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Effect of Administration of Magnesium Sulphate, Clonidine or Dexmedetomidine on Hemodynamics Due to Pneumoperitoneum in Patients undergoing Laparoscopic Procedures under General Anesthesia

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Abstract

Title: Effect of administration of Magnesium sulphate, Clonidine or Dexmedetomidine on hemodynamics due to pneumoperitoneum in patients undergoing laparoscopic procedures under general anesthesia. *Background*: Pneumoperitoneum and the positioning during laparoscopy induce pathophysiological changes which potentially complicate anesthetic management and require some intervention. *Aim:* To compare the effects of Magnesium sulphate ($MgSO_4$), clonidine, or dexmedetomidine on hemodynamic changes occurring after pneumoperitoneum in laparoscopic procedures. *Material and Method*: 60 adult, ASA Grade I & II, patients undergoing laparoscopies were randomly divided into three groups: Group M (magnesium sulphate), Group D (Dexmedetomidine) & Group C (Clonidine). In each group, boluses of study drugs were given before induction of anesthesia, followed by infusion prior to pneumoperitoneum. Heart rate, systolic/diastolic/mean blood pressure, end tidal CO_2, sedation score, VAS score for pain were recorded. Mean and standard deviation for each parameter was calculated using ANOVA. Sedation and pain (VAS) Score were calculated by Kruskal Willis test, p value<0.05 was considered statistically significant'. *Results:* Intraoperative heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure were below baseline & comparable in all three groups ($p<0.05$) but minimally disturbed in dexmedetomidine group. Most of the patients were pleasantly sedated at the extubation with maximum patients responding to verbal commands quickly in clonidine group. VAS Pain score were minimal in dexmedetomidine group.

Keywords: Laparoscopy; Pneumoperitoneum; Hemodynamic; Magnesium Sulphate; Dexmedetomidine; Clonidine.

Introduction

Laparoscopic surgical procedures, having the benefits of minimally invasive, are being successfully performed and accepted worldwide.[1,2] However, pneumoperitoneum and the position of the patient required for laparoscopy induce pathophysiological changes that may potentially complicate anesthetic management [3,4]. These changes include increases in blood pressure, end-tidal carbon dioxide ($EtCO_2$) pressure, and central venous pressure, which are the result of the increase in intrathoracic pressure and postural changes [5] Hypercapnia and pneumoperitoneum cause stimulation of the sympathetic nervous system leading to release of catecholamine and vasopressin [6]. Different pharmacological agents like α_2 adrenergic agonists [1], beta-blockers [7] and opioids [8] are often used to attenuate circulatory response due to pneumo-peritoneum. Use of α_2 adrenergic agonists such as clonidine or dexmedetomidine and beta blocking agents significantly reduce hemodynamic changes and anesthetic requirement [12]. The intraoperative stress response, however can be reduced by preoperative administration of α_2-agonist [12].

Clonidine, an α_2- adrenergic agonist, and dexmedetomidine, a new generation highly selective alpha-2 adrenoreceptor agonist, are well known to inhibit catecholamine release. Magnesium

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also is known to inhibit catecholamine release and attenuate vasopressin-stimulated vasoconstriction and intravenous administration of magnesium sulphate before pneumoperitoneum attenuates arterial pressure increases during laparoscopic cholecystectomy. Although magnesium sulfate 50 mg/kg produces hemodynamic stability comparable to clonidine 1μg/kg, clonidine in doses of 1.5μg/kg blunts the hemodynamic response to pneumoperitoneum more effectively [9].

Dexmedetomidine is a more selective alpha 2 adrenoceptor agonist with sedative and analgesic properties. Though approved for intensive care unit sedation, studies are being conducted on its off-label uses [10]. Dexmedetomidine, an α2 agonist, when used as an adjuvant in general anesthesia attenuates stress response to various noxious stimuli, maintains perioperative hemodynamic stability and provides sedation without significant respiratory depression postoperatively [11].

We have designed this randomized controlled study to compare the effect of clonidine, dexmedetomidine and magnesium sulphate in patients undergoing laparoscopic procedures. We got our study registered with clinical trial of India registration number CTRI/2016/-09/007325.

Aims & Objectives

1. To observe and compare the hemodynamic changes occurring after administration of magnesium sulphate, clonidine, or dexmedetomidine before and after creation of pneumoperitoneum in laparoscopic procedures.
2. To observe and manage other pharmacological effects if any.
3 To observe and manage any side effect and complication if any.

Material and Method

After approval from institutional ethical committee, All patients belonging to ASA I & II and well controlled hypertensive patients (on regular drugs) scheduled to undergo laparoscopic procedures lasting up to 2 hrs were included in the study.

Exclusion Criteria

Age ≤ 20 Yrs. and ≥ 65 yrs.

Uncontrolled hypertension

Any degree of heart block

Cardiac dysfunction (low ejection fraction state)

Impaired Kidney function

Impaired hepatic function

Patients on clonidine, alpha methyl dopa, Mao inhibitors

Patients allergic to Magnesium sulphate, clonidine, or dexmedetomidine

Total of 60 patients were included in study. Power calculations suggested that a minimum of 16 subjects per group was required to detect 10% difference in arterial pressure between groups (taking type I or α error of 5%, type II or â error of 20% and Standard Deviation=10).

Patients were admitted one day prior to the scheduled surgery, examined, interviewed and written informed consent was taken. No hypnotic medication was given on the evening before surgery. Upon arrival in the operating room, monitors were attached and baseline parameters, e.g. heart rate, NIBP, oxygen saturation and ECG, were recorded.

Patients were randomly divided into three groups by computer generated number system. We planned not to incorporate a control group in our study as hemodynamic alterations due to pneumoperitoneum and postural changes in laparoscopic surgeries are well documented and confirmed phenomena and leaving them untreated would not serve any purpose and might be unethical.

Group M

Received Magnesium sulphate bolus 30mg /kg, Infusion @10 mg/kg/hr.

$MGSO_4$ 6ml (3000mg) +44 ml of0.9% Normal saline (1ml =60mg).

(Total volume of 50 ml).

Group C:

Received clonidine bolus 2 mcg/kg, infusion @1mcg/kg/hr.

Clonidine 2ml (300mcg) +48 ml of 0.9%normal saline (1ml=6 mcg).

(Total volume of 50 ml).

Group D

Received Dexmedetomidine bolus 1 mcg/kg, infusion @0.5mcg/kg/hr.

Dexmedetomidine 2 ml (200mcg) +48 ml of 0.9% normal saline (1ml= 4mcg)

(Total volume of 50 ml)

All the study drugs were made in 50 ml normal saline and given by syringe pump. The preparation and labeling of the study drugs were performed by an anesthesiologist who was not involved in administration of study drugs.

The bolus of drug according to group was administered over 10 minutes before induction .A standard premedication of butorphenol 0.2 mg / kg, Glycopyrolate 0.02 mg/kg was administered. After pre-oxygenation for 3 minutes, anesthesia was induced with a standard anesthetic protocol using intra venous injection of Propofol till loss of eyelash reflex (1- 2mg/kg), and tracheal intubation was facilitated by vecuronium bromide 0.1 mg/kg intravenously.

Anesthesia was maintained by N_2O:O_2 (60:40) with controlled ventilation. After surgical field has been draped, infusion of the drug was started before creation of pneumoperitoneum as above mentioned.

Any decrease in mean arterial pressure more than 20% below baseline was considered hypotension .A bolus of 3-4 ml /kg of crystalloid over 5 -10 minutes was to be given to treat hypotension and over a period of 10 minutes. If no response, then rate of infusion of study drug was reduced to half. In case mean arterial pressure fell below 60, infusion was stopped.

Any increase in mean arterial pressure more than 20 % above baseline was considered hypertension. In that case the rate of infusion was increased. In case of no response, the depth of anesthesia was increased. Heart rate less than 50 beats per min was treated with increments of 0.3 mg of atropine. Heart rate more than 100 or 20% increase from baseline was treated by increasing the depth of anesthesia (increasing conc. of isoflurane).

Infusion was stopped at deflation of abdomen. Throughout the laparoscopic surgery, carbon dioxide pneumoperitoneum was established and maintained to a pressure of 14 mm Hg and $ETCO_2$ was maintained between 35-45 mm Hg.

Ringer lactate solution was administered intravenously at a rate of 15 mL/kg in the first hour, followed by 7.5 mL / kg / hr until the end of surgery in all patients. At the end of operation, neuromuscular blockade was antagonized with injection of neostigmine 0.05 mg/kg and Glycopyrolate 0.02 mg/kg intravenously and patient was extubated when respiration was deemed sufficient and they were able to obey verbal commands.

Observations

Arterial pressures and heart rates were measured upon arrival in the OT (baseline), at start of infusion, at induction of anesthesia, after intubation, and after every 10 minutes till release of CO_2, after deflation of pneumoperitoneum, and at extubation. Postoperative vitals were recorded in recovery room upon arrival and 20 minutes thereafter up to one hour. Time from switching of anesthetic agents to extubation and response to verbal commands were also noted. Intraoperative observations were recorded by anesthesiologist who was blinded to study drug and not directly involved in study. In post operative period sedation level, VAS score for pain, VAS for nausea and any episode of vomiting were recorded in addition to pulse rate, blood pressure and oxygen saturation one hour at interval of twenty minutes. Post operative observations were recorded by nursing staff posted in recovery room.

Statistical Analysis

Intraoperative and postoperative parameters among three groups were compared by using one way analysis of variance (ANOVA). The statistical data was expressed as mean and standard deviation. Categorical data were compared using Kruskal Willis test. A p -value of less than or equal to 0.05 was considered as statistically 'significant'.

Results

There were no significant differences between three groups with regard to demographic data such as age, sex, weight, ASA grade and duration of surgery, duration of anesthesia (Table1). Out of 60 patients, 33 patients underwent laparoscopic cholecystectomy,17 underwent laparoscopic appendecectomy, 5 had laparoscopy assisted vaginal hysterectomy and rest 5 underwent total laparoscopic hysterectomy.

Baseline heart rate was comparable among all three groups. After administration of bolus of study drug, there was fall in heart rate in all groups. Heart rate in group D showed maximum fall from baseline (8%) as compared to group C (5%) and group M (4.8%). Though there was noticeable increase in response to intubation as compared to pre

intubation heart rate in group M (3.9%) and group C (4.0%). There was hardly any change in heart rate in group D (0.13%). The difference in heart rate post intubation among groups was not statistically significant ($p>0.05$). Since study drug infusion was continued after intubation throughout surgery, so even after creation of pneumoperitoneum, heart rate remained below baseline throughout surgery. Though heart rate was comparable among groups, lowest pulse rate was recorded in dexmedetomidine group at all time intervals. As infusion of study drugs were stopped at deflation of pneumoperitoneum, increase in heart rate was noted at time of extubation in all three groups. Though difference in heart rate was not statistically significant among groups (p-0.14) but heart rate in group D show minimal increase at extubation (7.9%) as compared to group M (10%) and group C (10%) (Graph 1).

Preoperative baseline systolic blood pressure, diastolic blood pressure and mean arterial pressure were comparable among groups. After administration of bolus of study drugs there was fall in blood pressure below baseline. Fall in systolic blood pressure from baseline to pre-intubation was maximum in group D (15.5%) as compared to group M (12.1%)and group C (12.3%). Similar trend was seen in mean arterial pressure in group D (17.1%), group M (13.2%) and group C (12.8%) (Graph 2) Though there was slight increase in systolic blood pressure, diastolic blood pressure and mean arterial pressure after intubation as compared to pre intubation value but it was below baseline value and fluctuation was minimal in group D again. Blood pressure remained below baseline among three groups throughout procedure till extubation because of continuous infusion of study drugs. Even at extubation blood pressure was below base line in all three groups but there was rise in mean arterial pressure from pre extubation value (7.8%) in group M, (6.1%) in group D and (5.9%) in group C) Difference in systolic blood pressure, diastolic blood pressure and mean arterial pressure among groups was not significant at this time ($p>0.05$).

None of the patients had hypotension. Only one patient in group D had bradycardia that responded to 0.6mg of atropine.

Modified Ramsay Sedation Scale

Sedation score	Clinical response
0	Paralyzed, unable to evaluate
1	Awake
2	Lightly sedated
3	Moderately sedated, follow simple commands
4	Deeply sedated, responds to non painful stimulus
5	Deeply sedated, responds to painful stimulus
6	Deeply sedated, unresponsive to painful stimulus

Table 1: Demographic variables

Variables	Group M	Group D	Group C	p-Value
Age(years)	45.7 ±7.47	42 .0 ± 6.19	41.2 ±10.5	0.22
Gender				
M	10(47)	9(42)	5(27)	0.42
F	11(52)	12(57)	13(72)	
Weight(kgs)	59.6 ±8.36	60.4 ±8.36	60.65 ±9.06	0.93
ASA Physical status				
I	13	12	10	0.91
II	8	9	8	
Duration of surgery (minutes)	71±14.5	68.7±15.2	66±16	0.59
Duration of anesthesia (minutes)	101±14.5	97±16.7	96±16	0.57

Table 2: Recovery characteristics

Variables	Group M	Group D	Group C	p- Value
Extubation time(minutes)	9.4± 1.11	9.1± 0.85	6.9 ± 0.94	0.0001*
Eye opening to verbal commands(minutes)	10.1 ±0.78	10.4±1.10	7.9.±0.85	0.0001*

Recovery from anesthesia was smooth; there was no undue coughing on endotracheal tube. Time from Switching off of anesthetic agents to extubation and eye opening time was minimal in group followed by group D and group M ($p<0.05$) (Table 2). Out of all, patients in group D had sedation score 3 at extubation, maximum (17), followed by Group M(16) and 14 patients in group C (Table 3).

Post operative period was uneventful. Patients were calm during postoperative period. Heart rate, blood pressure remained within normal range with no hypotension and bradycardia. Most of our patients after extubation had Ramsay sedation score 3.Extubation time and eye opening to verbal commands was minimal in group C, followed by group D and group M ($p<0.05$). Sedation scores were statistically significant immediately on arrival in recovery room ($p< 0.05$). Patients in group C were least sedated among three groups on arrival in recovery room. Sedation score were comparable among groups after 20minutes, though still least in clonidine group. After 60 minutes, more number of patients start becoming awake in group D and group M ($p>0.05$).

VAS score for pain were comparable from arrival in recovery room up to 20 minutes and most of patients were pain free. At 40 and 60 minutes in recovery room, there was statistically significant

Table 3: Comparison of Sedation score in post operative recovery room

Time interval	Group M (sum of ranks)	Group D (sum of ranks)	Group C (sum of ranks)	p-Value
T0minute	28.5	40	23	0.0072*
T20 minutes	32.5	34.3	24.4	0.15
T40minutes	31.5	34.5	25.5	0.25
T60minutes	30	34	27	0.39

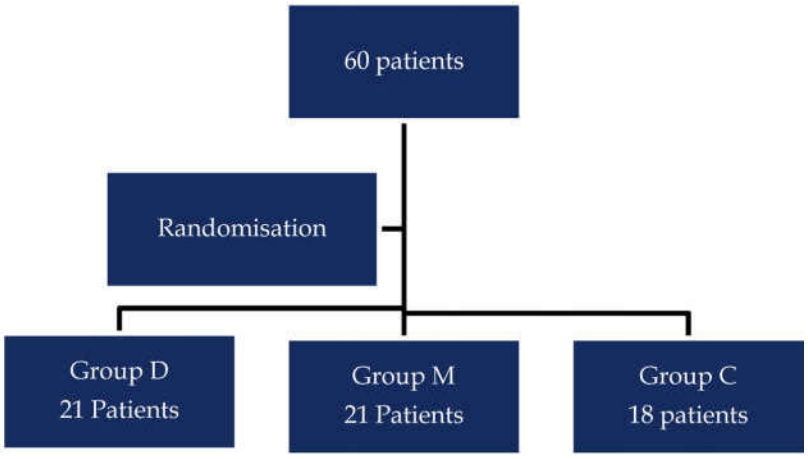
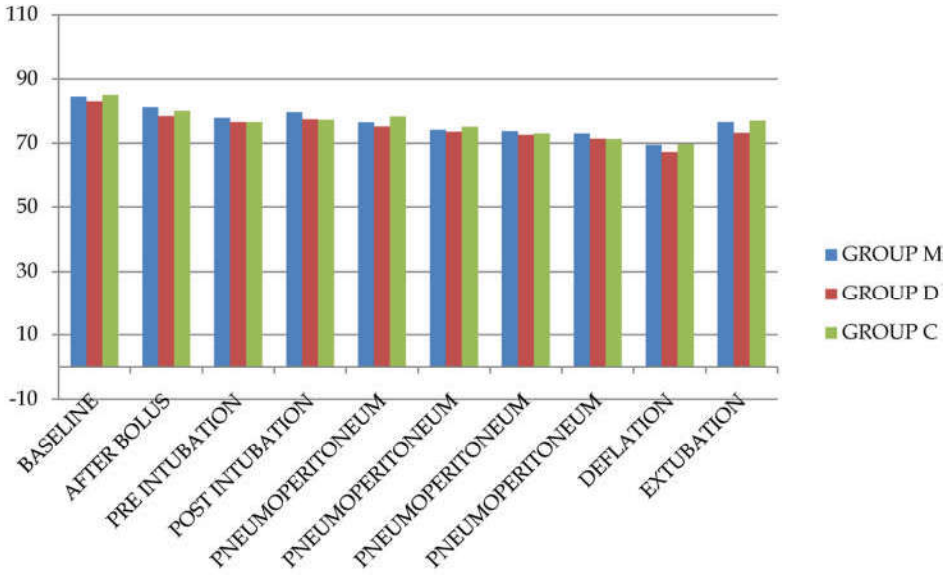
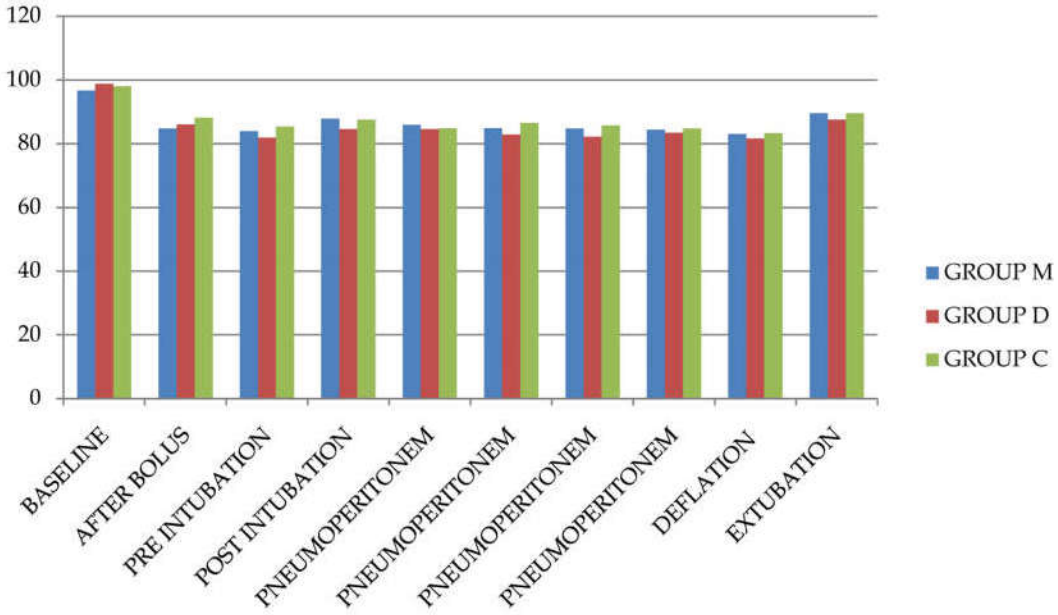


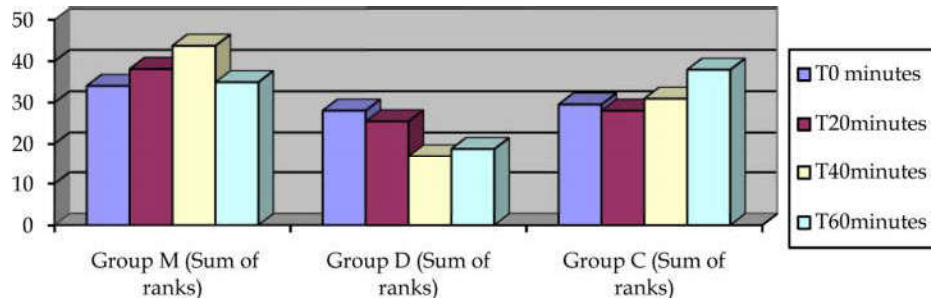
Chart 1: Consort chart



Graph 1: Comparison of Intraoperative Heart Rate among Groups



Graph 2: Comparison of intraoperative Mean Arterial Pressure Among Groups



Graph 3: Comparison of VAS score for pain in post operative period

difference in pain score ($p<0.05\%$). Pain scores were least (1-4) in group D followed by group M (2-6) and group C (2-5) (Graph 3). Only one patient in group M required analgesic. Only two patients complained of nausea in postoperative period in group M.

Discussion

Currently most preferred modality for abdominal surgeries is by laparoscopy. The preferred technique of anesthesia for laparoscopic abdominal surgeries is general anesthesia with tracheal intubation and muscle paralysis with intermittent positive pressure ventilation.

The hallmark of laparoscopy is the creation of pneumoperitoneum with carbon dioxide (CO_2). The pneumoperitoneum results in pathophysiological changes characterized by increase in arterial pressure and systemic and pulmonary vascular resistance (SVR and PVR). At intra-abdominal pressure of 15 mm Hg, Joris et al [13] found a 35% increase in mean arterial pressure, a 65% increase in systemic vascular resistance, a 90% increase in pulmonary vascular resistance, while there was a 20% decrease in cardiac output. Various pharmacological agents like magnesium sulphate, clonidine, dexmedetomidine, nitroglycerin, beta-blockers have been used to ameliorate pathophysiological changes during laparoscopy under general anesthesia. Perioperative use of α-2 adrenoceptor agonists' decreases sympathetic tone attenuates the stress responses to anesthesia and surgery, sedation and postoperative analgesia. Dexmedetomidine is a highly specific α-2 adrenergic receptor agonist [14]. We designed present study to compare magnesium sulphate, dexmedetomidine and clonidine during laparoscopic abdominal surgeries.

Clonidine, is a centrally acting selective partial α_2-agonist (α_2: α_1 = 220: 1). a α_2 agonist, inhibits the release of catecholamine and vasopressin hence causes decrease in heart rate and arterial pressure. This mechanism explains modulation of hemodynamic changes induced by pneumoperitoneum [15].

As bolus of study drugs was administered before induction of anesthesia, pressor response to laryngoscopy was also attenuated in all three groups. After administration of bolus of study drugs, heart rates start decreasing from baseline in all the groups. Heart rate in group D showed maximum fall from baseline (8%) as compared to group C & group M. Immediately after intubation there was rise in heart rate as compared to pre intubation value but remained below baseline in all three groups. Heart rate was minimally disturbed in group D. Jaakola et al [14] found decreased BP and heart rate during intubations following the administration of 0.6 μg/kg bolus of dexmedetomidine preoperatively. Perioperative use by Ray M [15] showed that of both clonidine and magnesium sulphate was able to attenuate the hemodynamic response to tracheal intubation.

Dexmedetomidine, with an elimination half life of 2 to 3 hours is a highly selective, potent and specific α_2-agonist (α_2: α_1 = 1620: 1), and is 7 to 10 times more selective for α_2 receptors compared to clonidine with a shorter duration of action [15]. Dexmedetomidine decrease sympathetic outflow from the locus coeruleus and this sympatholytic effect causes decrease of mean arterial blood pressure (MAP) and heart rate (HR) due to reduction of norepinephrine release. Further it causes release of substance P from the dorsal horn of the spinal cord and therefore exerting analgesic effect [16].

The effect of magnesium on hemodynamics is due to activation of membrane Ca-ATPase and Na-K-ATPase, enzymes involved in transmembrane ion exchanges during depolarization and repolarization phases, therefore behave as cell membrane stabilizer and intracytoplasmic organelles stabilizer [17]. This calcium inhibitory effect of Mg causes central arteriolar vasodilatation. The reduction of catecholamine release with sympathetic stimulation could be another mechanism responsible for amelioration of stress response to surgery. Magnesium exerts analgesic effect by blocking N-methyl-D-aspartate (NMDA) receptor which plays a significant role in the mechanisms underlying central sensitization in the spinal cord and is crucial for the establishment of several pain states [17,18].

In our study we did not notice significant hemodynamic disturbances during pneumoperitoneum. Heart rate remained below baseline throughout surgery. Infusion of study drug was stopped at deflation of pneumoperitoneum. At extubation there was increase in heart rate as compared to pre extubation value, rise was minimal in group D. There was no statistically significant difference among groups in heart rate at extubation ($P>0.05$).

Similarly, systolic blood pressure, diastolic blood pressure and mean arterial pressure start declining after bolus of study drugs (13.2% in group M,17.10% in group D and 12.8% in group C), though statistically no significant difference among groups. Though there was slight increase in systolic blood pressure, diastolic blood pressure and mean arterial pressure after intubation as compared to pre intubation value but it was below baseline value and fluctuation was minimal in group D again. Blood pressure remained below baseline among three groups throughout procedure till extubation because of continuous infusion of study drugs. There was slight rise in systolic blood pressure, diastolic blood pressure and mean arterial pressure at extubation because infusion was stopped at deflation of pneumoperitoneum. Statistically significant difference was not seen among all three groups in blood pressure at extubation. Observations in our study similar to those in a study conducted by Kalra et al [19] who assessed that which of magnesium or clonidine attenuates hemodynamic stress response to pneumoperitoneum better and found that systolic blood pressure was significantly higher in control group as compared to study groups during pneumoperitoneum with no significant difference between magnesium and clonidine given in dose of 1μg/kg.

Bryskin and Weldon [21] used a combination of dexmedetomidine and magnesium sulfate for hemodynamic control during laparoscopic resection of pheochromocytoma and reported that cardiovascular stability was achieved. In our study we used magnesium sulphate and dexmedetomidine individually in two different groups and found hemodynamic stability in both the groups.

Administration of clonidine or dexmedetomidine in a study by Rajdip Hazra et al [22] showed that before commencement of pneumoperitoneum effectively attenuates hemodynamic response to pneumoperitoneum.

Our findings concur with those of Pierre Zarif [23] et al, who stated in their study that Intraoperative infusion of either dexmedetomidine or magnesium sulfate could ameliorate the pressor responses to anesthetic and surgical manipulations

during laparoscopic colectomy under pneumoperitoneum in 30° Trendelenburg position.

Only one patient in group D had bradycardia. Otherwise there were no hemodynamic disturbances during procedure and no episode of bradycardia and hypotension.

In another study by Manjushree et al [24] administration of clonidine 3 μg/kg intravenously 15 minutes before induction and reduction of the infusion to 1 μg/kg/hour intraoperatively and observed significant incidences of bradycardia and hypotension. In our study, we reduced bolus of clonidine to 2 μg/kg and infusion @1μg/kg/hr. Hence, we did not find any significant bradycardia and hypotension in clonidine group in our study.

Use of $MgSO_4$ 40 mg/kg intravenously by Elsharnouby and Elsharnouby [25] over a period of 15 minutes before induction and 15 mg/kg/hour by continuous infusion intraoperatively resulted in more episodes of severe hypotension. In our study, we reduced the dose of $MgSO_4$ to 30 mg/kg before induction and 10 mg/kg/hour by continuous infusion intraoperatively. The dose selected by us resulted in a steady and smooth reduction of MAP and heart rate, with no episodes of severe hypotension and bradycardia. Most of our patients after extubation had Ramsay sedation score 3. Variation in sedation score was not significant though maximum patients in group D had score 3($p<0.05$). Extubation time and time for eye opening to verbal commands was minimal in clonidine group, followed by group D and group M ($p<0.05$).

Magnesium sulfate potentiates neuromuscular blockade induced by non-depolarizing neuromuscular blocking agents and this possibly was the cause of the prolongation of extubation time [10]. Difference in sedation scores among groups were statistically significant immediately on arrival in recovery room ($p< 0.05$).

Patients in group C were least sedated among three groups on arrival in recovery room. Sedation score were comparable among groups after 20minutes, though still least in clonidine group. After 60 minutes, more number of patients start becoming awake in group D and group M ($p>0.05$). Recovery time and sedation score were significantly higher in groups D (dexmedetomidine) and M (magnesium sulphate) as compared to control group during laparoscopic colectomy in a study by Pierre Zarif [23].

VAS score for pain were comparable from arrival in recovery room up to 20 minutes and most of patients were pain free. At 40 and 60 minutes in recovery room, there was statistically significant difference in pain score ($p<0.05\%$). Pain scores were least (1-4) in group D followed by group M (2-6) and group C (2-5). Only one patient in group M required analgesic. This effect of dexmedetomidine can be attributed to high selectivity for α_2 receptors.

Conclusion

Use of magnesium sulphate, dexmedetomidine and clonidine results in smooth and steady hemodynamic during laparoscopic abdominal surgeries under general anesthesia, clonidine being superior in terms of early extubation and responsiveness at given dosages. Dexmedetomidine exerts a tight control on hemodynamics and best postoperative analgesia.

Limitations of the Study

Use of BIS and end tidal isoflurane concentration, would have been ideal and more informative, especially in the terms of the depth as well as, whether any significant changes in requirement of the inhalational anesthetic agent. Some authorities have shown reduction in amount of anesthetic agents with use of these drugs.

Conflict of Interest

There is no conflict of interest.

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