Original Research Paper

Volume-7 | Issue-11 | November-2017 | ISSN - 2249-555X | IF : 4.894 | IC Value : 79.96

Anesthesiology

EVALUATION AND COMPARISON OF CLINICAL EFFICACY, POST-OPERATIVE ANALGESIA AND HEMODYNAMIC EFFECT OF INTRATHECAL HYPERBARIC BUPIVICAINE VERSUS INTRATHECAL HYPERBARIC BUPIVICAINE PLUS NEOSTIGMINE DURING LOWER ABDOMINAL AND LOWER LIMB SURGERIES.

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ABSTRACT

Background and Aims : Pain management especially in the post-operative period is an essential practice in the field of anaesthesiology. Providing purposeful and proper post-operative analgesia has become a popular practice for the sake of patient comfort. Neural blockade is commonly used to control post-operative pain.Additives like systemic benzodiazepines, synthetic and semi-synthetic opiods are simple, effective and commonly adopted way of post-operative pain relief.In this study we evaluated & compared clinical efficacy, post-operative analgesia and hemodynamic effect of intrathecal hyperbaric bupivicaine versus intrathecal hyperbaric bupivicaine plus neostigmine during lower abdominal and lower limb surgeries.

Methods: This was a Randomised Control trial.The patients were randomly assigned to one of the two groups with 30 patients each. Allocation into groups was done by using sealed envelopes.

Group C received intrathecally 2.5 ml of 0.5% of hyperbaric bupivacaine plus 1ml of normal saline.Group N received intrathecally 2.5ml of 0.5% hyperbaric bupivacaine plus 50 mcg of neostigmine (1ml) - Study Group. and they were compared with regards to clinical efficacy, post-operative analgesia , haemodynamic stability and side effects .

Results : Addition of 50 µg neostigmine significantly decreased the onset time of sensory analgesia (Group N 1.48±0.425 , Group C 2.85±0.671, *P* value as <0.05) & the Mean Time taken to achieve maximum level of sensory block(Group N 6.40±1.029 , Group C 7.53±1.167 , *P* value as <0.05).Duration of sensory regression to S1 level was 215.13±26.23 in Control group as compared to 272.87±59.52 in study group, p value = 0.001 . The mean duration of analgesia for control group was 223.80±42.302 min and for study group 462.70± 38.587 min.Side effects such as nausea & vomiting , shivering ,Vasopressor & anti-emetic requirement were comparable in both group & insignificant statistically.

Conclusions : 50mcg neostigmine seems to be an attractive alternative as an adjuvant to spinal bupivacaine in surgical procedures.Significant prolongation of analgesia & adequate motor relaxation without any side effects gives a safe edge in situations where there is unexpected prolongation of surgical procedure.

KEYWORDS : Post-op Analgesia, bromage scale,hyperbaric bupivacaine, neostigmine

INTRODUCTION

Pain is the most common symptom that brings patients to see a physician. Pain is not just a sensory modality but is an experience. The International Association for the Study of Pain (IASP)[1] defines pain as an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. This definition recognizes the interplay between emotional and psychological components. The response to pain can be highly variable among persons as well as in the same person at different times.

Pain management especially in the post-operative period is an essential practice in the field of anaesthesiology. Providing purposeful and proper post-operative analgesia has become a popular practice for the sake of patient comfort.

Various methods of post-operative pain relief are available:

1) Epidural catheter, peripheral nerve blocks, local anaesthetic drug infiltration at the surgical site.

Additives like systemic benzodiazepines, synthetic and semi-synthetic opiods are simple, effective and commonly adopted way of post-operative pain relief. Neural blockade is one of the answers to control post-operative pain .Neostigmine is universally used reversal agent whose post-operative pain relief property was first described by Naguib &Yaksh et al[2] in 1942 .Intrathecal neostigmine represents one of the promising methods of providing post-operative analgesia .Neostigmine is a synthetic quaternary ammonium compound. It is an anticholinesteras agent, which inhibits the breakdown of acetylcholine by competing with acetylcholine for the attachment of acetyl cholinesterase, as a result acetylcholine accumulates at cholinergic synapses and its effects are prolonged and exaggerated. Spinal neostigmine apparently activates descending pain inhibitory systems that rely on a spinal cholinergic interneuron, probably exacerbating a cholinergic tonus that is already activated during the post-operative period and seems to be extremely efficient for alleviating somatic pain. Neostigmine is being routinely used to provide post-operative analgesia**.** Neostigmine offers several advantages, easy availability and cost effectiveness to the patient, reliable and durable post-operative analgesia, availability of preservative free drug, no untoward side effects like respiratory depression, pruritis and drowsiness as experienced with intrathecal narcotics.

After extensive trials in animals regarding the efficacy and safety, it was tested on human volunteers. After its efficacy and safety was proved in human volunteers, it is being routinely used to provide postoperative analgesia in patients.

- Neostigmine offers several advantages such as:
- Easy availability and cost effectiveness to the patients
- Reliable and durable postoperative analgesia
- Availability of preservative free drugs
- No untoward side effects like respiratory depression, pruritus and drowsiness as experienced with intrathecal narcotics.

AIMS AND OBJECTIVE

1. To assess efficacy of intrathecal neostigmine and hyperbaric bupivicaine.
2. To evaluate and compare the post-operative analgesic effect of hyperbaric bupivicaine and hyperbaric bupivicaine plus neostigmine.
3. To assess the duration of analgesia, cumulative analgesia and time of rescue analgesia.
4. To evaluate and compare complications and side effects related to the use of hyperbaric bupivicaine and hyperbaric bupivicaine plus neostigmine.

MATERIALS AND METHODS

STUDY DESIGN:

Randomised Control trial.

SAMPLE SIZE

The patients were randomly assigned to one of the two groups with 30 patients each. Allocation into groups was done by using sealed envelopes.

Group C received intrathecally 2.5 ml of 0.5% of hyperbaric bupivacaine plus 1ml of normal saline. - Control Group.

Group N received intrathecally 2.5ml of 0.5% hyperbaric bupivacaine plus 50 mcg of neostigmine (1ml) - Study Group.

DURATION OF STUDY:

2013-2014

PLACE OF STUDY

The study was conducted in the Department of Anesthesia,Santosh Medical College and Hospital, Ghaziabad, U.P.

INCLUSION CRITERIA

1. ASA physical status 1 and 2 patients.
2. Age between 25 years to 60 years.
3. Patients undergoing lower abdominal and lower limb surgeries.
4. Provision of written consent.

EXCLUSION CRITERIA

1. Patient refusal to give consent
2. Inability to comply with study procedure e.g. language problems.
3. Non co-operative patient.
4. Patient with significant hepatic, renal or cardiovascular disease.
5. Patients with any history of bleeding abnormality or ulcer disease.
6. Allergy to either study drug.
7. A history of drug dependence.
8. Patient with contra-indications to spinal anaesthesia.

- Presence of neurological disease, infection of skin over the back
- potential risk of infection to the patient, surgeon's refusal to administration.
- Patients with abnormal bleeding and clotting parameters, liver disease.
- Anatomical difficulties that might make the administration of anaesthesia difficult. PRELOADING
- Patients were preloaded with 10 ml/kg body weight of Lactated ringer (crystalloid) solution.

METHODOLOGY

PRE-ANAESTHETIC CHECK UP

A thorough pre-anaesthetic evaluation will be done for all the patients. Routine hematological, biochemical and radiological investigations appropriate for the surgery will be done.

Preoperative pulse rate, blood pressure, respiratory rate and oxygen saturation were recorded on arrival of the patient in the operating room.Patients were given block in the left/right lateral position. The knees were flexed on the abdomen and the head was flexed with the chin to touch the chest.

The back was thoroughly cleaned with savlon, betadine, and spirit and draped with towels; 1-2 ml of 2% Lignocaine was given with disposable hypodermic needle at L3-L4 intervertebral space which was identified as the space just above or at the junction of line adjoining the highest points of the two iliac crests. 23G spinal needle with its bevel parallel to longitudinal dural fibres, was then advanced slowly to heighten the sense of tissue planes traversed and to prevent skewing of nerve roots until the characteristic change in resistance was noted as the needle pass through ligamentum flavum and dura. Correct placement of the tip of the needle into the subarachnoid space was confirmed by the free flow of CSF at the hub of the needle. Drug was injected into the subarachnoid space and the needle was thenwithdrawn. The patients were then placed in the supine position.
After injecting the drug, sensory and motor blockade were assessed and vital parameters noted. Pulse, non-invasive blood pressure and oxygen saturation were noted at 0 min (at the time of injecting the drug), 1 min, 2 min, 5 min, 10 min, and thereafter every 15 min till the surgery continued.

Onset the sensory block, maximum level of sensory block and time of achieving maximum level of sensory block was assessed by pin prick method.

ASSESSMENT OF PAIN RELIEF

According to Visual Linear Analogue Scale, pain score was recorded by the linear analogue method for assessing pain described by Ravil et al. This method includes of a 10cm line on a piece of a white paper on which a continuum of the patient's opinion on the severity of pain was represented. 10 was marked as the worst pain possible and 0 as the no pain at all.

VISUAL LINEAR ANALOGUE SCALE:

0-------1-------2-------3-------4-------5-------6-------7-------8------9-----
-10

The scoring was done every 15 min till rescue analgesic was administered. The duration of Effective Analgesia (Time taken from intrathecal injection to first dose of rescue analgesic) was recorded. Time taken from maximum level of sensory block to regression to S1 level was also recorded.

Motor blockade in the lower limbs was assessed using the Bromage Scale and modified by Axelsson and Windman of motor function.

Grade 0 = No paralysis
Grade 1 = Inability to raise extended leg
Grade 2 = Inability to flex the knee
Grade 3 = Inability to flex the ankle (complete motor block)

The quality of surgical analgesia was assessed by anaesthesiologist, the surgeon and the patient him/herself.

It was graded as:

Excellent- no supplementary drug required
Good- one bolus of rescue analgesic required
Poor- general anaesthesia required

Muscle relaxation was noted as:

Excellent- complete relaxation
Good- slight tightness
Poor- difficult to perform surgery

Hypotension was defined as a fall in systolic blood pressure of more of more than 30% from baseline value or a systolic pressure below 100 mmHg. It was managed initially by increasing the IV infusion and if not corrected, injection mephentermine 5 mg IV bolus was administered.

Observation & Results

The groups were comparable in terms of age, sex, weight, type and duration of the surgery,mean heart rate and mean arterial pressures in the intra and post operative periods .

Table 1

	Group N	Group C	P value
SENSORY BLOCK ONSET	1.48±0.425	2.85±0.671	<0.05
TIME TAKEN TO ACHIEVE MAXIMUM SENSORY BLOCK LEVEL	6.40±1.029	7.53±1.167	<0.05

Intrathecal Neostigmine in the dose of 50µg significantly decreases the onset time of sensory analgesia & the Mean Time taken to achieve maximum level of sensory block.

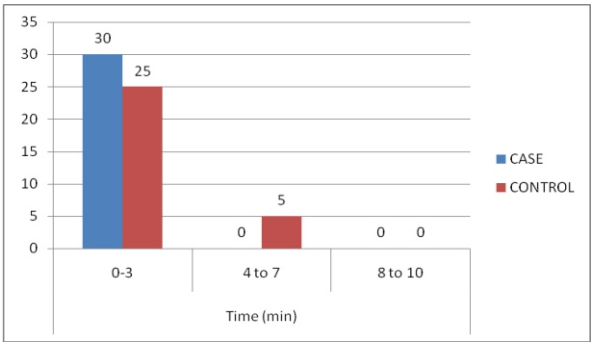

Fig 1 :SENSORY BLOCK ONSET

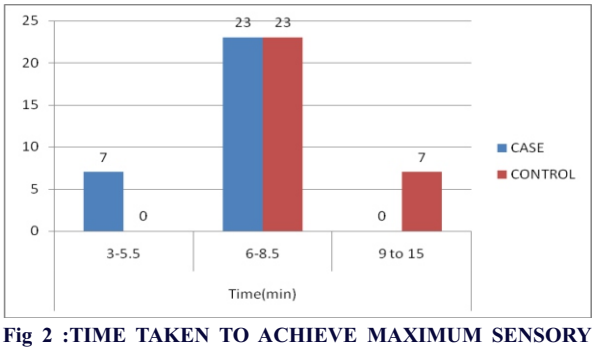

Fig 2 :TIME TAKEN TO ACHIEVE MAXIMUM SENSORY BLOCK LEVEL

Table 2 :VISUAL ANALOGUE SCORES: (MEAN ± STANDARD DEVIATION)

Group	VAS 15 min	VAS 45 min	VAS 90 min	VAS 180 min	VAS 360 min
N	0.00±0.00	0.00±0.00	0.00±0.00	0.43±0.679	3.70±1.055
C	0.00±0.00	0.00±0.00	0.03±0.183	1.03±1.129	4.67±0.959
P value	(1) >0.05(NS)	(1) >0.05(NS)	(0.892) >0.05(NS)	(0.014) <0.05(S)	(0.004) <0.05(S)

Mean VAS score in the control group remained zero for 45min after administration of the drug as compared to 90min in the study group. Mean VAS score at 180 min was 1.03± 1.129 for the control group as compared to 0.43± 0.679 for the study group. p value= 0.014 which was significant statistically.

Table 3 :VISUAL ANALOGUE SCORES

VAS Scale	VAS 15min		VAS 45min		VAS 90min		VAS 180min		VAS 360min
	N	C	N	C	N	C	N	C	N
Nil (0)	30	30	30	30	30	29	20	12	0
Mild (l-3)	0	0	0	0	0	1	10	17	12
Moderate (4-6)	0	0	0	0	0	0	0	1	18
Severe (7-10)	0	0	0	0	0	0	0	0	0

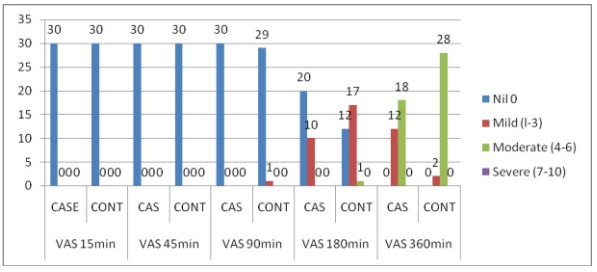

Fig 3 :VISUAL ANALOGUE SCORES

Table 4 :DURATION OF SENSORY REGRESSION TO S1 LEVEL

	Time (min)					
Group	90-139	140-189	190-239	240-289	290-339	340-420
N	1	1	5	10	11	2
C	0	6	17	7	0	0

P value =0.001
p<0.05 (Significant)

Duration of sensory regression to S1 level was 215.13±26.23 in Control group as compared to 272.87±59.52 in study group, p value = 0.001 this was significant statistically. The two segment regression of sensory block was significantly prolonged with addition of neostigmine.

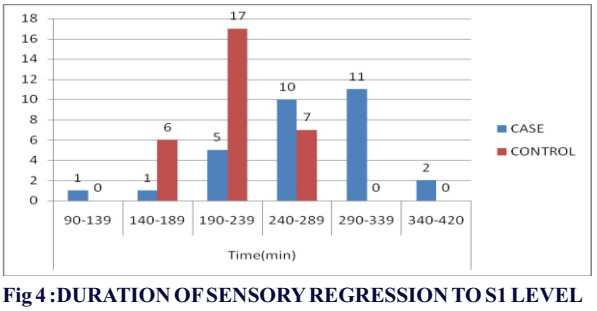

Fig 4 :DURATION OF SENSORY REGRESSION TO S1 LEVEL

Table 5 :ADMINISTRATION TIME (MIN) OF RESCUE ANALGESIA

Groups	TIME (MIN)							
	101-150	151-200	201-250	251-300	301-350	351-400	401-450	451-550
N	0	0	0	6	6	13	5	0
C	0	13	6	11	0	0	0	0

P value =0.001
p value<0.05(Significant)

The duration of analgesia which was assessed using VAS was observed in both the groups for 24 hours post-operative period. The mean duration of analgesia for control group was 223.80±42.302 min and for study group 462.70± 38.587 min. The statistical analysis showed that the time of duration of analgesia in study group was significantly more when compared to control group (p value =0.001).

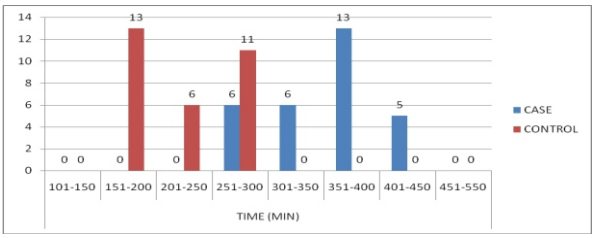

Fig 5 :ADMINISTRATION TIME (MIN) OF RESCUE ANALGESIA

All the patients in the study group had excellent quality of analgesia as compared to 96.66% in the control group. This was statistically not significant.

Grade of motor block according to the Bromage scale in study group was 3 in 100% & in control group 3 in 28 (93.33%) & 2 in 2 (6.66%); results were comparable and insignificant statistically.

As regards to the quality of relaxation,100% of the study group had excellent grade of relaxation as compared to the 96.66% patients of the control group, which was insignificant statistically and comparable.

SIDE EFEECTS such as NAUSEA & VOMITING , SHIVERING were comparable in both group & insignificant statistically.

Vasopressor & anti-emetic requirement in both groups were comparable in both group & insignificant statistically.

Discussion

This study "Evaluation and comparison of clinical efficacy, post-operative analgesia and hemodynamic effect of intrathecal hyperbaric bupivicaine versus intrathecal hyperbaric bupivicaine plus neostigmine during lower abdominal and lower limb surgeries. "was conducted in the Department of Anaesthesia, Santosh Medical College and Hospital, Ghaziabad, U.P.

After taking the informed consent, 60 patients of ASA 1 and ASA 2 were systematically randomized into 2 groups of 30 patients each.

Group A received intrathecally 2.5 ml of 0.5% of hyperbaric bupivacaine plus 1ml of normal saline. - Control Group.

Group B received intrathecally 2.5ml of 0.5% hyperbaric bupivacaine plus 50 mcg of neostigmine (1ml). - Study Group

The groups were comparable with respect to age, sex, weight and ASA physical status. There was no statistically significant difference in the type & duration of surgery.

The aim of our study is to produce a long lasting, continuous effective analgesia with minimum side effects. Commonly used local anaesthetics for intrathecal Anaesthesia are Lignocaine and Bupivacaine in India. Bupivacaine 0.5% heavy has more prolonged action compared to Lignocaine but the post-operative analgesic duration is limited. Other method of prolonging analgesia is using a continuous epidural analgesia. A intrathecal additive to these local anaesthetics forms a reliable and reproducible method of prolonged post operative analgesia. This technique being simple and less cumbersome has gained a wide acceptability. Commonly used intrathecal additives to local anaesthetics include Opioids, Clonidine, and Neostigmine.

Spinal administration of Neostigmine, an acetyl cholinesterase inhibitor, inhibits breakdown of the endogenous neurotransmitter acetylcholine, thereby inducing analgesia, hence it is an another alternative non opioid additive to local anaesthetics which lacks pruritis, respiratory depression, urinary retention , decreased motility of gut as their side effects.

Hemodynamic Effects:
Hemodynamic disturbances following intrathecal local anaesthetics depends upon: a) Segmental site of injection, b) Patient position, c) Rate of injection, d) Temperature of the injected solution, e) Preloading, f) The baricity of local anaesthetics employed, g) Adjuvant added intrathecally.
The present study did not show any significant changes on hemodynamic parameters. The mean heart rate and mean arterial pressures were comparable in both the groups in the intra and post operative periods and was found to be statistically insignificant. Concurs with Krukowski et al study, Hye MA et al study, Akinwale MO et al study, Dr. Yoganarasimha et al study.

Onset of sensory blockade:
In the present study, we noticed that in study Group onset time for sensory blockade was (1.48±0.425) compared to control Group (2.85±0.671), p value =0.001 (Significant), showing that neostigmine enhances action of spinally administered local anaesthetics. However, there was no clinically significant difference in the maximum level of sensory blockade achieved in both the groups (p =0.892) .Concurs with Dr. Yoganarasimha et al study which concluded mean onset time 2mins 42secs in control group, 1mins 38secs in study group.

Sensory regression to S1 level

Level of sensory block was assessed by pinprick method in post-operative period every 15 min and the time (in minutes) where the level of block regressed to S1 level were recorded. Duration of sensory regression to S1 level was 215.13±26.23 in Control group as compared to 272.87±59.52 in study group (p=0.001). This was significant statistically. The two segment regression of sensory block was significantly prolonged with addition of neostigmine. This result correlates with study of Pan PM1,et al significantly prolonged from 3.5 +/-1.1 in bupivacaine group compared to bupivacaine plus neostigmine group(7.1+/-1.6),Saini's et al , & Shobhana Gupta et al , (p<0.01).

Analgesia:-Duration and Quality

Duration of analgesia in the present study was considered as time from onset of sensory blockade to the onset of first pain of any degree and hence to the time of request for rescue analgesia, pain score was recorded by the linear analogue method for assessing pain described by Revil et al. This method includes the use of a 10 cm line on a piece of white paper on which a continuum of the patient opinion on the severity of pain was represented 10 was marked as the worst pain possible and 0 as no pain at all.

In our study, we found that the analgesic effect of intrathecal bupivacaine was potentiated by intrathecal neostigmine. The addition of 50 mcg of intrathecal neostigmine prolonged the postoperative analgesic effect of bupivacaine and also study group required less postoperative analgesic in the first 24 hours after surgery. Mean VAS score in the bupivacaine group remained zero for 45 min after administration of the drug as compared to 90 min of the neostigmine group. Mean VAS score at 180 min was 1.03±1.129 for the bupivacaine group as compared to 0.43±0.679 for the neostigmine .This was significant statistically (p value =0.014). At 360 min mean VAS score for the bupivacaine group was 4.67±0.959 and was 3.70±1.055 for the neostigmine group which was again significant statistically (p value =0.004). These results are comparable with the Tekin S et al (2006) , Lauretti GR(1997) et al , which concluded that addition of neostigmine to bupivicaine decreased overall 24 hrs visual analogue scale scores and the need for postoperative analgesics in 24 hrs (p<.001) Azim Honarmand et al (2009), Shobhana Gupta et al (2010) vas scores were significantly lower in 75µg group compared to 50µg group (p<0.01) , Yoganarasimha et al (2012) conducted a study to compare the effect of intrathecal neostigmine in the dose of 50 mcg plus 2.5 ml of 0.5% hyperbaric bupivicaine with 2.5ml of 0.5% hyperbaric bupivicaine in lower abdominal surgeries. They concluded that it provides long lasting analgesia upto 6 hours.

Akin Wale et al (2012), Jain A et al(2012) where addition of neostigmine increases the analgesic effects or provides a better post-operative analgesia.

In our study administration time of rescue analgesia was 223.8±42.302 in the control group while it was 462.70±38.58 in the study group which was higher in comparison. This was significant statistically (p value =0.001).

This clearly shows that, intrathecally administered neostigmine, significantly prolongs the duration of analgesia when administered with local anaesthetic agents.

Grade of motor block according to the Bromage scale in study group was grade 3 in 30(100%)& in control group grade 3 in 28 (93.33%) & grade 2 in 2 (6.66%); results were comparable and insignificant statistically.

Adverse effects:
Nausea and vomiting were considered as the minor side effects.

Krukowski et al (1997) found that the incidence of nausea and vomiting increases progressively with the increase in dose of intrathecal neostigmine and with 100µg doses, most of their patients had reported nausea and vomiting.

Lauretti et al (1998) conducted a multi center study of intrathecal neostigmine on 92 patients in doses of 25, 50 and 75µg posted for vaginal hysterectomy under spinal anaesthesia and found that only 75µg of intrathecal neostigmine increases nausea score.

The present study showed nausea and vomiting in 5 out of 30 patients belonging to study group with a dose of 50µg on intrathecal neostigmine. Nausea and vomiting incidences were controlled by Inj. Ondansetron 4 mg i.v. or Inj. Metoclopramide 10mg i.v.

CONCLUSION
The conclusions of our present study were as follows:

1. Intrathecal neostigmine in dose of 50µg can be used along with bupivacaine to provide safe, durable and predictable post-operative analgesia with minimal adverse effects in patients posted for lower abdominal, gynaecological and perineal surgeries.
2. Intrathecal Neostigmine in the dose of 50µg significantly decreases the onset time of sensory analgesia and motor blockade.
3. The duration and quality of post-operative analgesia following intrathecal administration of neostigmine was found to be statistically significant, thereby suggesting that 50µg of intrathecal neostigmine along with bupivacaine provided good post-operative analgesia. The requirement of rescue analgesia is reduced in neostigmine group
4. Intrathecal neostigmine in 50µg dose produces minimal nausea and vomiting which can be easily controlled with antiemetic such as ondansetron or metoclopramide.
5. In the dose of 50µg Neostigmine use intrathecally is not associated with any significant hemodynamic disturbance or respiratory depression.

In conclusion, 50mcg neostigmine seems to be an attractive alternative as an adjuvant to spinal bupivacaine in surgical procedures.

Significant prolongation of analgesia & adequate motor relaxation without any side effects gives a safe edge in situations where there is unexpected prolongation of surgical procedure.

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