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Original article:

Study of effect of intrathecal bupivacaine with neostigmine and fentanyl in lower abdominal surgery

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Abstract:

Introduction: Bupivacaine is the most commonly employed local anaesthetic for subarachanoid block, but has limited duration of action. Perioperative haemodynamic status is also a concern. Opioids, though useful as adjuvants, are associated with undesirable side effects.

Material and methods: The present prospective longitudinal study was undertaken to compare bupivacaine alone and with neostigmine or fentanyl used in lower abdominal surgery. 135 patients were grouped as per the drug received into:

Group C: 45 patients received 3 ml intrathecal bupivacaine (0.5%) heavy with normal saline 0.5 ml

Group F: 45 patients received 3ml intrathecal bupivacaine (0.5%) heavy with 0.5ml (25mcg) fentanyl.

Group N: 45 patents received 0.5 % of bupivacaine heavy 3ml with neostigmine 0.3 ml (150 mcg) with 0.2 ml normal saline

Results : Group F and Group N showed early onset of sensory block (98.71 and 97.33 secs respectively) as compared to Group C (160.11 secs) and this difference was statistically significant (**$p<0.05$**). The mean total duration of analgesia was prolonged in Group F and Group N (290.78 and 280.07 mins respectively) compared to Group C (210.22 mins). This difference was statistically significant as per ANOVA test ($p<0.05$).

Conclusion: Intrathecal neostigmine provides effective analgesia and reduced consumption of rescue analgesic whereas the dose was associated with much more prolonged duration of analgesia but at the cost of higher incidence of side effects such as nausea and vomiting.

Introduction:

Bupivacaine is the most commonly employed local anaesthetic for subarachanoid block, but has limited duration of action. Perioperative haemodynamic status is also a concern. Opioids, though useful as adjuvants, are associated with undesirable side effects. Hence ideal adjuvants that can be used with bupivacaine for stable intraoperative conditions and prolonging the post-operative analgesia with minimal side effects are being investigated. Fentanyl, a lipophilic opioid has rapid onset of action following intrathecal administration.it improves the quality of intraoperative analgesia and also provide post operative pain relief for longer duration.[1]

Neostigmine is a anticholinesterase agent which increases the acetylcholine concentrations at cholinergic synapses. 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 postoperative period[2] and seems to be extremely efficient for alleviating somatic pain.[2]

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Study type: An Observational study

Study design: Prospective longitudinal study

Study groups: patients between 20 to 60 years of age of either sex who scheduled for elective lower abdominal surgery at pmt,loni .

Period of study: 2 years

Study Area: In the department of Anaesthesiology and Critical Care, pmt, Loni.

Sample size: 135 (45 patients in each groups)

Inclusion Criteria

- Patients receiving intrathecal bupivacaine with neostigmine or fentanyl in lower abdominal surgery.
- Patient's age between 20 to 60 years
- Patients of either sex
- Patients with ASA grade 1 and Grade 2
- Patents undergoing lower abdominal surgery
- Patients willing for the study

Exclusion Criteria

- Patients with known hypersensitivity to study drugs
- Patients with neurological and psychiatric disorders
- Patients with bleeding disorders or on anticoagulants therapy
- Local infection at the site of injection
- Patients who are not willing for the surgery
- Morbidly obese patients

Results:

Comparison of Sensory charactertics among study groups

Group F and Group N showed early onset of sensory block (98.71 and 97.33 secs respectively) as compared to Group C (160.11 secs) and this difference was statistically significant (**p<0.05**). The mean total duration of analgesia was prolonged in Group F and Group N (290.78 and 280.07 mins respectively) compared to Group C (210.22 mins). This difference was statistically significant as per ANOVA test (**p<0.05**).

Table 1: Comparison of Sensory charactertics among study groups

Characteristics	Group C		Group F		Group N		p value*
	Mean	SD	Mean	SD	Mean	SD	
Mean Onset time (secs)	160.11	9.14	98.71	7.57	97.33	8.30	**<0.05**
Total duration of analgesia (mins)	210.22	23.86	290.78	24.19	280.07	20.85	**<0.05**

* - ANOVA test

Comparison of Motor charactertics among study groups

The mean time required to attain maximum motor block was significantly higher in Group C (221.09 secs) as compared to Group F and Group N (170.04 and 169.38 secs respectively). The quality of motor blockage was similar in all the groups. The duration of motor blockade was significantly shorter in Group C (183.78 mins) as compared to Group F and Group N (209.58 and 207.27 mins respectively) (**p<0.05**).

Table 2: Comparison of Motor charactertics among study groups

Characteristics	Group C		Group F		Group N		p value*
	Mean	SD	Mean	SD	Mean	SD	
Mean time reqd to attain max motor blk (secs)	221.09	11.55	170.04	9.85	169.38	10.43	**<0.05**
Quality of motor blockade	Bromage grade III -> 100%		Bromage grade III -> 100%		Bromage grade III -> 100%		
Duration of motor blockade (mins)	183.78	8.51	209.58	11.59	207.27	12.81	**<0.05**

* - ANOVA test

Discussion:

The present prospective longitudinal study was undertaken to compare bupivacaine alone and with neostigmine or fentanyl used in lower abdominal surgery.

There is a potential synergism between fentanyl and neostigmine along with bupivacaine as reported in an animal study by Wang C et al[3]. Intrathecal opioids bind to a family of G-protein-linked pre- and postsynaptic opioid receptors in Laminae I and II of the dorsal horn. Receptor activation leads to G-protein-mediated potassium channel opening (mu and delta) and calcium channel closure (kappa), with an overall reduction in intracellular calcium. This reduces the release of excitatory transmitters (glutamate and substance P) from presynaptic C fibres, but not A fibre terminals with consequent reduction in nociceptive transmission[4]. There are significantly greater number of opioid receptors located presynaptically compared with postsynaptically. Binding of opioids to postsynaptic receptor sites

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in the dorsal horn result in potassium channel opening and indirect activation of descending pathways from the brainstem[5].

Lipid soluble opioids also resemble local anaesthetics in terms of their pKa, molecular weight, and partition coefficients that may explain some of the analgesic effects of CSF opioids. Using a pig model[6]. They have demonstrated that fentanyl rapidly partitions into receptor and non-receptor binding sites (epidural fat, myelin, and the white matter). This has been ascribed to its high octanol: water partition coefficient (860), resulting in a high volume of distribution in spinal cord. After fentanyl administration, CSF concentration decreases rapidly; epidural space concentration increases; plasma concentrations increase rapidly with resultant systemic effects; and there is limited cephalad spread with segmental analgesia. lipophilic opioids with higher octanol: water coefficient and lower pKa values are retained for longer periods in the spinal cord resulting in longer duration of action.

The inhibition of spinal cholinesterase by neostigmine 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 terminate in the vicinity of primary afferent express muscarinic receptors. The endogenous acetylcholine produces analgesic effect through muscarinic presynaptic inhibition of glutamatergic afferents, similar to how it has been described in the neostriatum. Muscarinic receptor antagonists have been shown to reverse the analgesic effects of IT neostigmine.

A tonic cholinergic activity is an important prerequisite for the effectiveness of neostigmine. The enhanced analgesic efficacy of IT neostigmine 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[7].

The study of Bhavsar M et al[8] evaluating the analgesic efficacy of combined use of intrathecal fentanyl and neostigmine as an adjunct to Bupivacaine for postoperative pain relief for abdominal hysterectomy found no significant differences regarding age, weight, height, gender, and duration of surgery ($P > 0.05$).

Conclusion:

Intrathecal neostigmine provides effective analgesia and reduced consumption of rescue analgesic whereas the dose was associated with much more prolonged duration of analgesia but at the cost of higher incidence of side effects such as nausea and vomiting.

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