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Original Research Article

A Comparative Study between Intrathecal Neostigmine in Variable Doses (50µG and 100µG) Versus Fentanyl (25µG) for Postoperative Pain Relief

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Abstract:

Introduction: Spinal anaesthesia is a widely practiced technique in anaesthesiology. Spinal anaesthesia is thought to be an easy technique and has proved to be extremely safe when managed well. Post-operative pain is of great concern for patients and to control it a challenge for anaesthesiologist.

Aim: The aim of our study is to compare efficacy of analgesia following intrathecal administration of fentanyl and neostigmine, to assess the duration and extent of analgesia, to compare the haemodynamic changes and to study side effects.

Methods : Eighty patients of ASA I and II of age group 18-60 yrs physical status undergoing elective lower abdominal and lower limb surgery were enrolled into this study. The patients randomly divided into 4 groups of 20 patients each.

Group1-Neostigmine50µg(1ml)+Bupivacaine15mg(3ml).

Group2-Neostigmine100µg(1ml)+Bupivacaine15mg(3ml).

Group3-Fentanyl 25µg(1ml)+ Bupivacaine15mg(3ml).

Group4-Normal saline 1ml +Bupivacaine 15mg(3ml)

Level and duration of anaesthesia, VAS score, adverse effects were noted.

Results: The mean duration of analgesia (min) distributed among each group in relation to the first dose of rescue analgesia administered at VAS 4/5 are group1 – 302.65±47.36, group 2 – 280.55±31.26, group 3 – 215.25±29.47 and group 4 -156.65±32.08. Thus group1 had longest mean duration of analgesia as compared to other groups. Maximum level of sensory block T_4 achieved in more number (13) of patients in group 1 as compared to 12 in group 4, 9 in group 2 and 10 in group 3

Conclusion: Intrathecal neostigmine results in post-operative pain relief that too is dose dependent and more or less similar to analgesia obtained with fentanyl. Intrathecal neostigmine could be an alternative to opioids for postoperative pain relief and 50µg is better than 100µg having lesser adverse effects.

Key words: Intrathecal, Neostigmine, Fentanyl, Bupivacaine, Spinal Anaesthesia.

Introduction

Spinal anaesthesia is a widely practiced technique in anaesthesiology. Spinal anaesthesia is thought to be an easy technique and has proved to be extremely safe when managed well. Post-operative pain is of great concern for patients and to

control it a challenge for anaesthesiologist. . Pain is now widely accepted to be the 'fifth vital sign' that needs monitoring after temperature, pulse, respiration and blood pressure.[1]There has been recent interest in using analgesic additives to spinal local anesthesia to decrease the dose of local anesthetics and decrease their side effects like haemodynamic disturbances while maintaining or improving anesthetic success and also extending the analgesic effect beyond the intra-operative period.

Opoids analgesia have long been recognized as among the most effective treatment for pains. Fentanyl is perhaps the best studied and most commonly used lipophilic opiate use for intrathecal analgesia. It has a rapid onset of action with a short duration of action and provides a better quality of surgical block. However, its use is not totally devoid of significant adverse effects such as pruritus, nausea, vomiting, sedation, respiratory depression and urinary retention.

There have been many attempts in recent year to find a non-narcotic analgesic with equal or more clinically efficacy. A number of drugs have been used as an adjuvant in spinal anaesthesia like midazolam, clonidine, dexmedetomidine etc.[2] It is also postulated that the non-opioids endogenous analgesics system and neurotransmitters release may have a role in the modulation of pain.[3]

Acetylcholine (ACh) and more than 25 other neurotransmitters that participate in spinal cord modulation of pain processing have been identified.[4] Intrathecal injection of neostigmine inhibits the metabolism of spinally released ACh and produces analgesia in animals and humans without dangerous or bothersome side effects common to spinal opioids. Phase I safety assessments in human volunteers have been performed for both preservative-free (50– 750 µg) and paraben-containing hyperbaric preparations (10–100µg) of spinal neostigmine without clinical evidence of neurotoxicity.[5]

The aim of our study is to compare efficacy of analgesia following intrathecal administration of fentanyl and neostigmine, to assess the duration and extent of analgesia, to compare the haemodynamic changes and to study side effects.

Material and methods

Prior to commencing study approval was obtained from both the ethical and hospital research committee. Participants to this study were explained of the anaesthetic procedure and informed consent was taken. Eighty patients of ASA I and II physical status of age group 18-60 yrs undergoing elective lower abdominal and lower limb surgery were enrolled into this prospective, double-blinded, randomized sequential allocation study

Exclusion Criteria

- Patient refusal
- History suggestive of hypersensitivity to Bupivacaine, Fentanyl and Neostigmine
- Psychiatric illness
- Illness associated with vomiting and raised ICP
- Hypertension, Hypotension, Valvuler heart disease
- Patient having absolute contraindication to spinal anaesthesia

The patients randomly divided into 4 groups of 20 patients each-

Group1- received intrathecal neostigmine 50µg(1ml)+Bupivacaine15mg(3ml)

Group2- received intrathecal neostigmine 100µg(1ml)+Bupivacaine15mg(3ml)

Group3- received intrathecal fentanyl 25µg(1ml)+ Bupivacaine15mg(3ml)

Group4- received intrathecal normal saline 1ml +Bupivacaine 15mg(3ml)

All participants were premedicated with oral Alprazolam 0.5mg on the evening before surgery and on the morning of surgery. All patients were kept NPO for

solid foods 8 hrs and clear liqid 2 hrs. IV access was established using a 18 gauge cannula. Patients were preloaded with ringer lactate 10 ml/kg over 15 min. Patients baseline non-invasive blood pressure, pulse rate,O2 saturation were noted and continuous ECG monitoring was instituted. Skin was cleaned and draped in sitting or lateral position. Then spinal anaesthesia was performed with 25 G spinal needle quincke's type. Drug was injected after noting free flow of CSF. 4 ml drug was injected over 30 sec. Patients were placed supine immediately after injection.

Level of sensory block was assessed by pin prick method and motor block was assessed by bromage scale .

All patients were monitored for the following---

1. Heart rate, SpO2, and ECG was continuously monitored till end of surgery
2. NIBP was taken baseline then after every 2.5 min until completion of surgery Intraoperative hypotension was taken as systolic blood pressure < 90 mmHg or 20% below baseline value and was treated with ephedrine 5 mg IV bolus in incremental doses.
3. Heart rate < 50 was treated with incremental doses of Atropine 0.25mg IV.
4. Intraoperative nausea was treated with Metoclopramide 10 mg IV followed by Ondensetron 0.1mg/kg IV.

Assesment of pain

Pain Intensity Score [6]

It is scored by the observer on the 4 point scale

0 - No pain

1 - Mild pain

2 - Moderate pain

3 - Severe pain

Visual Analogous Scale [7,8]

In VAS the patients assessed by the degree of pain using standard 10 cm linear analogous scale system.

0 cm - No pain

10 cm - Worse pain

Bromage score [9]

Score	Description
1	Complete motor block
2	Unable to flex the knee but can flex the ankle articulation
3	Unable to perform the leg raise but can flex the leg on the knee articulation
4	No motor block the patient is able to performed a full straight leg raise over the bed

Results:

Table 1: comparison of demographic parameters

Parameters	Group1	Group2	Group3	Group4
Age(years)[mean±SD]	47.05±5.35	47.84±5.73	45.68±6.39	47.11±4.75
Gender				
Male	13(65)	11(55)	10(50)	8(40)
Female	7(35)	9(45)	10(50)	12(60)
Weight(kg)[mean±SD]	60.35±6.28	59.75±8.32	57.80±9.17	57.00±6.64
Height(cm)[mean±SD]	161.28±7.86	160.85±8.18	159.45±7.37	157.40±6.07
Duration of surgery(min)	95.35±20.60	87.40±18.82	90.50±22.87	89.05±22.17

All the demographic parameters were comparable among different groups and were statistically not significant.

Table 2: Distribution of patients according to extent of analgesia

Level of spinal block achieved	Group							
	Group 1		Group 2		Group 3		Group 4	
	No.	%	No.	%	No.	%	No.	%
T_4	13	65.0	9	45.0	10	50.0	12	60.0
T_5	6	30.0	8	40.0	6	30.0	8	40.0
T_6	1	5.0	3	15.0	4	20.0	-	-

As shown in table 2, maximum level of sensory block T_4 achieved in more number (13) of patients in group 1 as compared to 12 in group 4,9 in group 2 and 10 in group 3. Level of sensory block T_5 achieved in 8 patients in group 2 as compared to 8 in group 4 and 6 in group 3 and group 1 .All patients in this study achieve minimum level of sensory block T_6 that is a level sufficient for surgeries below the umbilicus.

Table 3: Comparison of the duration of analgesia (minutes) in various groups

Group	Time of first dose of analgesia (minutes) (Mean±SD)
Group 1	302.65±47.36
Group 2	280.55±31.26
Group 3	215.25±29.47
Group 4	156.65±32.08

As shown in Table 3 ,the mean duration of analgesia distributed among each group in relation to the first dose of rescue analgesia(min) administered at VAS 4/5 are group1 – 302.65±47.36, group 2 – 280.55±31.26, group 3 – 215.25±29.47 and group 4 -156.65±32.08. Thus group1 had longest mean duration of analgesia as compared to other groups. On comparing between the groups, there is statistically highly significant difference between group1 versus group4 ($p<0.001$) and statistically highly significant difference between group2 versus group4 ($p<0.001$) and group1 versus group3 is significant ($p<0.001$). On comparing between Group3 versus group4, there is statistically significant difference ($p<0.01$) and significant between group2 versus group3, however there is statistically insignificant difference between group1 versus group2 ($p>0.05$).

Table 4: VAS Score of different groups at different time interval

VAS Score (Mean±SD)	Group 1	Group 2	Group 3	Group 4
1 hr	0.00	0.00	0.00	0.15±0.37
2 hrs	0.35±0.67	0.45±0.69	0.65±0.81	1.25±1.21
3 hrs	1.40±1.10	1.45±1.14	2.05±1.28	2.35±1.50
4 hrs	2.05±1.31	2.15±1.19	2.05±1.28	3.75±1.55
8 hrs	2.65±1.30	2.50±1.60	4.00±1.21	4.10±1.37
12 hrs	2.90±1.65	3.20±1.82	3.10±1.61	4.35±1.59

Table 4 shows VAS scores of various groups at different time intervals. On comparing them nonsignificant difference ($p>0.05$) is found between group 1 and 2. Statistically significant ($p<0.05$) difference is found between group 1 and group 4 and also between group 2 and group 4.

Table 5: Distribution of patient according to adverse effect

	Group I		Group II		Group III		Group IV	
	No.	%	No.	%	No.	%	No.	%
Restlessness	3	15.0	1	5.0	1	5.0	-	-
Hypotension	1	10.0	2	5.0	2	10.0	4	20.0
Hypoxia	-	-	1	5.0	1	5.0	-	-
PONV	6	30.0	3	15.0	2	10.0	-	-
Pruritus	-	-	-	-	5	25.0	1	5.0
Urinary retention	-	-	1	5.0	-	-	-	-
Bradycardia	2	10.0	1	5.0	1	5.0	2	10.0
No side effects	8	40.0	11	55.0	8	40.0	13	65.0

Discussion

Opioids have been used as an additive in spinal anaesthesia since long time. However, the analgesic effect obtained with intrathecal opioids had to pay a high price in terms of side effect especially respiratory depression, pruritus and vomiting [10]. Several attempts has been made to overcome this problem by adjusting dose of additives, using less local anesthetics or by using different additives like clonidine, midazolam, ketamine etc. However, the analgesic effect of these additives when used intrathecally is yet to be ideal. Thus, the need for continuous search for that ideal additive which will possess an excellent analgesic effect without serious side effect like cardiorespiratory depression was felt by researchers and clinicians.

Intrathecal administration of cholinergic receptor agonist or cholinesterase inhibitors produces an antinociceptive effect, which is mediated by spinal muscarinic receptors [11]. Intrathecal administration of neostigmine inhibits the metabolism of spinally released acetylcholine that produces analgesia without any neurotoxicity. An abstract report of a double-blind, placebo controlled examination using a single dose of intrathecal neostigmine (100µg) concluded that this drug was unlikely to be of clinical use because of the high incidence of side effects.[12] Intrathecal neostigmine in a dose more than 50 µg is required for effective postoperative analgesia. Hood et al and Tan et al observed a threshold dose for analgesia to be approximately 50 µg.[13] This study is aimed to compare the different doses of neostigmine as to find an effective additive dose for relief of postoperative pain and complications and also to compare with widely used lipophilic opioid fentanyl.

The spread of analgesia as evidenced by level of sensory block was not affected by neostigmine. Maximum level of sensory block T_4 achieved in more number (13) of patients in study group (100µg) which was similar to control group. However the spread of analgesia was comparatively less in group2(50 µg) and fentanyl group. It is clearly evident from these observations that neostigmine when used in dose of 100 µg results in higher spread of analgesia. However, these observations need further confirmation. There was no statistically significant difference ($p > 0.05$) in the level of block achieved in the study and control groups. Similar observations were also made by Honarmand et al [14], Klamt et al[15] and Ping-Heng Tan et al[16].

Pulse rate, and blood pressure was stable in both study group as well as in fentanyl and control group. Changes in heart rate and blood pressure were not statistically significant ($p>0.05$). Similar observation was also made by Lauretti et al[17], Savita Saini et al[18]. Changes in mean oxygen saturation was also statistically comparable ($p>0.05$). Similar observations were also made by Lauretti et al, Savita Saini et al.

Table 6: Duration of analgesia with different doses of intrathecal neostigmine observed in previous studies

	First rescue dose of analgesia (min) with intrathecal neostigmine in different doses				
	25µg	**35µg**	**50 µg**	**100 µg**	**150 µg**
G.R.Lauretti et al (1997) n=20	225±59	-	191±40	196±52	-
Ping-heng et al (2001) n=20	-	-	560±130	-	-
Savita Saini et al (2006) n=20	-	-	339±85.4	-	697±194.3
J GKlamt et al (1997) n=15	-	-	-	642±260	-
A Yegin et al (2003) n=15	180±17.82		211.46±50.12	-	-
Azim Honarmand et al (2009) n=20	510	950	-	-	-
Present study	-	-	280.55±31.26	302.65±47.36	-

The duration of analgesia was definitely better (p value<0.05) in study group than the control group. Duration of analgesia in neostigmine (100µg) was 302.65±47.36 min., which was comparatively more than with neostigmine(50 µg) 280.55±31.26 min.The duration of analgesia with fentanyl and control group were 215.25±29.47 min and 156.65±32.08 min respectively. It is clerarly evident from these observations that duration of analgesia was prolonged in neostigmine group as compared to fentanyl and control group (p <0.05). furthermore the duration of analgesia was dose dependent. However Lauretti et al concluded that neostigmine causes dose independent analgesia for the doses between 25µg -100µg but several other studies including the present study does not support this observation(Table 6). A minimal increase in duration of analgesia with 100µg neostigmine as compared to 50µg(p>0.05) neostigmine resulted in increased incidence of adverse effects. The intrathecal neostigmine resulted in better quality of analgesia that too for longer duration. However, an insignificant difference (p>0.05) in terms of duration and quality was observed by increasing the dose from 50 µg to 100 µg. Similar observation was also concluded by Lauretti et al.

Wide variation in duration of analgesia in previous studies could be attributed to different criteria used by them eg. some have used VAS > 4 and others have used patient's request as the time for providing rescue analgsia. The duration of analgesia observed with neostigmine (50µg) group with 280.55±31.26 min, was slightly more than the observation made by Yegin et al (2002)[19] 211.46±50.12 min of analgesic effect. This discrepancy may be attributed to the lower dose of bupivacaine used in their study (10 mg compared to 15mg in our study). The duration of analgesia observed by Klamt et al (1997)[20] was 10.7±4.3 hrs with 100 µg neostigmine which was more than observed in our study.(5.0± 0.75 hrs). This discrepancy may be attributed to larger dose of bupivacaine used by them (20mg as compared to 15mg used in our study).

The duration of analgesia observed with addition of 25µg fentanyl with 15 mg of heavy bupivacaine given intrathecally in this study 215.25± 29.47 min which was very close to the duration of analgesic effect observed by Lauretti et al[21] (1998) , Shahriari et al[22] and Dilip shende et al[23] (2002). Prakash B et al[24] and Palwade RD et al[25] have shown that Intrathecal neostigmine precipitated the onset of sensory and motor blockade and

prolonged the sensory and motor block significantly when used with fentanyl.

Other studies like Singh R et al,[26] Jha RK et al,[27]Lakhanpal M et al[28] have concluded that 50 mcg neostigmine is optimal dose for intrathecal use which is also found in our study.

There were few cases of hypotension observed in both the study as well as control group but the incidence was statistically insignificant ($p>0.05$). Maximum incidence of hypotension (20%) observed in control group as compared to 5% in neostigmine (100 µg) group and 10% each in neostigmine (50 µg) and fentanyl group. Higher incidence of hypotension in control group may be a coincidental observation and surprisingly the incidence of hypotension was minimal in study group which cannot be explained and need further further evaluation. The minimal incidence of hypotension in neostigmine group confirms the observation made by Lauretti et al.

Three patients (15%) in neostigmine (100µg) group, one (5%) each in neostigmine (50µg) group and fentanyl group reported restlessness as compared to none in control group which was relieved by intravenous midazolam. No such observation was made in previous studies. This restlessness may be due to anxiety of patients about surgery.

Table 7: Incidence of nausea and vomitting with different doses of intrathecal neostigmine observed in previous studies

	Incidence of nausea and vomitting with intrathecal neostigmine in different doses				
	25µg	**35 µg**	**50 µg**	**100 µg**	**150 µg**
G.R.Lauretti et al (1997) n=20	-	-	1	6	-
Ping-heng et al(2001) n=20	-	-	7	-	-
Savita Saini et al(2006) n=20	-	-	7	11	-
J G Klamt et al (1997) n=15	-	-	-	8	-
A Yegin et al (2002) n=15	7		8	-	-
Azim Honarmand et al (2009) n=20	7	8	-	-	-
Present study	-	-	3	6	-

The incidence of nausea and vomiting was noted to be much higher (30%) among the neostigmine (100µg) group than other groups, As compared with 15% in neostigmine (50µg) group, 10% in fentanyl group none of the patient reported nausea vomiting in control group. A dose dependent increase in the incidence of nausea and vomiting was observed by us which was similar to the observation made by Lauretti et al and Kalmt et al (Table 7). Two patients in neostigmine 100µg group had nausea and vomitting not responding to intrvenous ondensetron and needed intravenous propofol infusion. This refractoriness to intravenous ondensetron and response to intravenous propofol infusion needs further evaluation.

Pruritus was observed in 25% in fentanyl group as compared to 5% in control group and none of the patients in neostigmine group, similar to the observation made by Azim Honarmand et al. Thus use of neostigmine is devoid of pruritus, a commonly observed adverse effect with fentanyl.

One patient in neostigmine 100µg group had prolonged hiccough which resolved spontaneously.This may be due to central effect of neostigmine or may be due to gastric upset of patient and needs further evaluation**.**

Conclusion

From this study we conclude that intrathecal neostigmine results in post-

operative pain relief that too is dose dependent and more or less similar to analgesia obtained with fentanyl. However, the incidence of respiratory depression and pruritus was practically absent in neostigmine group which may be plus point. However, the incidence of nausea and vomting was more with intrathecal neostigmine that too was dose dependent responding to commonly used ondensetron. From this study we draw a conclusion that intrathecal neostigmine could be an alternative to opioids for postoperative pain relief and 50µg is better than 100µg having lesser adverse effects.

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