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Evaluation Of Intrathecal Neostigmine As A Postoperative Analgesic Adjuvant In Caesarean Section Patients

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Summary :

Intrathecal (IT) neostigmine has been reported as an analgesic adjuvant without any neurotoxicity in human studies. The present study was undertaken to evaluate the efficacy of IT neostigmine for the relief of postoperative pain and assess its possible side effects. Sixty patients of ASA I or II scheduled for non emergent caesarean section under spinal anaesthesia were randomly allocated to two groups. Group N (n= 30) received IT lignocaine 5% (50 mg) and 50 μg of neostigmine while Group C (n= 30) received IT lignocaine 5% (50 mg) with normal saline. The onset, level and regression of spinal anaesthesia were similar in both the groups. There was no difference in haemodynamics between the groups. The time to first analgesic, cumulative analgesic requirements and pain scores in the first 12 hours were similar. Statistically significant higher incidence of intraoperative retching, postoperative nausea and vomiting were found in Group N ($p< 0.005$).

Key words : Spinal anaesthesia, intrathecal neostigmine, postoperative analgesia

Introduction :

Postoperative analgesia has been revolutionized by the concomitant intrathecal administration of various drugs along with local anaesthetics. Opioids, clonidine, ketamine, midazolam and neostigmine have all been used with variable results. Opioids have the potential of the dreaded complication of respiratory depression. The absence of sedation and respiratory depression makes IT neostigmine potentially advantageous for postoperative analgesia.[1,2,3,4] Hence we attempted to study its analgesic efficacy and note the side effects especially perioperative nausea and vomiting.

Methods :

Sixty patients of ASA I or II scheduled for non emergent caesarean section at Government headquarters hospital, Kumbakonam were selected for the study. After prior clearance from the institutional ethics committee and informed consent from the patients in the age group of 19-30 were randomly allocated to two groups of thirty each using coded envelope technique. The following patients were excluded from the study.

1. Emergency cases.
2. Sepsis.
3. H/O motion sickness.
4. Mentally retarded and drug addicts.

All the sixty patients had a normal preoperative checkup and the Numerical Rating Scale (NRS of pain) of 0-10 was clearly explained to them. As per this they were asked to rate pain from 0-10, 0 being no pain and 10 meaning the worst pain ever possible. All the patients received Inj. Ranitidine 100 mg and Inj. Atropine 0.6 mg as premedication 20 minutes before anaesthesia. Patients of Group N received an additional Inj. Metoclopramide 10 mg IM. This was done due to the following reason. In our initial *trial* study of twenty patients (IT neostigmine 50 μg n=10, IT neostigmine 100 μg n=10), 50 % of patients whom IT neostigmine 50 μg had severe vomiting and all the patients in whom 100 μg was given vomited. With this in mind we opted to give Inj. Metoclopramide

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10 mg to all patients of Group N only to utilize the analgesic efficacy and to avoid its side effects. This was compulsory for ethical reasons. Routine monitors like SaO_2 and noninvasive blood pressure were connected and vital parameters were noted. All patients were preloaded with 10 ml /kg of Ringer lactate. Spinal anaesthesia was administered either with 50 mg of 5% lignocaine with 50 μg of neostigmine (Group N) or 50 mg of 5% lignocaine with normal saline (Group C) using insulin syringe. The blinded anaesthetist conducted the anaesthesia and it was uneventful in all the cases. All the patients received 10 units of Inj. Oxytocin immediately after the delivery. The regression of two segments of spinal level was taken as "0" hours. Pain scores (NRS), pulse, blood pressure respiratory rate and sedation was monitored by a blinded staff nurse every three hours for a period of 12 hours. All patients received Inj Pentazocine 30 mg. IM as analgesic when ever there was pain or NRS > 7.

The sedation scores were monitored as follows :

1. Asleep and comfortable
2. Awake and comfortable.
3. Awake with pain.

The time to first analgesia (TFA) and any postoperative side effects were noted with special reference to nausea and vomiting. All data were entered in a proforma and subjected to statistical analysis using ANOVA, Students "T" test and test of proportions whichever is applicable and a *p* value of less than 0.05 was considered significant.

Results :

The mean age, weight and duration of surgery were comparable in both groups. (Table 1.)

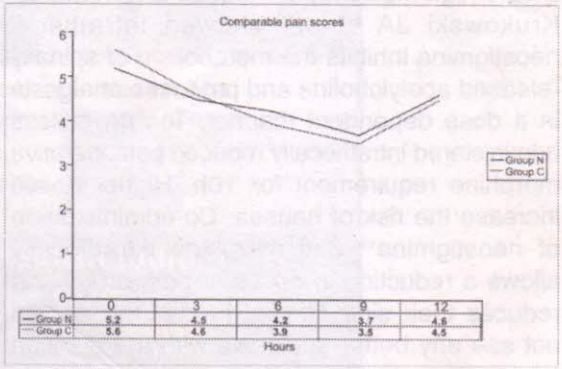
Table 1 showing demographic data.

	Group N (mean & SD)	Group C (mean & SD)
Age	24 ± 2.5	25 ± 2.6
Weight	52 ± 5.7	54 ± 6.1
Duration of surgery	22 ± 8.2 (min.)	24 ± 7.9 (min.)

All the patients had adequate spinal level of T4 to T6 and intraoperative haemodynamics were stable and comparable in both the groups. Five patients of Group N had severe intraoperative retching and vomiting without any other known cause. No patient of either group received prostaglandins. The duration of anaesthesia was similar and comparable in both groups. No patient of either Group showed extended motor block or weakness of limbs. The TFA was 60.2 ± 8.2 minutes in Group N and 58.6 ± 8.5 minutes in Group C which was statistically insignificant. 28 out of thirty in Group C and 27 out of thirty in Group N received two doses of narcotics in the first twelve hours. The analgesic requirements were hence similar and comparable in both groups. The NRS scores and sedation scores were similar in both groups. *See fig 1.* Eight patients of Group N and no patient of Group C had postoperative vomiting. All the eight patients received an additional Inj. Metoclopramide 10 mg IM. All the sixty patients had otherwise normal postoperative period and discharged according to the normal hospital criteria.

Discussion :

Fig. 1 showing the comparison of mean pain scores



Neostigmine is a reversible cholinesterase inhibitor and when administered produces an increase in Acetylcholine in cholinergic nerve terminals. After the establishment of cholinergic mechanisms in the spinal analgesic pathways, IT neostigmine was considered.[5] Hood[6] et al observed a threshold dose of 50 μg of intrathecal neostigmine for analgesia. The doses of 100 – 250 μg produced more side effects like bradycardia, nausea and vomiting. Hence we decided to stick on to 50 μg. Our study did not show any improvement of analgesia as shown by the comparable pain scores and analgesic requirements. Enhancement of anaesthesia duration, better postoperative analgesia was not found in our patients. But five out of thirty patients in Group N had severe intraoperative retching and a very high incidence of postoperative vomiting was noted in Group N despite administering an additional dose of metoclopramide. IT neostigmine directly stimulates preganglionic sympathetic neurons in the spinal cord and can counteract spinal hypotension.[7] Laureti et al[8] observed no difference with the use of 75 μg of IT neostigmine in haemodynamics which coincided with our findings. Saini et al[9] showed statistically insignificant higher incidence of bradycardia with 150 μg of IT neostigmine. They also showed a prolongation of sensory anaesthetic block with 150 μg of IT neostigmine which was not found in our study of using 50 μg of neostigmine. Gosavi et al[10] showed a prolongation of sensory and motor blockade with addition of 250 μg of neostigmine with intrathecal bupivacaine but with a very high incidence of nausea and vomiting. Krukowski JA et al[11] showed intrathecal neostigmine inhibits the metabolism of spinally released acetylcholine and produces analgesia in a dose dependent manner. Ten μg or less administered intrathecally reduced postoperative morphine requirement for 10h. Higher doses increase the risk of nausea. Co-administration of neostigmine[12] and morphine intrathecally allows a reduction in doses of both drugs and reduces their side effects. In contrast we did not see any better analgesia with the addition of 50 μg of neostigmine. Pin Heng Tan et al[13] observed IT neostigmine 50 μg produced postoperative analgesia lasting about seven hours with fewer side effects and better satisfaction ratings than IT morphine 300 μg in knee surgeries. Chitora et al[14] observed an increase in the postoperative analgesic effect with increase in doses of 50 to 150 μg IT neostigmine but with unacceptable side effects like sweating, bradycardia and vomiting, but we did notice the side effects without better analgesia.

Conclusion :

We conclude that intrathecal neostigmine in the dose of 50 μg is not useful as a postoperative analgesic supplement. With a higher incidence of intraoperative and postoperative nausea and vomiting its use should be with caution until further studies confirm its efficacy with minimal side effects.

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References :

1. Hood DD, Eisenach JC, Tuttle R. Phase I safety assessment of intrathecal neostigmine in humans. Anesthesiology1995; **85**: 331–343.
2. Klamt, JG., Slullitel, A., Garcia, I. V. & Prado, W. A. Postoperative analgesic effect of intrathecal neostigmine and its influence on spinal anaesthesia. Anaesthesia, 1997; **52** (6), 547-551.
3. Yegin A, Yilmaz M, Karsli B, Erman M. Analgesic effects of intrathecal neostigmine in perianal surgery. Eur J Anaesthesiol 2003; **20**: 404–408.
4. Lauretti GR, Mattos AL, Reis MP, Prado WA. Intrathecal neostigmine for postoperative analgesia after orthopaedic surgery. J Clin Anesth 1997; **9**: 473–477.
5. Yaksh TL, Dirksen R, Harty G J. Antinociceptive effects of intrathecally injected cholinomimetic drugs in cat and rat. Eur J Pharmacol 1985; 117:81-88.
6. Tan PH,Kuo JJ, Liu K, Hung CC. Efficacy of intrathecal neostigmine for the relief of post inguinal hernioraphy pain. Acta Anaesthesiol Scand 2000; 44: 1056-1060.
7. Carp H, Marrow D, Jayaram A. Intrathecal cholinergic agonist lessen buipivacaine spinal block induced hypotension in rats. Anesth Analg 1994; 79:112-116.

8. Lauretti GR, Hood DD, Eisenach JC. A multi-center study of intrathecal neostigmine for analgesia following vaginal hysterectomy. Anesthesiology 1998; 89:913-8.
9. Savita saini, Sunil Sethi, Naveen Malhotra. Evaluation of intrathecal neostigmine for postoperative analgesia. J Anaesth Clin Pharmacol 2006; 22(1) :35-40.
10. Gosavi, Poddar. Analgesic effects of intrathecal neostigmine. European Journal of Anaesthesiology 2003; 20: 984–992
11. Krukowski JA, Hood DD, Eisenach JC, Mallak KA, Parker RL. Intrathecal neostigmine for post-cesarean section analgesia: dose response. Anesth Analg 1997; 84:1269-75.
12. Chung C-J, Kim J-S, Park H-S, Chin Y-J. The efficacy of intrathecal neostigmine, intrathecal morphine, and their combination for post-cesarean section analgesia. Anesth Analg 1998; 87:341-6.
13. Ping-Heng Tan, MD Intrathecal bupivacaine with morphine or neostigmine for postoperative analgesia after total knee replacement surgery. *Canadian Journal of Anesthesia* 2001; 48:551-556.
14. Chittora, Fareed Ahmed, Rajneender Sharma. A comparative analysis of neostigmine as an additive to lignocaine for postoperative analgesia in intrathecal and epidural anaesthesia. Indian J. Anaesth. 2003; 47 (3): 185-189.