ORIGINAL ARTICLE

COMPARATIVE STUDY OF INTRAVENOUS INFUSION OF CLONIDINE AND/OR MAGNESIUM SULPHATE ON HAEMODYNAMIC STRESS RESPONSE TO TRACHEAL INTUBATION AND PNEUMOPERITONEUM DURING LAPROSCOPIC SURGERY

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ABSTRACT

Introduction: Laryngotracheal intubation and co_2 pneumoperitoneum in laproscopic surgery is associated with significant stress response. In this prospective, randomized study, we investigated the efficacy of magnesium sulfate and clonidine to prevent adverse hemodynamic stress response.

Methodology: 60 patients of either sex (18-60yrs) undergoing elective laproscopy surgery were randomly divided in two groups. 1. In Goup C, IV infusion of Inj clonidine 1.5 μg/ kg while in group M, Inj magnesium sulphate 50mg/kg diluted in 100ml NS over 15 min was started 30 min before surgery and intraoperatively, IV infusion of clonidine 1μg /kg/hr and magnesium sulphate 10mg/kg/hr was started respectively before creation of pneumoperitoneum.

Results: Mean heart rate was significantly high immediately after intubation in group M compared to group c and significantly less in clonidine group before and immediately after pneumoperitoneum. No significant difference was observed in mean blood pressure in both groups. Time for rescue analgesic was prolonged in group M. Sedation, extubation time and discharge time was significantly longer in group M.

Conclusion: Administration of clonidine and magnesium sulfate produces hemodynamic stability during intubation and pneumoperitoneum in laproscopic surgery.

Keywords: clonidine, magnesium sulfate, laproscopic surgery, hemodynamic response

INTRODUCTION

"Jacobeus" applied technique to insufflate air in abdomen of human being in 1910 (Sweden) and named the procedure "laproscopy". 1968, Semm was the first to develop CO_2 pneumo-insufflator for pneumoperitoneum. Laparoscopic procedure results in multiple benefits compared with open procedure due to better maintenance of homeostasis, less trauma, smaller scar, less postoperative pain and pulmonary impairment, reduction in postoperative ileus, earlier ambulation, and shorter hospital stay.

The pressure response to tracheal intubation has been recognized by King and his colleague in 1951. The increase in blood pressure is usually transitory and is thought to be result of laryngotracheal stimulation which results in reflexive sympathoadrenal stimulation.[1] It may result into increase in myocardial oxygen demand which may cause myocardial ischemia, left ventricular failure or cerebral haemorrhage. These changes may be well tolerated in healthy individuals, but hazardous in patients with cardiovascular disease, raised intraocular and intracranial pressure.[2] Such hemodynamic changes are also associated during laproscopic procedure result from co_2 insufflation as consequences to hypercarbia induced release of catecholamine, vasopressin or both. In this prospective randomized study we compare effectiveness of intravenous infusion of clonidine and/or magnesium sulphate to attenuate hemodynamic stress response to tracheal intubation and CO_2 insufflations in patients undergoing laparoscopic surgery.

METHODOLOGY

After approval from institutional ethical committee, written informed consent was obtained from each patient. Sixty patients aged 18 to 60 years, belonging to ASA grade I & II physical status, scheduled for elective laparoscopic surgery were randomly divided

in two groups: Group C (clonidine) and Group M (magnesium sulfate). Patients with Cardiovascular, respiratory, renal, liver, neuromuscular, endocrine diseases and in whom laparoscopy converted in to open laparotomy were excluded from the study. Thorough preoperative anesthetic evaluation was done on the day before surgery. All patients received tab alprazolam 0.5 mg in the night before surgery and kept NBM overnight. On the day of surgery, in the recovery room, vitals were confirmed. After securing iv line, Inj Ringer lactate 5ml/kg/hr was started to all patients and premedicated with Inj glycopyrrolate 0.004mg/kg and Inj butorphenol 1mg IM ,30 min before surgery. IV infusion of Inj clonidine 1.5 µg/ kg in group C while Inj magnesium sulphate 50mg/kg diluted in 100ml NS over 15 min in group M was started 30 min before surgery. In operation theatre after preoxygenation for 3min with 100% oxygen, all patients were induced with injection propofol 2mg/kg and injection succinyl choline 2mg/kg intravenously and intubated with cuff endotracheal tube within 30seconds.

All patients were maintained with oxygen, nitrous oxide, isoflurane and injection vecuronum bromide 0.06mg/kg and infusion of injection propofol 100µg/kg/min.

Intraoperatively Group (C) and group (M) were received, IV infusion of clonidine 1µg /kg/hr and magnesium sulphate 10mg/kg/hr respectively before creation of pneumoperitoneum. Veccuronium bromide was supplemented when TOF stimulation shows two twitch responses on PNS. Intraoperatively, pulse rate, mean arterial blood pressure, SPO_2, $ETCO_2$, ECG were monitored before induction, after intubation, before and after pneumoperitoneum then every ten minute till the surgery is over and after extubation.

During surgery, intraabdominal pressure was maintained between 11 to 15 mm of hg and recorded every 10min after creation of pneumoperitoneum. At the end of surgery, all infusions were stopped immediately after release of pneumoperitoneum. When TOF stimulation shows all 4 twitch response on PNS, patients were reversed. Postoperatively, mean pulse rate, mean blood pressure, Ramsay score for sedation, VAS score for pain, nausea and vomiting score, Aldrete score for recovery room discharge and any complications like hypotension, bradycardia, hypoxia were recorded every 15 minute initially for 2 hours.

Statistical Analysis: The results obtained from the study were presented in tabulated manner. The results are expressed as mean SD. The data were analysed by using student's t-test. Categorial data was compared using chi-square test. P value<0.05 was considered statistically significant and p<0.01 was highly significant. Statistical analysis was done using SPSS software.

RESULTS

Both groups were comparable with respect to age, sex, body weight, duration of surgery and duration of pneumoperitoneum (p>0.0.5) (Table 1).

Basal mean heart rate in Group C (86.4 ± 6.9 per minute) and in group M (89 ± 7.5 per minute) was comparable and statistically not significant (p>0.05). Before induction and after intubation mean HR was increased in both the groups but rise in HR was less and statistically highly significant in group C (P<0.01) compared to group M, while before and immediately after pnemoperitoneum, mean HR was reduced in both the groups but more in group C which was statistically highly significant (p<0.01).

No significant difference was observed in mean arterial blood pressure intra and post operatively. Time for postoperative analgesic requirement was earlier in group C (82.16±13.6) min as compared to group M (146.33±19.56) min which was statistically highly significant (P<0.01). Postoperatively up to two hours sedation score was high in group M (3.6±0.4 to 2.5±0.5) compared group C (3.03±0.4 to 2±0.18) which was statistically highly significant (P<0.01) so more sedation was observed in magnesium group and had longer time (12.8min) for extubation as compared to clonidine group (6.1min). Recovery of patients from anaesthesia and discharge to ward was earlier in clonidine group (90 min) compared to magnesium group (120 min). So, patients were discharge to home earlier in clonidine group as compared to magnesium group. No other side effects like hypertension, hypotension, nausea and vomiting, respiratory depression, shivering were observed in patients of both the groups.

Table 1: Patient characteristics given as mean (SD)

Parameter	Group C (n=30)	Group M (n=30)	p Value
Age (Years)	35±9.47	31±12.2	0.16
Gender (Male / Female)	11 / 19	7 / 23	0.26
Weight (Kgs)	52.03±11.4	47.8±10.4	0.14
Duration of Surgery (in minutes)	97.33±22.99	88.83±22.27	0.15
Duration of Pneumoperitoneum (in minutes)	75.16±22.68	67.00±21.67	0.16

Table 2: Mean heart rate (per minute) given as mean SD

Time	Group C Mean ± SD	Group M Mean ± SD	p Value
Baseline	86.46 ± 6.96	89.06 ± 7.55	0.12
Intraoperative Period			
Before induction	88.4 ± 10.15	93.2 ± 14.6	**0.02**
After intubation	90.03 ± 10.8	96.9 ± 2.3	**0.01**
Before PP	79.76 ± 9.71	88.6 ± 10.9	**0.001**
After PP	77.5 ± 11.9	86.5 ± 12.15	**0.005**
10 min	79.3 ± 13.6	86 ± 10.7	**0.03**
30 min	80 ± 12.4	83.1 ± 9.6	0.2
60 min	74.9 ± 8.9	76.7 ± 11.9	0.5
90 min	67.8 ± 6.7	74.8 ± 5.5	0.07
120 min	71.8 ± 3.3		
Postoperative Period			
30 min	81 ± 8.6	81.1 ± 8.7	0.9
60 min	81 ± 8.0	81.8 ± 8.7	0.7

Table 3: Mean arterial pressure (mm of hg) given as mean SD

Time	Group C Mean ± SD	Group M Mean ± SD	p Value
Baseline	87 ± 7.3	88 ± 7.4	0.6
Intraoperative Period			
Before induction	88 ± 8.3	91 ± 8.2	0.1
After intubation	85 ± 11.1	90 ± 10.8	0.07
Before PP	83 ± 11.6	85 ± 11.8	0.5
After PP	89 ± 13.6	93 ± 12.8	0.2
10 min	92 ± 13.7	94 ± 12.9	0.5
30 min	92 ± 12.1	92 ± 11.9	0.9
60 min	89 ± 11.7	91 ± 8.7	0.5
120 min	87 ± 11.6	-	-
After extubation	93 ± 6.4	94	0.7
Postoperative Period			
30 min	90 ± 7.9	87 ± 6.2	0.7
60 min	88 ± 6.9	89 ± 6.2	0.5

DISCUSSION

Stress response under general anaesthesia has been universally recognized phenomenon. Direct laryngoscopy and passage of endotrachial tube are noxious stimuli that can provoke adverse (stress) response.[3] Hemodynamic changes observed during laparoscopy results from the combine effects of position of patients require for laparoscopy, hypercarbia from the absorbed CO_2 used for pneumoperitoneum, raised intraabdominal pressure and general anesthesia.[3]

Various methods have been used to attenuate stress response like: Alpha2-adrenergic agonists, beta-blocking agents, opioids, vasodilators, magnesium sulphate etc. In present study, effect of clonidine and /or magnesium sulphate is compared to attenuate hemodynamic stress response.

Ray M, Bhattacharjee D et al 2010[2] used 3mcg/kg of clonidine IV over 15 min before induction and 1mcg/kg /hr by continuous infusion during surgery and observed significance incidence of bradycardia and hypotension in their study. Altan and turgut et al in 2005 [4] used 3mcg/kg of clonidine IV over 15 min before induction and 2mcg/kg /hr by continuous infusion during surgery and observed similar findings. In this study, we reduced the dose of clonidine 1.5 mcg/kg IV over 15 min in 100ml NS, 30min before induction as well as 1mcg/kg/hour infusion before pneumoperitonium and didn't observe any such side effects.

Elsharnouby et al in 2006[5] used magnesium 40mg/kg IV before induction and 15mg/kg/hr by continuous infusion intraoperatively. They noticed more episode of hypotension using this dose of magnesium. While bhattacharjee, et al in 2010[2] used intravenous magnesium sulphate (30mg/kg before induction and 10mg/kg/hr infusion intra-operatively). They noted that HR was significantly lower in both the groups. We used IV magnesium in a dose of 50mg/kg as a bolus preoperatively and reduced IV magnesium infusion to 10mg/kg/hr intraoperatively and observed that none of the patients developed bradycardia/ tachycardia and hypotension/ hypertension which was comparable with the study of D. Jee, D.lee et al in 2009.[6]

So both clonidine & magnesium sulphate prevent the stress response to laryngoscopy & pneumo-peritoneam but clonidine is more effective then magnesium sulphate which can also be supported by study of Abbady A. Ahmed et al in 2009 and Kalra, Anil verma, et al in 2012.

Clonidine stimulates alpha-2 adrenergic inhibitory neurons in the medullary vasomotor centre, results decrease in the sympathetic nervous system outflow from the CNS to the peripheral tissue, which is manifested as peripheral vasodilatation and a decrease in systolic BP, HR and cardiac output.[7]

Magnesium sulphate blocks the release of catecholamines from adrenergic nerve terminals and adrenal glands associated with tracheal intubation moreover magnesium sulphate produce vasodilatation by acting directly on blood vessels and attenuates vasopressin stimulated vasoconstriction which ultimately modulate hypertension and tachycardia and neurohumoral response in patients during CO_2 pnemoperitoneum.[4]

In present study, sedation and extubation time as well as postoperative analgesia was more in magnesium group. So, recovery of patients from anaesthesia and discharge from RR to ward and home readiness is prolonged in magnesium group as compared to clonidine group. Results of Kalra, Anil Verma, et al in 2012 and Ray M, Bhattacharjee D et al 2010 were consistent with the present study.

Perioperative application of magnesium sulphate is associated with better analgesia, reduced PONV and

shivering, less discomfort and better quality of sleep thus improved patients satisfaction but compare to clonidine , CNS depressent effects and synergestic effect of magnesium sulphate with vecuronium on neuromuscular junction may be contributing factor for prolong recovery in magnesium group.

α_{2a} receptors mediate sedation, analgesia and sympatholysis, are founded densely in the pontine locus coeruleus which is an important source of sympathetic nervous system innervation of the forebrain and a vital modulator of vigilance. The sedative effects of clonidine most likely reflect inhibition of this nucleus.[7]

Magnesium has a depressant effect at synapses by relative competition between calcium and magnesium, mainly inhibiting presynaptic release of acetylcholine at neuromuscular junction. It has an antagonist effect at NMDA receptors thus decreasing stimulus for excitatory postsynaptic potentials (EPSP) which indicate intrinsic analgesic properties.[4] NMDA receptors play a significant role in neuronal plasticity and processes leading to central sensitization to pain. Thus magnesium has been shown to be useful in the reduction of acute postoperative pain, analgesic consumption, or both.

Clonidine also produces drowsiness by modifying the potassium channels in the CNS and thereby hyperpolarize the cell membrane may be the mechanism but CNS effect of magnesium was more than clonidine.

CONCLUSION

Administration of IV Clonidine 1.5mcg/kg was more effective than IV magnesium sulphate 50mg/kg given 30 min before induction to suppress hemodynamic stress response to laryngoscopy and tracheal intubation.

Administration of clonidine and/or magnesium sulphate infusion just before pnemoperitonium effectively and equally attenuates hemodynamic stress response to pneumoperitonium.

Perioperative use of magnesium sulphate provides postoperatively prolong analgesia and more sedation than clonidine without respiratory depression or any other adverse effects. Recovery of patients from anaesthesia and discharge to ward and home readiness were earlier in clonidine group compared to magnesium group.

So, both clonidine and magnesium sulphate can be used as an effective adjuvant to general anaesthesia reduce pain, analgesic consumption and stress response to intubation and pneumoperitonium in patients undergoing laparoscopic surgery. But, Synergetic effect of magnesium sulphate with vecuronium on neuromuscular block, CNS depressant effect, and direct interaction with calcium ions needs careful management particularly in patients with impaired renal function or atria-ventricular conduction disturbances.

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