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Evaluation of intrathecal neostigmine methylsulphate in different doses added to hyperbaric bupivacaine hydrochloride for postoperative analgesia

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Abstract

Pain is a natural protective gift but postoperative pain or its abnormal persistence, has a lot of harmful effects. Postoperative pain is associated with delayed recovery from surgery, hypoventilation and its consequences, delayed ambulation with increased thromboembolic phenomenon, increased sympathetic stimulation with consequent tachycardia, hypertension and increased cardiac work load. Poorly relieved and prolonged pain may produce negative physical and psychological effects leading to sleeplessness, depression and psychosomatic changes. Hence this study is undertaken to evaluate Inj. neostigmine methylsulphate as spinal additive to evaluate their feasibility for postoperative pain relief.

Objective

1. Comparison of postoperative analgesia-duration and quality
2. Postoperative vitals monitoring
3. Assessment for need of analgesic, if any
4. Occurrence of side effects if any.

Keywords: Pain, post-operative, bupivacaine, neostigmine

Introduction

Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage [1]. Postoperative pain is associated with delayed recovery from surgery, hypoventilation and its consequences, delayed ambulation with increased thromboembolic phenomenon, increased sympathetic stimulation with consequent tachycardia, hypertension and increased cardiac work load. Poorly relieved and prolonged pain may produce negative physical and psychological effects leading to sleeplessness, depression and psychosomatic changes. A recent meta-analysis of multiple comparisons of neuraxial blockade to general anesthesia has shown a significant reduction in mortality and morbidity with regional techniques [2]. Neuraxial (epidural and intrathecal) routes for drug administration have been used for postoperative analgesia since long. Here local anesthetics and/or other drugs are deposited in the vicinity of the spinal cord and nerve roots in minimal effective doses to limit the ill-effects. By providing excellent analgesia this technique helps in improving pulmonary functions (proper diaphragmatic movement), protecting cardiac function (chemical sympatholytic) and decreasing stress response (partial blockade of hormonal and metabolic components). The cholinergic system is thought to modulate pain perception transmitted by spinal mechanism. Intrathecal administration of neostigmine methylsulphate (cholinesterase inhibitor) as spinal additive, provides analgesia by increasing the acetylcholine, which itself is ant nociceptive [3]. Pain impulses are transmitted by two fiber systems. The presence of two pain pathways explains the existence of two components of pain: fast, sharp and well localized sensation (first pain) which is conducted by A δ fibers; and a duller slower onset and often poorly localized sensation (second pain) which is conducted by C fibres. A δ fibres are myelinated, 2-5 μ m in diameter and conduct at rates of 12-30 m/s, whereas C fibres are unmyelinated, 0.4-1.2 μ m in diameter and conduct at rates of 0.5 to 2 m/s. Both fibre groups end in the dorsal horn of the spinal cord. A δ fibres terminate predominantly on neurons in laminae I and V, whereas the dorsal root C fibres terminate in laminae I and II [4].

Physiological sequelae of surgical pain

1. Autonomic hyperactivity: Tachycardia, rise in blood pressure and increased systemic vascular resistance.
2. Cardiovascular stress: Increased sympathetic stimulation may lead to MI or HF.
3. Tissue breakdown: Production of a catabolic hormone with suppression of anabolic hormones, increased metabolic rate and negative nitrogen balance.
4. Pulmonary dysfunction: splinting of diaphragm, decreased total lung compliance and hypoventilation. These promote atelectasis, ventilation perfusion mismatch, hypoxemia, pulmonary consolidation and pneumonitis.
5. Hypercoagulability: Increased platelet adhesiveness, diminished fibrinolysis, and promotion of a hypercoagulable state. These increase the risks of thromboembolic events when combined with the immobility in the postoperative period.
6. Endocrine effect: Rise in catabolic hormones such as catecholamine, cortisol, angiotensin II, antidiuretic hormone, adrenocorticotrophic hormone, growth hormone and glucagon & decrease in anabolic hormones such as testosterone and insulin.
7. Dysfunction of immune system: Decreases both cellular and humoral immunity.
8. Delayed return of bowel function: Reflex inhibition of gastrointestinal function. This promotes postoperative ileus, which contributes to postoperative nausea, vomiting, discomfort and delays resumption of a regular diet.
9. Development of chronic pain syndromes.

Pharmacology of bupivacaine hydrochloride

Bupivacaine hydrochloride is an amide local anesthetic. It was first synthesized by A.F. Ekenstam in 1957 [5]. Bupivacaine hydrochloride binds to the intracellular portion of voltage-gated sodium channels and blocks sodium influx into nerve cells, which prevents depolarization. Without depolarization, no initiation or conduction of a pain signal can occur. Bupivacaine hydrochloride is 3-4 times potent than lignocaine, so that 0.5% solution is roughly equivalent to 2% lignocaine. Longer duration of action makes it more suitable for prolonged surgeries. The onset of action following intrathecal injection occurs in 3-4 minutes and maximum anesthesia can be obtained in 15-20 minutes. The duration of anesthesia lasts for 3.5-4 hours. Clinically Bupivacaine hydrochloride is used as 0.125%, 0.25% or 0.5% solution. Very dilute concentration of bupivacaine hydrochloride 0.0625% is used for labor analgesia/walking epidural. Common adverse effects of bupivacaine are PR interval prolonged, Light headedness, QRS interval increased, Dizziness, Hypotension and bradycardia, Tinnitus, Cardiac output decreased, Drowsiness, Heart block, Disorientation, Cardiac arrest, Muscle twitching, Tremor of face and extremities Shivering, Generalized tonic clonic convulsion.

Pharmacology of neostigmine methylsulphate

Neostigmine methylsulphate was synthesized by Aeschliman and Reinst in 1931. It is a white crystalline powder which is odorless and readily soluble in water. It is a synthetic quaternary ammonium compound. It consists of carbamate moiety and quaternary ammonium group. The former provides covalent bonding in acetylcholinesterase.

The later renders the molecule lipid insoluble, so that it cannot pass through blood brain barrier. Neostigmine methylsulphate is an anticholinesterase agent which inhibits the hydrolysis of acetylcholine by inhibiting the enzyme acetylcholinesterase, therefore increasing acetylcholine concentration, which itself is antinociceptive. Acetylcholine accumulates at cholinergic synapses and its effects are prolonged and exaggerated. Intrathecal neostigmine methylsulphate has been shown to prolong motor and sensory blockade and reduce postoperative analgesic requirements. It also appears to stimulate the release of nitric oxide (NO) in the spinal cord [6].

Material and Methods

This study was conducted after getting approval from the institutional review committee.

Inclusion criteria

1. ASA grade I and II adult patients between 18-60 years of both sex.

Exclusion criteria

1. Peripheral neuropathy (post chemotherapy neuropathy)/ polio or any neurological affection
2. Coagulation disorder or any anticoagulant therapy
3. Local infection at the site of injection
4. Drug allergy/drug abuse
5. ASA grade > III

After informed consent 75 patients undergoing lower abdominal and lower limb surgeries under spinal anaesthesia were selected.

Patient group division

1. Group C (control group) (n=25) Only Inj. hyperbaric bupivacaine hydrochloride 0.5% 4ml intrathecally.
2. Group N1 (n=25) 50 mcg Inj. Neostigmine methylsulphate with hyperbaric Inj. Bupivacaine hydrochloride 0.5% 4 ml intrathecally.
3. Group N3 (n=25) 150 mcg Inj. Neostigmine methylsulphate with hyperbaric Inj. Bupivacaine hydrochloride 0.5% 4 ml intrathecally.

Drugs Used

1. Inj. bupivacaine hydrochloride 0.5% heavy-4ml (5mg/ml) taken in 5 ml syringe.
2. Inj. neostigmine methylsulphate (preservative free) 1ml (0.5mg/ml) taken in insulin syringe

After taking Inj. neostigmine methylsulphate, it will be added to 4ml of hyperbaric Inj. bupivacaine hydrochloride (0.5%) taken in 5ml syringe.

Methods

- Pre-anaesthetic checkup of all patients
- Pre-medication and nil by mouth for 8 hrs
- Monitoring of vital parameters
- Lumbar puncture performed with 23 G Quincke needle in L2-L3 or L3-L4 intervertebral space using interlaminar midline approach with full aseptic and antiseptic precautions.
- Intraoperative Observation-Pulse, blood pressure, Spo₂, respiratory rate and highest level of sensory block.
- Postoperative Observation-Pulse, mean arterial

- pressure, Spo2, pain assessment.
- Postoperative pain assessment will be done on Visual analogue scale (VAS)
Graded from 0-10
0-3-mild pain
4-7-moderate pain
8-10-severe pain
- Patients with VAS ≥ 4 will receive rescue analgesia in the form of inj. diclofenac sodium 1.2 mg/kg i.m.

Statistical analysis

The parameters recorded were entered on a computer and compared between the three groups using one-way ANOVA test for continuous variables and p value <0.05 is deemed significant. Categorical data between three groups were compared using chi-square test. Statistical software from

below mentioned site was used. Statistical software: www.graphpad/instat3 software

Significant figures

Level of significance is determined by “p” Value
p value ≥ 0.05 not significant
p value < 0.05 Significant

Observation and results

The effect of adding different doses of intrathecal Inj. Neostigmine methylsulphate to hyperbaric Inj. bupivacaine hydrochloride (0.5%) were compared in 75 patients belonging to ASA grade I and II, posted for elective lower abdominal, gynaecological, genitourinary and lower limb surgery.

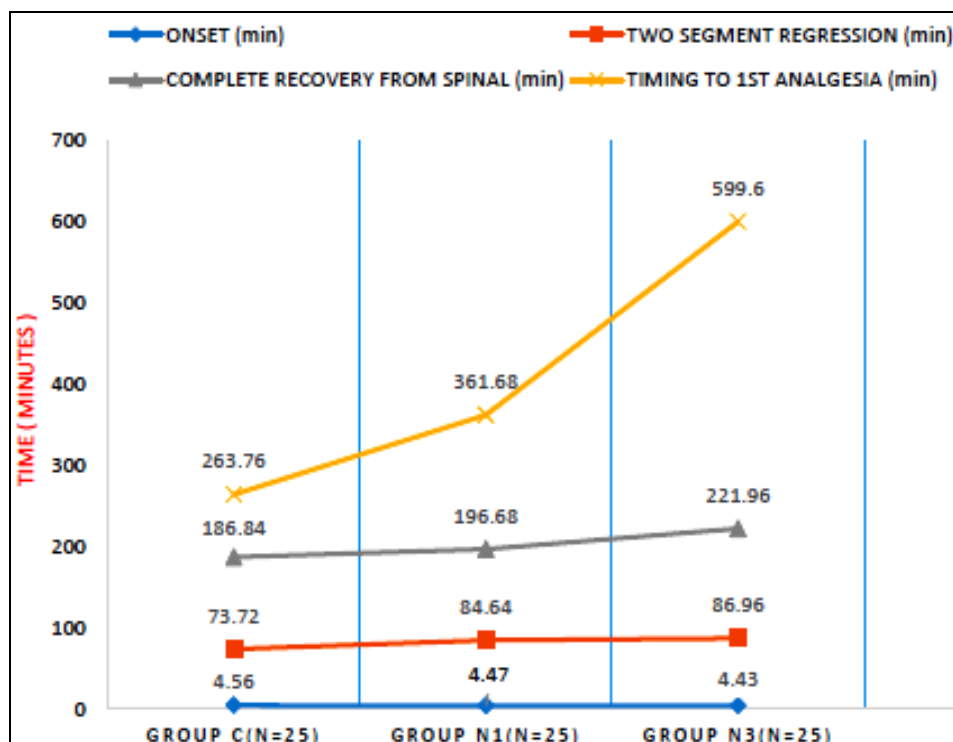
Table 1: General demographic features

Variables		Group C (n=25)	Group C1 (n=25)	Group C3 (n=25)
Age Groups	18-29 years	6	3	5
	30-39 years	4	5	6
	40-60 years	15	17	14
Sex Distribution	Males	13	11	11
	Females	12	14	14
Heights (in Cm)		159.44±5.17	158.48±6.23	157.96±5.65
Weight (in Kg)		61.12±6.24	57.72±7.49	57.48±8.95
Duration of Surgery (in Minutes)		114.12±22.89	123.92±19.93	122.16±17.20
Types of Surgical Procedures	General Surgery	6	4	6
	Gynaecological Surgery	5	9	8
	Ortho Surgery	10	7	8
	Uro Surgery	4	5	3

On comparing all the three groups with respect to demographic data and types and duration of surgery the p value is > 0.05. Hence this is insignificant

Table 2: Spinal block characteristics

	Onset (min)	Two segment regression (min)	Complete recovery from spinal (min)	Timing to 1 st analgesia (min)
Group C(n=25)	4.56±0.4	73.72±2.41	186.84±4.07	263.76±4.7
Group N1(n=25)	4.47±0.44	84.64±2.94	196.68±4.67	361.68±19.17
Group N3(n=25)	4.43±0.44	86.96±1.54	221.96±6.41	599.6±16.26



Graph 1: Spinal block characteristics

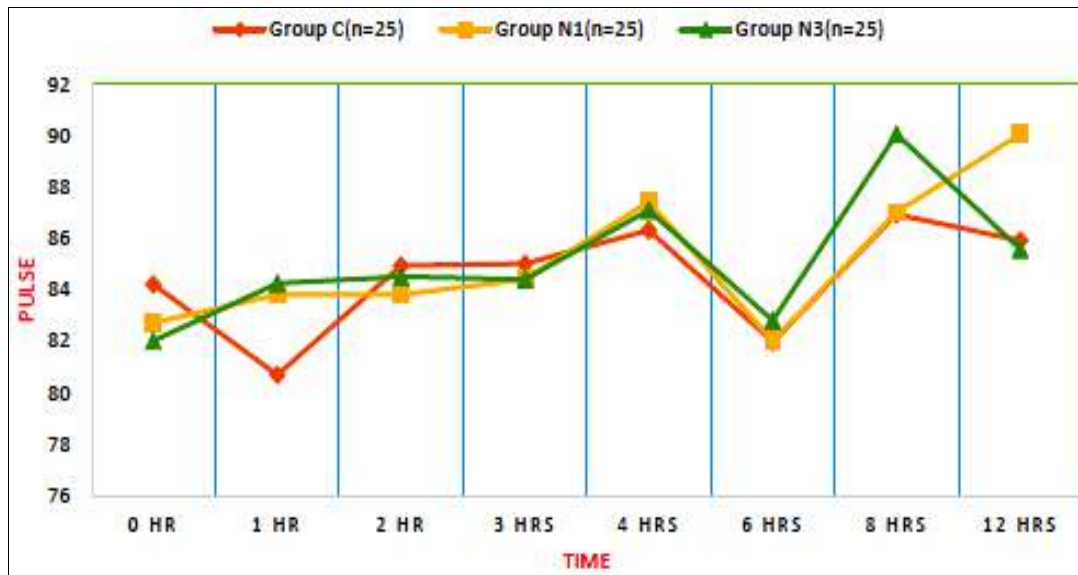
Table 3: P-value of spinal characteristics

P Value	Onset (min)	Two segment regression (min)	Complete recovery from spinal (min)	Timing to 1st analgesia (min)
C vs Ni		<0.001 (S)	<0.001 (S)	<0.001 (S)
C vs N3	0.55(NS)	<0.001 (S)	<0.001 (S)	<0.001 (S)
N1 vs N3		<0.01 (S)	<0.001 (S)	<0.001 (S)

Table 4: Post-operative Heart Rate (Mean + SD)

Time	Group C(u=25)	Group NI (u=25)	Group N3 (u=25)
0 hr	84.2±5.18	82.7±7.85	82±7.29
1 hr	80.68±6.03	83.8±7.66	84.24±7.62
2 hrs	84.92±5.87	83.8±5.52	84.5±6.06
3 hrs	85±5.98	84.4±5.42	84.4±5.42
4 hrs	86.3±3.92	87.4±2.92	87.08±4.41
6 hrs	81.96±3.32	82±3.32	82.8±3.52
8 hrs	86.92±3.34	87±3.39	90.04±1.72
12 hrs	85.9±3.33	90.04±1.72	85.56±4.04

On comparing all the three groups with respect to spinal block characteristics the p value is < 0.05 except for onset of block. Hence this is significant. Time for onset of block is not significant amongst groups (p value >0.05).

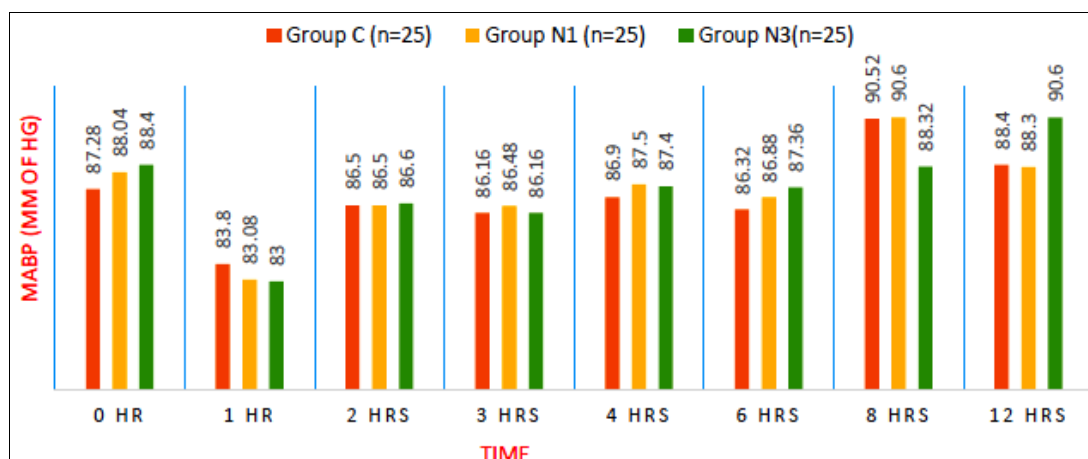


Graph 2: Post-operative Heart Rate

p value is > 0.05 in postoperative period till 12 hours and thus is insignificant. There was no incidence of bradycardia ±in postoperative period in any group.

Table 5: Post-operative mean blood pressure (mm Hg)

Time	Group C (n=25)	Group Ni (n=25)	Group N3 (n=25)
0 hr	87.28±3.51	88.04±5.28	88.4±5.45
1 hr	83.8±4.49	83.08±4.88	83±4.95
2 hrs	86.5±4.25	86.5±4.91	86.6±4.11
3 hrs	86.16±4.28	86.48±4.09	86.16±4.28
4 hrs	86.9±5.17	87.5±4.48	87.4±4.86
6 hrs	86.31±5.023	86.88±4.48	87.36±4.5
8 hrs	90.51±2.43	90.6±2.3	88.31±3.03
12 hrs	88.4±2.83	88.3±3.04	90.6±2.31



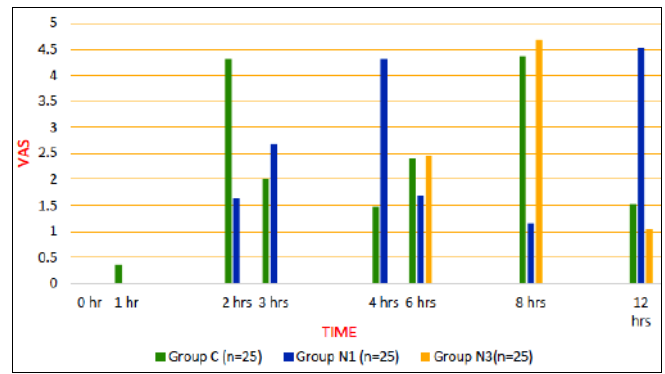
Graph 3: Post-operative mean blood pressure (mm Hg)

P-value is > 0.05 and is insignificant. There was no incidence of hypotension in any group in postoperative period.

Table 6: Pain assessment using VAS score

VAS Score	Group C(n=25)	Group N1(n=25)	Group N3(n=25)	P-Value
0 hr	0	0	0	NS
1 hr	0.36±0.49	0	0	<0.001(S)
				<0.001(S)
				>0.05 (NS)
2 hrs	4.321±0.9	1.641±0.49	0	<0.001(S)
3 hrs	2±1.04	2.68±0.63	0	<0.01(S)
				<0.001(S)
				<0.001(S)
4 hrs	1.48±0.51	4.3±0.69	0	<0.001(S)
6 hrs	2.41±0.65	1.68±0.69	2.44±0.51	<0.001(S)
				>0.05 (NS)
				<0.001(S)
8 hrs	4.36±0.86	1.16±0.8	4.68±0.95	<0.001(S)
				>0.05 (NS)
				<0.001(S)
12 hrs	1.52±0.65	4.52±0.51	1.04±0.68	<0.001(S)
				<0.05 (S)
				<0.001(S)

***-p Value in order group C vs N1, C vs N3 and N1 vs N3 respectively.

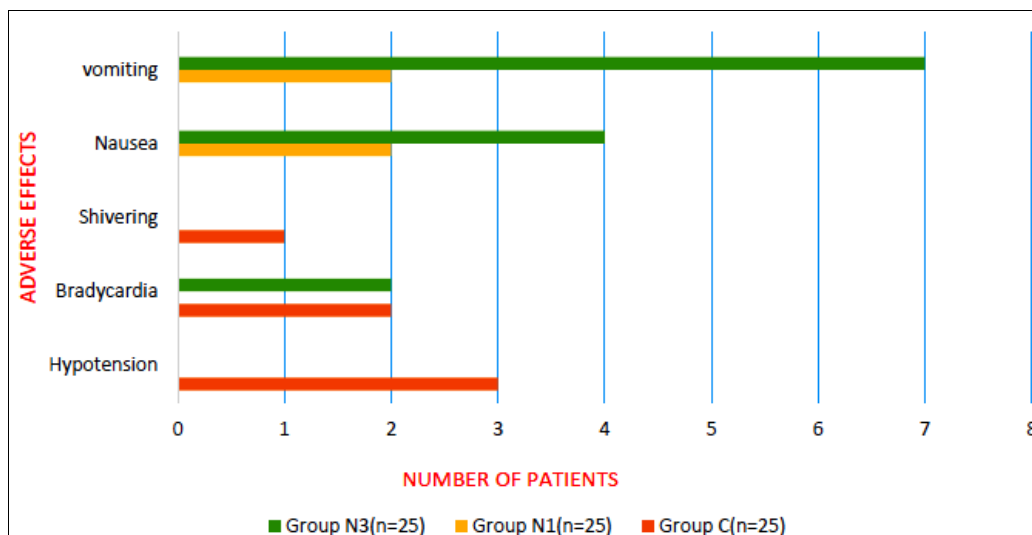


Graph 4: Postoperative pain assessment using VAS score

There is significant pain relief in group N1 and N3 as compared to group C.

Table 7: Adverse effects

	Group C(n=25)	Group N1(n=25)	Group N3(n=25)	Period
Hypotension	3	0	0	Intraoperative
Bradycardia	2	0	2	Intraoperative
Shivering	1	0	0	Intraoperative
Nausea	0	2	4	Intra and Post-operative
vomiting	0	2	7	Intra and Post-operative



Graph 5: Adverse effects

The incidence of side effects in all three groups is not statistically significant except for vomiting and hypotension (p value 0.007 and 0.044 respectively). Otherwise incidence of bradycardia, nausea, and shivering is not statistically significant (p value >0.05).

Discussion

Postoperative pain is a very distressing symptom which hinders early mobilization and recovery and may have deleterious effects on body function. The aim of good postoperative analgesia is to produce a long lasting continuous effective analgesia with minimal side effects. Intrathecal additives to local anesthetics forms a reliable and reproducible method of prolonged postoperative analgesia. Commonly used spinal additives are Opioids, Clonidine and Neostigmine. Intrathecal administration of Neostigmine methylsulphate produces anti-nociception, which is mediated by spinal muscarinic receptors [7]. It produces

analgesia by inhibiting the metabolism of acetylcholine without causing any neurotoxicity in animals and humans [6]. The inhibition of spinal cholinesterase by neostigmine methylsulphate results in an increase of endogenous acetylcholine, which is most likely released from intrinsic cholinergic neurons within the dorsal horn of the spinal cord. These cholinergic neurons which terminate in the vicinity of primary afferent express muscarinic receptors. The enhanced analgesic efficacy of intrathecal neostigmine methylsulphate results from greater release of spinal acetylcholine from the more intense and prolonged discomfort of postoperative pain, and consequent action at muscarinic M1 and M3 and presynaptic nicotinic receptors present in the cholinergic interneurons at the lamina III and V of the dorsal horn. An action at nicotinic receptors at the dorsal horn ganglion and at the spinal meninges has also been suggested [8]. The potency of intrathecal neostigmine methylsulphate is increased in postoperative period because

the descending noradrenergic or cholinergic antinociceptive spinal system is activate by ongoing pain, causing an increase in release of acetylcholine, which, in the presence of neostigmine methylsulphate results in augmented selective analgesia. Intrathecal neostigmine methylsulphate also increases the duration of analgesia and decreases the analgesic consumption when given along with fentanyl citrate. The interest in cholinergic mechanism of pain was rekindled by Pleuvry and Tobias [8]. In the present study, two different doses of Neostigmine methylsulphate 50 mcg and 150 mcg were selected on the basis of previous study by Saini *et al.* [9], where they observed that intrathecal Neostigmine methylsulphate in dose of 50 mcg was ineffective for analgesia and associated with increased incidence of vomiting whereas intrathecal Neostigmine methylsulphate in the dose of 150 mcg provides postoperative analgesia for 8-10 hrs and is associated with increased incidence of nausea, vomiting, sweating and salivation. The groups were compared with respect to age, sex, height, weight duration and type of surgery. There was no statistically significant difference in demographic data and the duration and type of surgery (P value >0.05). Recent studies suggest that analgesic action of intrathecal neostigmine methylsulphate is greater in females due to increased cholinergic tone by estrogenic stimulation [10]. During intraoperative period only in Group-C, 3 patient developed hypotension which was managed successfully by intravenous fluid. None of the patient in group N1 and group N3 developed hypotension in intraoperative period. The lower incidence of hypotension in neostigmine methylsulphate group might indicate an antagonism of intrathecal neostigmine methylsulphate against the hypotension induced by spinal anesthesia as demonstrated in animal model. Sweating above the level of sensory block is a sign of sympathetic activity that may account for protective effect of neostigmine methylsulphate against hypotension produced by spinal anesthesia [11]. Bradycardia in intraoperative period was managed successfully with intravenous atropine sulphate 0.5mg. Atropine because of its anticholinergic property causes vagolysis. Intravenously administered atropine, in a dose of 5000 mcg/kg produces hyperalgesia by affecting intraspinal release of acetylcholine (ACh) as studied by Abelson KS *et al.* in rats [12]. In our study the postoperative heart rate in all the three groups were comparable and were statistically insignificant. On comparing the haemodynamic parameters, we found that mean arterial blood pressure did not differ significantly between the three groups. In postoperative period none of the patients developed symptomatic bradycardia (pulse <50/min) or hypotension, defined as a decrease in mean arterial blood pressure by more than 20%. Lauretti *et al.* (1996) [13] showed similar observations but our study was in contrast to Hood *et al.* (1995) [14] where they found that spinally administered cholinergic agonist or cholinesterase inhibitors increase blood pressure and heart rate. The small dose (50-150 mcg of neostigmine) could explain the lack of cardiovascular stimulation seen in our study. Hood *et al.* used 500-750 mcg of neostigmine in their study. SpO₂ was compared between the three groups and was found to be statistically insignificant. Our results are also consistent with the study done by Liu *et al.* (1999) [15] where they observed that Neostigmine at doses <50 mcg had no effect on respiratory parameters. The rostral dermatome level of sensory anaesthesia was determined by pinprick. The

highest sensory level achieved and the time for onset of block were compared. There was no any statistically significant difference (p value > 0.05).

The time for two segment regression for sensory block was prolonged in both Group N1 (84.64±2.94) and Group N3 (86.96±1.54) as compared to Group C (73.72±24.07) and was statistically significant (p value <0.05) which was similar to the results of Liu *et al.* (1999) [15] where they observed that the addition of 50 mcg of Neostigmine prolonged the duration of sensory and motor block. However high incidence of side effects and delayed recovery from anaesthesia with the addition of 6.25 to 50 mcg Neostigmine may limit the clinical use of these drugs for outpatient spinal anaesthesia. The duration of block was prolonged in group N3 and N1 which was statistically significant indicating that block could be dose dependent (p value <0.05). This finding was consistent with the study of Liu *et al.* (1999) [15] where they found that addition of 50 mcg Neostigmine significantly increased the duration of sensory and motor block. Analgesia provided by intrathecal neostigmine methylsulphate, as assessed by visual analogue scale, was also observed. VAS score, first described by AITKEN in 1966, is one of the most commonly used method. The subject makes a mark on a 10 cm line-horizontal or vertical, one end of which is marked as "No pain" and the other as "The worst pain one can imagine". The VAS scores were compared at 0, 1, 2, 3, 4, 6, 8 and 12 hrs in postoperative period and showed a prolong duration of analgesia when the 50 and 150 mcg neostigmine methylsulphate groups were compared with the control group. Our results are in agreement with Chung *et al.* [16] and Lauretti *et al.* [17], where they demonstrated statistically significant lower visual analogue scale scores in the doses ranging from 25-75µg neostigmine group compared to saline group. On statistical analysis, the VAS score in Group N1 and Group N3 was significantly lower up to 3 hr and 6 hr respectively in postoperative period (p value < 0.05) as compared to the control group. The total duration of analgesia was 263.76 ± 4.7 min in Group C, 361.68±19.17 min in Group N1, and 599.6±16.26 min in Group N3. The requirement of rescue analgesia in the form of inj. diclofenac sodium intramuscularly was significantly lower in both the test groups (p value < 0.05). We found greatly enhanced analgesia in 150mcg dose of neostigmine methylsulphate, as evident by less consumption of analgesics in form of i.m. diclofenac sodium. We found that intrathecal neostigmine methylsulphate in doses of 50 mcg and 150 mcg prolonged the postoperative analgesia in terms of total VAS scores, duration of analgesia and lesser requirement of total number of rescue analgesic consumption as compared to the control group. Lauretti *et al.* [13, 17] showed a dose independent reduction of postoperative analgesia requirement, but a dose dependent increase in the incidence of PONV following addition of various doses of IT neostigmine ranging from 10 to 25 mcg to 15 mg of hyperbaric bupivacaine 0.5%. They observed that the use of 25-50 mcg neostigmine intrathecally during vaginal hysterectomy produced significant analgesia. The study attributed analgesia with smaller doses of neostigmine to increased potency of neostigmine in response to painful stimulus as well as to the use of intravenous morphine through patient controlled analgesia in all their patients. Our results were similar to Saini *et al.* [9] where they observed greatly enhanced analgesia by intrathecal neostigmine in the

150 mcg dose, shown by significantly less consumption of rescue analgesics. They also concluded that intrathecal neostigmine in dose of 50 mcg was ineffective for analgesia which is in contrast to our study in which intrathecal neostigmine methylsulphate in a dose of 50 mcg was associated with lower VAS score, prolonged duration of analgesia and lesser consumption of rescue analgesic in 12 hrs as compared to the control group. All the patients were observed for any possible complications. The comparison of side effects like nausea, bradycardia and shivering in all the groups were statistically insignificant except vomiting (intra and postoperative) and hypotension (intraoperative) as compared between groups (p value <0.05). Hypotension and bradycardia was not seen in postoperative period in any group. Intrathecal neostigmine methylsulphate produces nausea and vomiting in dose dependent manner [18]. In clinical studies we also observed a significantly higher incidence of nausea and vomiting associated with intrathecal neostigmine methylsulphate which may be due to cephalad migration of neostigmine methylsulphate to brain stem, with accumulation of acetylcholine at chemoreceptor trigger zone induces vomiting. To minimize cephalad spread and reduce the incidence of nausea and vomiting, injection of neostigmine methylsulphate in a hyperbaric solution while maintaining the patients in a head up position helps. Other similar studies done by Hood *et al.*, Lauretti *et al.*, Klamt JG *et al.* showed similar increase in the incidence of nausea and vomiting with similar dosages of neostigmine. Vomiting was severe in some patients in group N3 but successfully controlled by i.v. fluid and antiemetic. Thus, neostigmine methylsulphate with its various effects on human physiology, is a very important drug in effective management of postoperative pain and specially should be extensively used due to its easy availability and low cost. Position of the mark on the line measures how much pain the subject experiences.

Summary and Conclusion

The present study was conducted in 75 patients (ASA grade I and II) of either sex in age group 18-60 yrs undergoing elective lower limb or lower abdominal surgery including gynecological and urogenital surgery. They were divided into 3 groups each consisting of 25 patients, Group-C given inj. bupivacaine hydrochloride only, Group N1 given inj. neostigmine methylsulphate 50mcg with Inj. bupivacaine hydrochloride while Group-N3 given inj. neostigmine methylsulphate 150mcg with Inj. bupivacaine hydrochloride. After proper examination and evaluation for vitals before surgery, subarachnoid space was punctured at L2-3 or L3-4 interspace with 23 G Quincke needle in lateral position and drug was injected. Appropriate standard clinical monitoring of patients was done intraoperatively. Pulse rate, blood pressure, analgesia and side effects were observed postoperatively at different time intervals and postoperative pain relief was evaluated. Noteworthy side effects of nausea and vomiting observed in intraoperative and postoperative period can be minimized by using lower doses of neostigmine methylsulphate and maintaining head up position of patient during intrathecal administration to avoid cephalad spread. Intrathecal neostigmine methylsulphate in different doses added to hyperbaric bupivacaine hydrochloride significantly reduced pain and analgesic requirement in postoperative period without affecting pulse rate, blood pressure and respiratory rate.

Easy availability, benefit of reducing paralytic ileus, minimal hemodynamic changes, significant reduction in postoperative pain and reduction in need for rescue analgesia in postoperative period makes neostigmine methylsulphate a good additive. Hence we conclude that the intrathecal neostigmine methylsulphate is a good additive to local anesthetic which significantly reduces postoperative pain without dangerous side effects.

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