.79±2.12 t value was 2.021 which is just significant. Over all 24 hours VAS score in group II was 5.62±3.79. t value was 1.214 and p >0.05 which is not significant. The difference in over all 24 hours VAS score in control group and group II (midazolam group) is not significant. In group III mean VAS score at 1st complaint of pain was 3.12±0.92, at 1st rescue of analgesia was 5.25±1.12 and overall 24 hour VAS score was 3.58±2.12 (p<0.05). The

difference in VAS score in group in group I and group III is significant. There was no statistically significant change in systolic blood pressure, diastolic blood pressure, Pulse rate and respiratory rate attributable to intrathecal Midazolam and neostigmine. (p>0.05). Spo2 remains 98 to 100 %in all the patients thouroughout intraoperative and post-operative period (Table 10-13).

Table 10: Changes in systolic blood pressure.

Time (SBP in mm of Hg)	G I Mean±SD	G II Mean±SD	t test GI and G II	G III Mean±SD	t test GI and G III
Pre-operative	124.60±7.51	125.80±6.79	>0.05	124.40±5.95	>0.05
5 min after SAB	120.60±4.82	120.80±4.07	>0.05	120.70±3.65	>0.05
15 min after SAB	107.90±2.79	107.80±2.75	>0.05	108.50±2.18	>0.05
30 min after SAB	108.70±7.68	108.20±7.79	>0.05	107.40±7.88	>0.05
1 hour after SAB	113.60±4.18	113.40±4.29	>0.05	113.00±4.12	>0.05
6 hour after SAB	117.10±4.17	117.90±3.59	>0.05	115.80±4.08	>0.05
12 hour after SAB	121.20±3.12	121.30±2.12	>0.05	120.60±2.76	>0.05
18 hour after SAB	123.90±0.00	124.00±3.58	>0.05	123.00±3.32	>0.05
24 hour after SAB	122.10±3.43	121.90±3.43	>0.05	121.70±2.98	>0.05

Table 11: Changes in diastolic blood pressure.

Time	G I Mean±SD	G II Mean±SD	t test GI and G II	G III Mean±SD	t test GI and G III
Pre operative	80.40±4.59	81.30±4.44	>0.05	80.50±3.57	>0.05
5 min after SAB	79.30±2.92	79.70±2.03	>0.05	79.60±1.74	>0.05
15 min after SAB	68.60±1.43	68.80±0.98	>0.05	69.00±1.00	>0.05
30 min after SAB	71.80±2.82	71.90±3.00	>0.05	71.30±2.70	>0.05
1 hour after SAB	74.30±3.48	74.20±3.63	>0.05	73.70±3.45	>0.05
6 hour after SAB	74.40±2.91	77.00±3.00	>0.05	77.00±3.00	>0.05
12 hour after SAB	79.80±2.18	80.00±1.67	>0.05	80.10±1.73	>0.05
18 hour after SAB	79.80±1.90	79.70±2.03	>0.05	79.60±1.74	>0.05
24 hour after SAB	80.10±2.41	80.03±2.78	>0.05	79.90±2.23	>0.05

Table 12: Changes is pulse rate.

Time	G I Mean±SD	G II Mean±SD	t test GI and G II	G III Mean±SD	t test GI and G III
Pre operative	79.40±5.87	78.80±6.01	>0.05	77.80±5.44	>0.05
5 min after SAB	81.10±2.57	80.70±2.47	>0.05	80.60±2.54	>0.05
15 min after SAB	74.60±2.46	74.20±2.36	>0.05	74.20±2.27	>0.05
30 min after SAB	75.20±5.64	75.40±5.18	>0.05	74.20±5.29	>0.05
1 hour after SAB	75.90±4.61	75.80±4.31	>0.05	75.00±4.49	>0.05
6 hour after SAB	80.60±2.01	50.20±1.89	>0.05	8.30±2.12	>0.05
12 hour after SAB	79.00±2.24	78.00±2.37	>0.05	79.00±2.65	>0.05
18 hour after SAB	80.00±3.52	70.00±4.07	>0.05	79.00±3.87	>0.05
24 hour after SAB	80.10±3.30	79.20±3.74	>0.05	79.20±3.54	>0.05

Table 14 shows distribution of patients according to the adverse effects noted after giving spinal anaesthesia in all 3 groups.

Nausea and vomiting was seen in 1 patient (5%) of group I and 12 patients (60%) of group III. While in group II no patient complained of nausea or vomiting. Urinary retention was seen in 1 patient (5%) of group I, II and none in group III. Shivering was seen in 2 patients (10%) of group I and 1 patient (5%) of group III. Dizziness was seen in 1 patient (5%) of group II only. No patient had Headache or backache or dryness of mouth.

Table 13: Changes in respiratory rate.

Time	G I	G II	t test GI & G II	G III	t test GI & G III
	Mean±SD	Mean±SD		Mean±SD	
Pre operative	15.20±1.12	14.90±0.89	>0.05	15.00±0.89	>0.05
5 min after SAB	16.70±1.14	16.65±1.11	>0.05	16.60±1.11	>0.05
15 min after SAB	17.20±1.33	16.90±1.34	>0.05	16.90±1.18	>0.05
30 min after SAB	15.50±1.07	15.25±0.89	>0.05	15.20±0.87	>0.05
1 hour after SAB	15.70±1.45	15.40±1.28	>0.05	16.00±1.41	>0.05
6 hour after SAB	15.90±1.30	15.30±1.10	>0.05	15.80±1.44	>0.05
12 hour after SAB	16.10±0.94	15.70±0.64	>0.05	15.80±0.81	>0.05
18 hour after SAB	15.90±1.34	15.55±1.16	>0.05	16.10 +1.30	>0.05
24 hour after SAB	15.55±1.02	15.35±0.79	>0.05	15.35±0.55	>0.05

Table 14: Side effect of drugs.

Side Effect	Group I		Group II		Group III	
	No	%	No	%	No	%
Nausea & Vomiting	1	5%	0	0%	12	60%
Hypotension	0	0%	0	0%	0	0%
Brady Cardia	0	0%	0	0%	0	0%
Shivering	2	10%	0	0%	1	5%
Res. Depression	0	0%	0	0%	0	0%
dizziness	0	0%	1	5%	0	0%
pruritus	0	0%	0	0%	0	0%
Urinary retention	1	5%	1	5%	0	0%
Dryness of mouth	0	0%	0	0%	0	0%
Headache	0	0%	0	0%	0	0%
Backache	0	0%	0	0%	0	0%
Significance test between group			I & II		I & III	
t value			9.055		15.103	
p value			<0.001		<0.001	

DISCUSSION

Patients received intrathecalmidazodam and neostigmine had significantly rapid onset of analgesia. ($p<0.05$) P.H. Tan et al observed onset of anaesthisia with tetracaine (15 mg) was 5.5+1.9 min., with tetracain + neostigmine 50 µg, it was 2.3+0.9 min and with tetracaine + neostigmine 100 µg onset of anaesthesia was 106+07 min. The onset was faster in added group (local anaesthetic + neostigmine) than local anaesthitic alone when given intrathecally. These results were like present study.[8]

Duration of sensory and motor block

Tan PH et al found that motor block was significantly prolonged when neostigmine 100 µg is added to tetracaine. Duration of block was 4.9±0.94 with tetracaine and 6.4+1.9 hour with tetracaine + neostigmine. Ping Heng Tan et al found that addition of 50 µg neostigmine prolongs motor block from spinal bupivacaine via acetycholine mediated reduction in motor neuron outflow. The duration of motor block with 15 mg bupivacaine is 4.7+0.3 hour and with bupivacaine +50 µg neostigmine is 5.7+0.46hour.[8,9]

Batra YK et al found that addition of 2 mg midazodam to spinal bupivacaine increased the duration of sensory analgesia from 229.8+41.4 min. to 267.6+67.38 min.[10] The results of our study are similar to studies of P.H. Tan et al, Ping Heng Tan et al, Batra YK et al, Mahima Gupta M, Shailaja S, Hegde KS.[8-11]

Duration of analgesia

The duration of analgesia is significantly prolonged in group II and III patients ($p<0.05$). M.H. Kim and Y.M. Lee used 1 mg and 2 mg midazolam with bupivacaine on 45 patients undergoing haemorrhoidectomy. The duration of analgesia with bupivacaine was 3.99±0.78 hours, with1 mg midazolam 6.02±1.49 hours and with 2 mg of midazolam the duration of analgesia was 8.37±2.51 hours. The results of their study are like present study.[12] Batra YK et al found that addition of midazolam (2 hours) to bupivacaine produces better postoperative

analgesia (upto 6 hours) without prolonging recovery, which is similar to our study.[10]

Tan PH, Kuo JH et al observed that intrathecal neostigmine 50µg and 100 µg provided analgesia lasting for 6-9 hours. Addition of 100 µg of neostigmine to teracaine provided absolute analgesia up to average 523 min. and effective analgesia up to 12.3±3.5 hours. These results are like present study. Ping Heng Tan et al compared the analgesic effect of intrathecal morphine and neostigmine. They found the duration of absolute analgesia was 615.3+64.7 min. in morphine group and 443.2+25 min. (i.e. 7.55±0.59 hours.) in neostigmine group. These results are similar to present study.[8,9]

Degree of analgesia

Quality of analgesia was assessed by 10 cm visual analogue scale which was explained to the patients before they were taken for operation. The difference in mean of VAS score between group I and II was just significant at 1st complaint of pain and at 1st rescue of analgesia and not significant in overall 24 hours ($p>0.05$). Patients of group III and IV had significantly lowered VAS score) $p<0.05$). Kim MH, et al found no significant difference in VAS score after administration of midazolam.[12] Batra YK et al found a significantly higher VAS score (6.6+3.05 to 55.00+0.00) in bupivacaine group from 90 to 360 min. as compared to midazolam group during this period (1.43+2.90 to 15.00+5.53). VAS score was assessed on 100mm scale in their study.[10]

Degree of analgesia

Quality of analgesia was assessed by 10 cm visual analogue scale which was explained to the patients before they were taken for operation. The difference in mean of VAS score between group I and II was just significant at 1st complaint of pain and at 1st rescue of analgesia and not significant in overall 24 hours ($p>0.05$). Patients of group III had significantly lowered VAS score ($p<0.05$). Kim MH, et al found no significant difference in VAS score after administration of midazolam.[12]

Ping Heng Tan et al found that 24 hours. VAS score was higher for patient in saline group (i.e. 3.6+0.9) than in patients in morphine (1.6 + 0.5) or neostigmine (2.2±0.7) group.[8] Lauretti GR found that all doses of intrathecal neostigmine (25µg to 75 µg) reduced VAS score in the recovery room to a similar degree.[13] P.H. Tan et al found overall 24 hours VAS score was lower in neostigmine group (1.8±05) as compared to tetracaine group (3.7±0.8).[8] Chan Jong et al found that VAS scores were significantly lower after intrathecal neostigmine administration.[14]

Effects on vital parameters

There was no statistically significant change in pulse rate, blood pressure and respiratory rate attributable to intrathecal Midazolam and neostigmine during intra operative and post-operative period Kim MH, et al found no episodes of hypotension, bradycardia, sedation or dizziness in any patient receiving intrathecal midazolam.[12] 12 patients (60%) of neostigmine group (group III) reported nausea and vomiting which was most significant side effect of this study and 1 patient (5%) of group I (control group) complained of nausea and vomiting. Incidence of nausea and vomiting was very high in group III (neostigmine group) which was not effectively controlled by inj. metoclapramide or ordensetron and resolve with thime as the effect of intrathecal neostigmine weaned off. This adverse effect probably caused by cephalad migration of neostigmine to the brain stem. These findings are comparable with the study of Tan PH et al who compared intrathecal morphine and neostigmine. In their study 7 patients out of 20 reported nausea/vomiting after intrathecal neostigmine and 14 patients out of 20 reported pruritus after intrathecal morphine administration.[8,9]

Lauretti GR found nausea and vomiting in 61% patients in their study on intrathecal neostigmine.[13] Liu SS et al found that addition of neostigmine to spinal bupivacaine did not affect hemodynamic (H.R. and systolic blood pressure) or respiratory (respiratory rate, end tidal CO_2, pulse oximeter saturation) parameter. They also found that addition of neostigmine to spinal bupivacaine produced dose dependent increase in incidence of nausea and vomiting after administration of 5 µg intrathecal neostigmine.[15] Chan Jong Chung et al found nausea and vomiting in 73% patients in their study on intrathecal neostigmine.[14] W. Thomas et al in their study on intrathecal buprenorphine for postoperative pain relief found nausea in 10% patients, vomiting in 13.3% patients and urinary retention in 26.7% patients.[16] Kim MH, et al in their study on intrathecal midazolam for postoperative pain relief found no episodes of bradycardia, hypotension, and sedation of dizziness in any patients. 3 of 15 patients developed urinary retention, which are similar to present study.[12]

CONCLUSION

Addition of preservative free midazolam to inteathecal bupivacaine prolongs duration of effective analgesia as compared to bupivacaine alone without any side effects. Addition of preservative free neostigmine to intrathecal bupivacaine prolongs duration of effective analgesia and sensory and motor block without any significant side effects. Adequate motor relaxation with sensory block gives a safe edge in situations where there is unexpected prolongation of surgical procedure require. On the basis of observation and results of our study we conclude that both the drugs have been found to be superior for postoperative analgesia as compared to control group.

ACKNOWLEDGEMENTS

Authors would like to thank all the faculty and technical staff members of the Department of Anesthesiology, CCM Medical College, Durg Chhattisgarh, India, for their immense cooperation and support during the entire study period.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

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Cite this article as: Dubey R, Ali R, Vachhani R, Baghel N. A comparative study on post-operative analgesic effect by intrathecal midazolam and neostigmine with control group. Int J Res Med Sci 2017;5:863-70.