COMPARATIVE CLINICAL EFFICACY OF INTRATHECAL MAGNESIUM SULPHATE AND NEOSTIGMINE WITH BUPIVACAINE HEAVY FOR INFRA UMBLICAL SURGERIES: A RANDOMIZED CLINICAL STUDY

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Abstract

Objectives: To assess the efficacy of neostigmine and magnesium sulphate on characteristics of subarachnoid block, hemodynamic stability and postoperative analgesia, when added to 0.5% hyperbaric bupivacaine, in patients undergoing infraumblical surgeries.

Material and Methodology: In this randomised study, double blind study, 60 adult patients of American society of anaesthesiologist status I and II, aged between 18-50 years, of either sex (M & F), scheduled for elective infraumblical surgeries were assigned in two groups. The patients were randomly allocated to receive bupivacaine 3ml [15 mg] with preservative free magnesium sulphate 0.5 ml [50mg] in group I and Group II patients received bupivacaine (3ml) with neostigmine 0.5 ml [25µg]. We recorded the following parameters. Duration of sensory & motor blockade, quality of block, perioperative vitals and duration of post operative analgesia.

Results: Magnesium sulphate significantly increases the duration of sensory block in group I(397.67±14.003) as compared to group II(188.67±23.887), duration of motor block in group I(213.67±13.767) as compared to group II(164.67±23.154), duration of analgesia in group I(349.00±22.453) as compared to group II(327.83±31.61). Hemodynamic parameters were stable in both group I and II. Quality of block was much better in group I (3.83±0.40) as compared to group II (3.49±0.68).

Conclusion: In patients undergoing infraumbilical surgery, addition of 50mg of magnesium sulphate as an adjuvant to intrathecal bupivacaine is better in view of duration of sensory & motor blockade, quality of block and duration of analgesia, without any significant adverse effects.

Keywords: *Magnesium sulphate, Neostigmine, Hyperbaric Bupivacaine, Subarachnoid block, Motor block, Sensory block*

1. Introduction

Subarachnoid block is a safe and relatively inexpensive technique for ambulatory surgery and for major surgery when combined with long acting intrathecal opioids, extradural or

regional lower limb block. Regional anaesthesia is widely used in different surgical procedures including those performed below umbilicus. [1] Previous studies have demonstrated that both subarachnoid and epidural block tend to have reduced blood loss and occurance of deep venous thrombosis (DVT), less general induced adverse effects such as nausea, vomiting, sore throat, alteration of mental status, and cognitive dysfunction, and allowing an improved pain control. [2–3]Regional techniques may lead to conduction blockade or reduced pain ranged for several hours. Better pain control may result in an early hospital discharge and less hospital expense, with improved patient stability in postoperative period. [4] In addition, it is usually easy to administer and readily available. [5]It has become a common practice to use different therapeutic regimens for treating intra and postoperative pain and increasing the regional anaesthetic period, because no drug has yet been identified to have this advantage without associated therapeutic side effects. [6] One method to increase the duration and reduce side effects, is to administer combinations of other classes of analgesics with local anaesthetics. Intrathecal neostigmine has been shown to prolong motor and sensory blockade and reduces postoperative analgesic requirements. It inhibits the breakdown of 3 acetylcholine in dorsal horn and spinal meninges, therefore increasing acetylcholine concentration, which causes analgesia through action on spinal cholinergic muscarinic receptors M_1& M_2. We choose a dose of 25µg because this dose would be unlikely to cause side effects and has produced evidence of analgesia in clinical trials. [7, 8] Magnesium blocks calcium influx and is a noncompetitive antagonist to NMDA receptors, it has the ability to prevent central sensitization from peripheral nociceptive stimulation.[9,10] Due to the fact that both neostigmine and magnesium sulphate have shown effects on local anaesthetic effects, we considered these two drugs and compared their equivalent doses effects as an adjuvant. Because the effects of adding these two non-opioid drugs in such a concentration and comparing their effects have not studied formerly.The purpose of this study was to assess the efficacy of adjuvant therapies with neostigmine or magnesium sulphate, compared with bupivacaine intrathecally, in patients undergoing infraumblical surgeries under subarachnoid block.

2. Materials And Methods

In this comparative observational hospital based study, a total of 60 adult patients ofAmerican society of anaesthesiologist status I and II, aged between 18-50 years, of either sex (Male & Female), scheduled for elective infraumblical surgeries were included in this study.

After approval from the Institutional Ethics Committee. All the patients were subjected to detailed pre-anaesthetic evaluation with clinical history, thorough physical and systemic examination, including all routine investigations. Procedure was explained to the patient in their language followed by informed written consent. The patients with neurological disabilty, spinal or neurological deformity, skin infection at the site of subarachnoid block, bleeding diasthesis, history of drug allergy to bupivacaine, magnesium sulphate and neostigmine, were excluded from the study.The patients were randomly divided into two groups of 30 patients each with the help of a random number table. The groups were assigned as group I, II respectively. Group I patients received bupivacaine 3ml [15 mg] +

preservative free magnesium sulphate 0.5 ml [50 mg].The 50 mg $MgSO_4$ was prepared by 1 ml of $MgSO_4$ 50% plus 5 cc Normal Saline 0.9%.Group II patients received bupivacaine (3ml) + neostigmine 0.5 ml [25µg]. The 25µg neostigmine was prepared by 1 cc of neostigmine 0.5% plus 10 cc Normal Saline 0.9%. Materials required for the procedure is Spinal trolley with 25G quinckes type spinal needle, 2ml and 5 ml disposable syringes, lignocaine 2% vial for local infiltration. All equipments necessary for resuscitation were kept ready like emergency drugs, cardiopulmonary resuscitative equipments, oxygen sources etc. Drugs required in this study include, one ampoule of bupivacaine 0.5% (H), one ampoule of neostigmine (0.5 mg/ml),one ampoule of magnesium sulphate (50% W/V). Once patient in operation theatre, Peripheral line was secured by inserting i.v cannula [18-20G], preloaded with ringer lactate solution 15 ml/kg. All the monitoring equipments (like NIBP Cuff, Pulse oxymetry, ECG) were attached to the patient and baseline values of heart rate, blood pressure, SpO_2 and respiratory rate were recorded. Patients were kept in supine position. Inj. ondansetron 4 mg and inj. ranitidine 50 mg was given intravenously to all the patients as an antiemetic prophylaxis, prior to induction. After strict aseptic precautions, skin and subcutaneous tissue was infiltrated with 2% inj. lignocaine, then subarachnoid block was performed in sitting position, using midline approach with 25 G spinal needle in L3-L4/L4-L5 intervertebral space. After the appearance of free flow of CSF, the mixture of drugs according to assigned group was injected. Utmost care was taken to avoid any leakage of any of these drugs. The spinal needle was removed and patient turned to supine position. Supplemental oxygen at4 L/min was given throughout the procedure via facemask.Blinding was achieved with the use of equal volume of the drugs (3.5 ml) and syringes labelled as A and B as per their content.Various parameters were then assessed and recorded on a prescribed proforma like duration of sensory block (time for regression of sensory block to S_2 dermatome was), motor block (time to achieve grade 0 motor blockade from grade 3 motor blockade), quality of block[Grade 1-(unsuccessful) patient needs general anaesthesia Grade 2 - (moderate) complaints that require supplemental analgesia. Grade 3- (good) minor complaints with no need of supplemental analgesia.Grade4-(excellent) no complaints], duration of analgesia (time from intrathecal injection of drug until the patient request for additional analgesia, which further assessed by visual analogue score of ≥ 4). Demographic parameters like age, height, weight, sex were also recorded on prescribed proforma. Hemodynamic variables like heart rate, blood pressure, respiratory rate, systolic and diastolic blood pressure, SpO_2 were recorded preoperatively and at 5^{th} min, 10^{th} min and 150^{th} min. The surgical anaesthesia was considered effective when T_{6-8} dermatome was blocked and grade 3 motor block was achieved. After establishment of adequate level of block upto T_{10}, surgery was started and time of beginning of surgery and duration of surgery was noted. Patients in both the groups were observed for any adverse events in the intraoperative and postoperative period for 24 hrs. Those patients in whom sensory block was inadequate and those requiring general anaesthesia were excluded from the study.

Statistical Analysis: All the data in the form were filled using Microsoft excel sheet. Statistical Analysis was done by using descriptive and inferential statistics using chi-square test and student's unpaired t test and software used in the analysis were SPSS 22.0 version

and Graph Pad Prism 6.0 version. $p<0.05$ is considered as level of significance [s]. HS means highly significant and NS means non- significant.

3. Observation And Results:

A total of 60 patients were included in the study based on inclusion and exclusion criteria with 30 in each group. Mean duration ofanalgesia was maximum in group I i.e. 348.00 ± 21.453 min and it was 326.73±30.61min in group II. There was statistically highly significant difference found in duration ofAnalgesia between the two groups, (p=0.001). It also shows comparisonof quality ofblockin twogroups. Mean quality of block score was highest in group I i.e. 3.93 ± 0.45 min and it was minimum in group II i.e.3.53 ± 0.67 min. There was statistically highly significant difference found in quality of blockbetween two groups, (p=0.001). The mean duration of surgery was 94.00 min in group I &92.00 min in group II. There was statistically no significant difference found in duration of surgery between two groups,(p>0.05).Among the complications nausea was seen among 3 patients intraoperatively and 1 patient in postoperative period in group II. Shivering was found in 2 patients intraoperatively in group I. Bradycardia was seen only in one patient in group II**.** Vomiting was seen in 1 patient postoperatively in group I and II and in 2 patients intraoperatively in group II. Pruritis was not seen in any of the patients.

TABLE-1

PARAMETER	**GROUP I**		**GROUP II**		**P-value**
	Mean	**SD**	**Mean**	**SD**	
Age(18-50 Year)	34.67	10.02	37.87	9.68	**0.581(NS)**
Height(incm)	166.52	8.70	164.00	7.84	**0.280(NS)**
Weight(inKg)	56.50	5.80	57.13	6.98	**0.457(NS)**

Table 1 shows age, height and weight distribution in the two groups. All the patients were 18-50 years old. Mean age was 34.67 years in group I & 37.87 years in group II. Mean height was 166.52 cm in group I &164.00 cm in group II. Mean weight was 56.50 kg in group I &57.13 kg in group II. There was statistically no significant difference found in age, height & weight between two groups.

TABLE-2

Gender	**GroupI N (%)**	**GroupII N (%)**	**Total**	**P-value**
Male	18(60.0%)	16(53.3%)	31(56.7%)	**0.863(NS)**
Female	12(40.0%)	14(46.7%)	29(43.3%)	
Total	30	30	60	

Table 2 shows demographic profile of patients in two groups according to gender. Out of 60 patients 31(56.7%) were male and 29 (43.3%) were females. There was statistically no significant difference found in distribution of patients according to gender, (p=0.873).

TABLE-3

Parameters	**GroupI**	**GroupII**	**P-value**

	Mean	**SD**	**Mean**	**SD**	
Duration of sensory blockade (min.)	396.66	13.003	187.67	22.877	**0.001(HS)**
Duration of Motor blockade (min.)	214.68	12.667	165.67	22.154	**0.001(HS)**
Duration of Analgesia (min.)	348.00	21.453	326.73	30.61	**0.001(HS)**
Quality Score	3.93	0.45	3.53	0.67	**0.001(HS)**
Duration of surgery(min.)	94.00	18.72	92.00	20.28	**0.919(NS)**

Table 3 shows comparisonofduration ofsensoryblockade(min.) in between twogroups**.** Duration ofsensoryblockadewas maximum in group I i.e. 396.66 ± 13.003 min and was 187.67±22.877 min in group II. There was statistically highly significant difference found in duration ofsensoryblockadebetween two groups, (p=0.001). Durationofmotorblockade was maximum in group I i.e. 214.68 ± 12.667 min and it was 165.67±22.154 min in group II. There was statistically highly significant difference found in duration ofmotorblockade between the two groups, (p=0.001).

4. Discussion:

Subarachnoid blocks is now a days most popular and commonly used for infraumblical surgeries. Subarachnoid block is preferred over epidural block, because of its rapid onset, good density block, lower failure rates, no catheter-related complications, and cost-effectiveness, but has the limitations of shorter duration of block and inability to extend the analgesia into the postoperative period [11]. Recently, intrathecal adjuvants are being used popularly with the aim of maintaining the hemodynamic vitals, reducing the dose of intrathecal local anaesthetics, delaying the receding of sensory block, during the postoperative period, and thus reducing the demand for postoperative rescue analgesics. Addition of adjuvants ensures faster recovery, enabling patients to return to their routine activity more quickly [12]. Most commonly used adjuvant in central neuraxial blocks are opioids [13], however, their adverse effects such as respiratory depression, nausea, vomiting, hypotension, constipation, and pruritis have prompted further research to develop nonopioid adjuvants with less worrisome side effects [14]

Magnesium sulphate is NMDA receptor antagonist. N methyl D aspartate receptors plays an important role in neuronal plasticity and processes leading to central sensitization of pain. Intrathecal magnesium sulphate blocks NMDA receptors at dorsal horn thus preventing central sensitization to pain and improving anaesthetic and analgesic quality [15].Hood et al.in 1995 first reported postoperative analgesia of intrathecal neostigmine acholinesterase inhibitor, the effectiveness of which being comparable to morphine. Several studies have suggested neostigmine to be an effective adjuvant for prolonging the duration of the subarachnoid block with better hemodynamic stability [16]. Many studies found synergism between intrathecal neostigmine with local anaesthetic agents. Considerable evidence exists to support the role of cholinergic agonists and anticholinesterase agents in the spinal inhibition of nociceptive transmission [17]. Intrathecal administrations of neostigmine produce antinociception, which is mediated by spinal muscarinic and nicotinic receptors in animals and human beings [18]. It produces analgesia by releasing of nitric oxide and inhibiting the metabolism of acetylcholine and binding to M_1 and M_3 muscarinic and to nicotinic receptors

[19]. Whereas local anaesthetic agents/bupivacaine act by blocking voltage gated Na^+ channels in spinal cord.Since all the groups were demographically similar (P > 0.05 in all the comparisons), it can be presumed that the groups are comparable for the purpose of the study.All the patients of study group were preloaded with ringer lactate to counterbalance the effect of relative hypovolemia or hypotension.In this study, they found that magnesium sulphtate in a dose of 50 mg when added to bupivacaine-fentanyl combination for subarachnoid block could provide prolonged post-operative analgesia without any side effects in patients undergoing lower limb orthopaedic surgery and also prolongs the duration of sensory blockade.Malleeswaran et al. **[20]**in their study also observed similar results with a combination of bupivacaine-fentanyl and magnesium intrathecally in patients with mild preeclampsia undergoing caesarean section. Arcioni et al **[21]** also observed that intrathecal and epidural magnesium sulphate, potentiated and prolonged the motor blockade.Unlugenc et al. **[22]** in their study showed prolongation of the duration of sensory block in magnesium group.Dayioglu et al **[23]** also concluded from their study that addition of intrathecal magnesium sulfate to subarachnoid block, prolonged the time to first analgesic requirement.In our study all the patients were hemodynamically stable in both the groups with respect to pulse rate, systolic blood pressure & diastolic blood pressure, respiratory rate and SpO_2 (P>0.05).In our study, the incidence of nausea, vomiting and shivering, showed no significant difference among the two groups and this may be related to similar hemodynamic and absence of significant hypotension among groups.

5. Conclusion:

We carried out our study in 60 patients divided in two groups. The study was carried out to compare the effect of intrathecal magnesium sulphate 50mg, intrathecal neostigmine 25µg added to intrathecal bupivacaine heavy and found that both can be used to prolong the duration of sensory and motor block, duration of analgesia and quality of block and it is prolonged more significantly with magnesium sulphate as compared to neostigmine.

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