The Effects of Magnesium Sulfate Loading on Hemodynamic Parameters During Laparoscopic Cholecystectomy: Randomized Controlled Trial

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Background: This study was designed to investigate the effect of intravenous magnesium sulfate on hemodynamic changes induced by pneumoperitoneum in patients undergoing laparoscopic cholecystectomy.

Methods: A randomized, placebo controlled study was performed on 52 ASA class I or II aged 20-70 years patients undergoing laparoscopic cholecystectomy with pneumoperitoneum with carbon dioxide. Before induction, Magnesium group received 50 mcg.kg-1 magnesium sulfate, within 10 minutes, in 100 ml of normal saline and control group received 100 ml normal saline. Hemodynamic variables were recorded before induction, before the infusion of magnesium sulfate, during intubation, during pneumoperitoneum and finally during extubation, every 10 minutes. Postoperative pain and other complications were recorded in post anesthesia care unit (PACU) also.

Results: Variations in heart rate and mean arterial pressure between the two groups during pneumoperitoneum were not significantly different ($P>0.05$). Propofol consumption in the magnesium group compared with the control group was significantly decreased ($P<0.05$). The prescribed dose of TNG and total amount of administrated TNG (SUM), both were significantly higher in control group than in the magnesium group (respectively $P=0.02$ and $P=0.042$). In PACU, patients in the magnesium presented lower shivering, nausea vomiting and post operative pain than the control group ($P <0.05$).

Conclusion: Magnesium sulfate reduces the amount of anesthetic drug (propofol), TNG and intraoperative blood pressure, during pneumoperitoneum induced by laparoscopy. The postoperative pain of laparoscopy and anesthesia side effects such as nausea, vomiting and shivering were blunted, with bolus administration of magnesium sulfate before induction of anesthesia.

Keywords: carbon dioxide; hemodynamics; laparoscopy; magnesium sulfate

Laparoscopic surgeries are increasing in both developed and developing countries because of its lower hospital stay and postoperative pain over laparotomic surgeries [1].

But, the pneumoperitoneum induces, hemodynamic instability, as increase in mean arterial pressure (MAP) with no significant change in heart rate [2].

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These hemodynamic changes occur due to increased catecholamine secretion, vasopressin or both [3].

Therefore, the appropriate method of anesthesia which prevents severe hemodynamic changes, is very important. Alpha-adrenergic agonists, beta-blocker drugs, opioids and vasodilator drugs [4] are often used to avoid circulatory response to the pneumoperitoneum and each of above medications, has its own advantages and complications.

The effect of magnesium sulfate (Mg) on reduction of blood pressure could be attributed to vasodilatory effect of Mg [5]. Mg as an antagonist of N-methyl D-Aspartate (NMDA) receptor and its related canals, presented hemodynamic effects in several parts of anesthesia protocol [6]. Mg has many other physiological activities, and especially has the effects of calcium channel blocking and therefore, Mg decreases blood pressure also [7]. Also, time to response to verbal commands was significantly prolonged in patients receiving Mg. This delay could be due to central nervous system (CNS) depressant effects of Mg [8]. Also studies have reported that administration of Mg, would lead to a significant reduction in requirement of intravenous anesthesia agents, including analgesic, anesthetic and muscle relaxant agents in the perioperative period [8].

This study is designed to investigate the effect of intravenous Mg administration on intraoperative hemodynamics, respiratory parameters and anaesthetic consumption and postoperative pain, when Mg is used as adjunctive premedication.

Methods

The study was randomized, double blind placebo-controlled clinical trial. Fifty-five patients who had been referred to operation room of Firoozgar hospital (a referral and educational hospital) in Tehran, Iran (from August 2012 to June 2013) were enrolled. In order to prevent bias, the study was designed double blinded and none of the patients and their anesthesiologist knew what their syringe content is and those who filled checklists. One of the authors was aware from number of the cases and grouping, and also syringe content, and this author delivered syringes to the anesthesiologist. This study was approved by the regional ethics committee of Firoozgar Hospital and was registered on Iranian Registry of Clinical Trials (IRCT) with IRCT2013022311398N2 code. Informed consent form was obtained from each patient before anesthesia.

Patients with age range of 20 to 70 years, an American Society of Anesthesiologists (ASA) physical status of I or II, and the indication of laparoscopic cholecystectomy with carbon dioxide (CO_2), were included in this study.

Exclusion criteria include, chronic use of beta-adrenergic blockers and calcium-channel blockers, use of psychoactive drugs affecting hemodynamic including lithium and tricyclic antidepressants, hypertension, diabetes mellitus, uncontrolled cardiovascular disease, and uncontrolled renal disease, acute cholecystitis, and sensitivity to magnesium sulfate.

Patients randomly were assigned to magnesium group (n=28) and control group (n=27) using a computer-generated randomization list. Routine monitoring of electrocardiogram (ECG), pulse oximetry, capnography and non invasive blood pressure (NIBP) was conducted prior to induction.

In the operating room, 8-12 ml/kg/h isotonic saline infusion (N/S) was started and continued during surgery, for all patients.

Magnesium group, received 50 mg/kg of magnesium sulfate infusion in 100cc N/S, during 10 min before the induction. The control group received the same volume of an isotonic saline solution.

After at least 2 minutes of pre-oxygenation, all patients were intubated with fentanyl 2mcg/kg, propofol 2 mg/kg and atracurium 0.5 mg/kg. Repeated doses of fentanyl (0.75mcg/kg), were administered at more than 20% changes of baseline of heart rate (HR) or mean arterial pressure (MAP).

The anesthesia was maintained by propofol 50-120 μg/kg min. Tidal volume was set on 8 cc/kg and respiratory rate 12 per min. By capnography monitoring, the respiratory rate was adjusted based on 30-35 mmHg end tidal carbon dioxide (CO_2). The gas pressure of CO_2 of pneumoperitoneum, was 14 mmHg. The $ETCO_2$ exactly before insufflation of CO_2, was named baseline $ETCO_2$. Mean value of $ETCO_2$ of tracheal tube, which was recorded every 10 min during the pneumoperitoneum period, was named pneumoperitoneum $ETCO_2$.

The hemodynamic variables and SPO_2, were recorded at preoperative anesthesia clinic visit (as baseline MAP and HR), at pre-induction, one minute after intubation, prior to pneumoperitoneum, in 10, 20, 30, 40, 50 and 60 post pneumoperitoneum and prior to extubation The anesthesia nurse who evaluated the hemodynamic variables of the patients was unaware of the type of groups. The hemodynamic variables were measured by using B5 Alborz monitoring apparatus, SADAT Company, Iran.

In case of increase in systolic blood pressure (SBP) more than130 mmHg, the propofol dosage was increased to its maximum dosage in the study (120 μg/Kg/min). In case of increase in patient’s blood pressure to more than 150/90 mmHg, infusion of 10-20 μg/min trinitroglycerin (TNG) was administered, 5 μg increase was applied every 10 minutes, if it was needed. In case of decrease in SBP to less than 90 mmHg, propofol infusion was reduced to 50%. The total amount of propofol and TNG dosages were recorded.

After the end of surgery, postoperative pain was assessed by the patients in post anesthetic care unit (PACU), with visual analogue scale (VAS)- an 11 points scale-, divided between the zero= no pain to 10 = worst or 10 centimeters (100 mm) in length imaginable pain.the grading manner in VAS: no pain (0–4 mm), mild pain (5–44 mm), moderate pain (45–74 mm), and severe pain (75– 100 mm) [9].

We determined a sample size of 55 for this study which would be sufficient to detect a difference of MAP, estimating a standard deviation of 13 mmHg (α=0.05, β=0.20).

The Statistical Package of Social Science version 16.0 (SPSS, Chicago, Illinois, USA) was used for data analysis. Statistical significance was noted for p value of ≤ 0.05. Age, sex, BMI, surgery time, intraoperative dosage of anesthesics, side effects and the VAS pain score were compared between two groups by independent sample t-test and chi-square. Two-way analysis of variance (ANOVA), and post hoc Student-Newman-Keuls test were used to analyze measured hemodynamic parameters across time within two groups. Data are expressed as mean ± SD.

Results

In total, 62 patients were eligible for our study, but 55 patients were included in the study and they were divided into the two groups of magnesium group (28 patients) and control group (27 patients) randomly and blinded by a person who was not informed of the type of administered drugs. Of those numbers, the surgical operation of two patients in control group and one in magnesium group was changed to laparotomy and due to different intraoperative hemorrhage and postoperative pain of laparatomy, they were excluded from the study and the finally, 25 subjects followed in control group and 27 ones in magnesium group (totally 52) and statistical analyses were performed with these subjects (Figure 1).

In the present study, no statistically significant differences were found between the two groups with respect to patient characteristic data, and any underlying diseases, and the other demographic data including BMI, ASA class and history of underlying diseases (Table 1).

In terms of the operation time, gas time and anesthesia time, no differences were found between the two groups (Table 2). In addition, average SPO_2 was not different 98.94% for magnesium group and 98.82% for control group; also the baseline and pneumoperitoneum $ETCO_2$ had not any significant difference. Intraoperative data are presented in (Table 2).

The baseline MAP and HR showed no significant differences between two groups, in all intervals except after intubation (the P value for HR=0.01 and for MAP=0.03) and before extubation (the P value for HR=0.02 and for MAP=0.001). The trends of MAP and HR of the patients in both groups are shown in Figure 2, which were not significantly different, even during pneumoperitoneum (P>0.05). To find the effect of Mg on hemodynamic changes caused by intubation, the difference between MAP of min 1 with baseline time, was studied (P=0.001). To find the net effects of gas insufflation, the difference between the MAP of prior to insufflation time and min 10 were compared (P=0.03) and to find the durability of Mg effect during anesthesia, MAP of the extubation time was compared with the baseline time, showing no statistical significance (P=0.06).

The HR of before extubation showed on increase compared to baseline, in control group and decrease in magnesium group; however, the difference was not significant. In the same interval MAP in magnesium group increased from 89±8 to 99±14 mmHg and in control group increased from 83±13 to 108±17 and the amount of changes in magnesium group was lower (Figure 2).

In control group, 10 individuals from the 25 ones received TNG in comparison with 5 ones from 27 patients in magnesium group (P=0.01). The TNG dosage and total amount (SUM) was calculated and were significantly different between two groups (Table 2).

Figure 1- Eligibility and follow-up flow chart of Study.

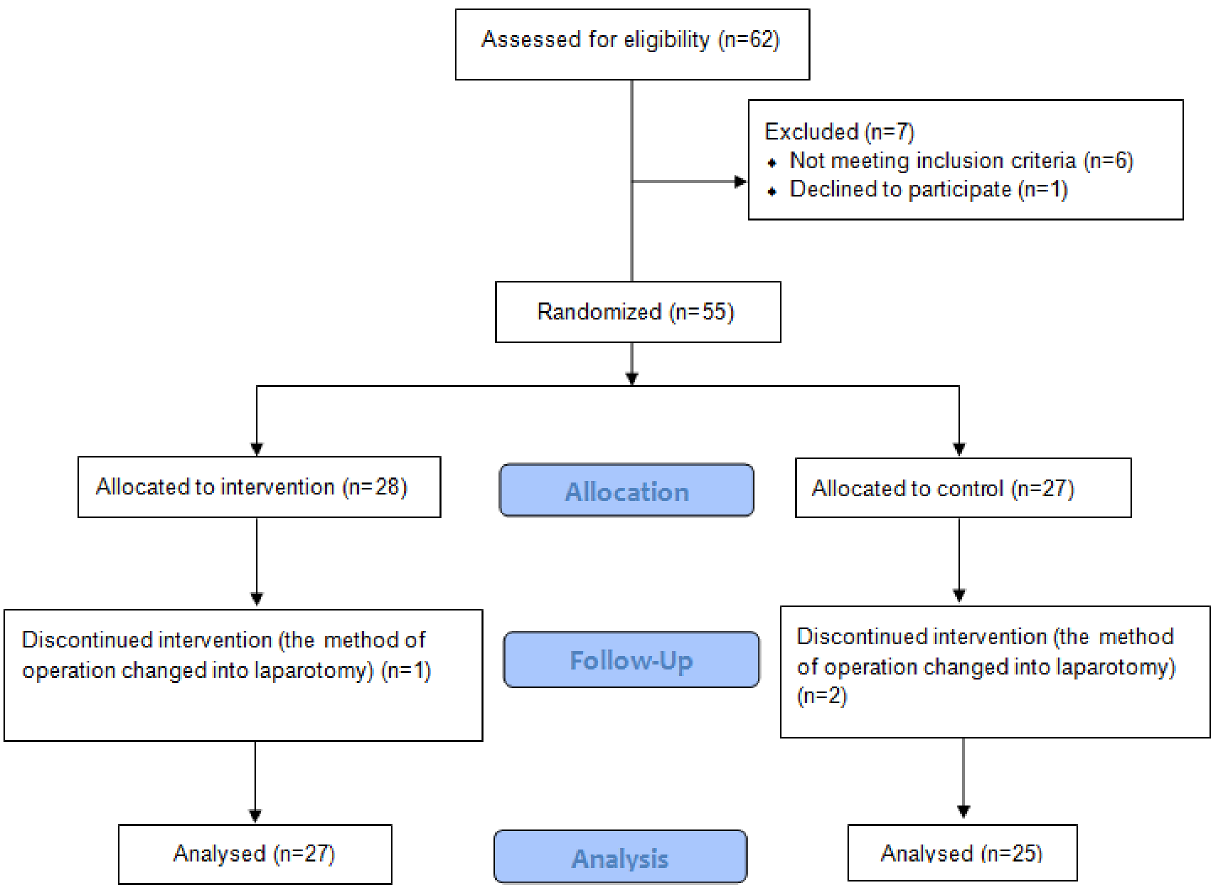

Table 1- Demographic data (Mean±SD).

Parameters	Control (n=25)	Magnesium (n=27)	P value
Age (years)	45.13 ± 11.74	41.33 ± 10.06	0.57
Sex (M/F)	5/20	6/21	0.36
BMI (kg/m2)	26.44 ± 2.11	26.17 ± 2.18	0.86
ASA (I/II)	16/9	17/10	0.4
Hypertension (Y/N)	2/23	3/24	0.67
Other CVD (Y/N)	1/24	2/25	0.22
DMT2 (Y/N)	2/23	2/25	0.64
Hypothyroidism (Y/N)	2/23	1/26	0.54

ASA: American society of anesthesiologists; CVD: Cardio vascular diseases; DMT2: Diabetes mellitus type 2.
*P<0.05

Figure 2- Trends of intraoperative mean arterial pressure (MAP) [1] and heart rate [2] means, in two groups.

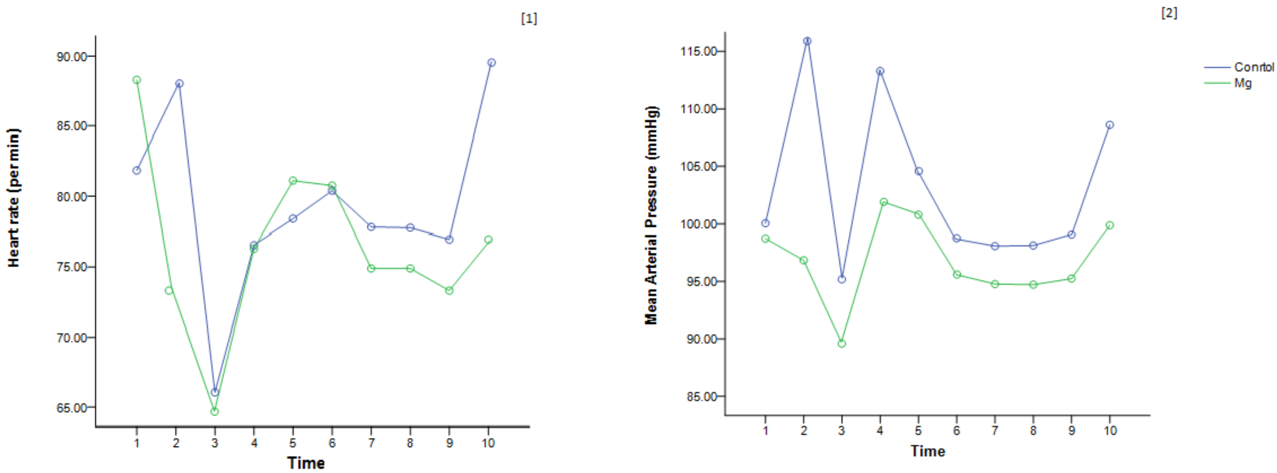

Table 2- Intra operative data (Mean±SD).

Parameters	Control (n=25)	Magnesium (n=27)	P value
SPO2 (%)	98.82 ± 0.91	98.94 ± 0.92	0.6
Baseline ETCO2 (mmHg)	26.12 ± 3.98	26.38 ± 3.87	0.51
Pneumoperitoneum ETCO2 (mmHg)	28.62 ± 3.33	28.50 ± 4.19	0.4
Propofol maintenance (mg/kg)	7.57 ± 2.31	6.61 ± 1.23	0.04*
TNG (Y/N)	10/15	5/22	0.01*
TNG dosage (mcg/kg/min)	13.28 ± 5.30	9.28 ± 3.45	0.02*
TNG SUM (mcg)	485 ± 34	175 ± 17	0.042*
Operation Time (min)	93.05 ± 28.91	94.66 ± 28.35	0.32
Gas Time (min)	84.70 ± 27.83	91.28 ± 28.31	0.06
Extubation Time (min)	112.50 ±37.89	119.57 ± 38.28	0.75

SPO2: Pulse oximeter oxygen saturation; ETCO2: End tidal carbon dioxide; TNG: Trinitroglycerol.
*P<0.05

The maintenance dosage of propofol was 7.57±2.31mg/kg in the control group which was more than the magnesium group (6.61±1.23 mg/kg) (P=0.04).
In PACU, the patients in magnesium group showed lower incidence of shivering, nausea and vomiting and VAS pain score than control group (P>0.05); however, in terms of agitation (RSS), hemodynamic and SPO2, the two groups showed no significant differences (Table 3).

Table 3- Post anesthesia care unit data (Mean±SD).

Parameters	Control (n=25)	Magnesium (n=27)	P value
SPO2 (%)	94.91 ± 4.92	96.66 ±3.25	0.06
Heart rate (per min)	82 ±15	80 ± 12	0.64
SBP (mmHg)	126.75 ±29.47	124.88 ± 27.69	0.37
DBP (mmHg)	82.66 ± 13.64	80.88 ± 12.22	0.25
Pain (VAS)	4 ± 2	3 ± 1	0.04*
Sedation (RSS)	2 ± 1	1 ± 2	0.2
Shivering (Y/N)	7/18	2/25	0.001*
Nausea vomiting (Y/N)	4/21	0/27	0.01*

SPO2: Pulse oximeter oxygen saturation; SBP:Systolic blood pressure; DBP: Diastolic blood pressure; VAS: Visual analogue scale; RSS: Ramsay Sedation Score.
*P<0.05

Discussion

The findings of this randomized, double-blind, placebo-controlled study showed that the administration of Mg before pneumoperitoneum attenuates increases in arterial pressure, the vasodilator (TNG) and anesthetic drugs, during CO2 pneumoperitoneum, in patients under general anesthesia.

In present study, the differences between HR and MAP were insignificant but it was revealed that in those differences, the magnesium group had more sustained and uniform conditions in absolute values, differential absolute values and trend of changes, showing much smaller and limited range of variations. The changes of MAP and HR of the patients in both groups were not significant different, even during pneumoperitoneum (P>0.05); however, it was noticed that:

First, CO2 insufflation in the first 10 minutes and extubation caused an apparent increase in HR and MAP, second, the range of variations of HR and MAP in magnesium group was significantly lower than control group, third, HR at the end fell in magnesium group compared to the base; however, it had increased in control group and MAP at the end showed no significant changes than the base in magnesium group while it had increased in control group. As previous studies confirmed, Mg attenuates catecholamines release, via lowering sympathetic stimulation. In fact, by lowering the sensitivity of peripheral nociceptors, Mg reduces the stress response to surgical operations [10-11].

Nonetheless, this study showed that Mg caused reduction in dosage of intraoperative hypnotic drug (Propofol) same as Seyhan et al. study, and also reduced the dosage of vasodilator drug (TNG) during pneumoperitoneum of laparoscopy. Pearson et al. demonstrated that the release of nitric oxide as a potent endogenous vasodilator, has an efficient relation with Mg, in the coronary endothelium [12].

In addition, in present study, the degree of anesthesia side effects, at PACU, including nausea, vomiting and shivering and also postoperative pain were reduced by prescribing bolus Mg, prior to anesthesia induction.

Elsharnouby and Elsharnouby, administrated 40 mg/kg over 15 min before induction of anesthesia, followed by 15 mg/kg/hr infusion, during the operation. They reported higher episode of serious hypotension by using this dosage of Mg [13]. Ray et al. decreased the dosage of Mg, to 30 mg/kg, prior to induction followed by 10 mg/kg/hr infusion while during operation and the selected dose caused a gradual and sustained reduction in MAP and HR of the patients with no episodes of serious hypotension and no serious bradycardia [14]. Telci et al. used similar dosages [18], also. But Shariat Moharari et al. used the dosage of 40 mg/kg/hr, prior to induction and infusion of 10 mg/kg/hr while during operation, and no episodes of serious hypotension or bradycardia were reported [6]. In all those studies, the increase in anesthesia time was reported in magnesium group compared to control group.

In the present study, the infusion dose of Mg was omitted and similar to Schulz-Stübner et al. study, only the bolus dose of Mg, was prescribed in 50 mg/kg, prior to anesthesia induction. In none of the subjects of magnesium group, serious hypotension or bradycardia occured during the anesthesia time. In addition, there was no significant increase in the anesthesia length compared with control group [19].

In the study of Jee et al., only one bolus dose of Mg (50 mg/kg) was prescribed prior to pneumoperitoneum and the amount of plasma rennin activity showed no differences in the magnesium group with control group, showing absence of serious hemodynamic fall in patients [15].

In a recent randomized controlled trial (RCT) in 2011, which had been conducted by Kalra et al., clonidine and Mg were studied on hemodynamic responses during laparoscopic cholecystectomy. It was reported that clonidine and Mg decreases the hemodynamic response to pneumoperitoneum; nevertheless, Mg established more sustainable situation in patient’s hemodynamics [21].

It has been reported that Mg improves general anesthesia, and Mg increases the effects of local anesthetics also [16]. The depressant effects of Mg on CNS have been reported in animals too which caused a dose dependent neuroprotective effect in spinal cord injury [17]. Acting as an antagonist of NMDA receivers, Mg has the potential of pain relief. This pain relief effect of Mg was documented for intra and postoperative periods [6,18-19]. In a recent meta-analysis in 2013, perioperative administration of Mg and post operative pain was evaluated in 25 trial studies and reported lesser cumulative postoperative morphine consumption by 24.4% reduction and lesser pain score in the first 24 hours after surgery [20].

Our study confirmed that Mg attenuates administered dosages of both hypnotic and analgesic also. Nevertheless, the NMDA receptors do not justify the reduction in total dosage of intraoperative hypnotic drugs such as propofol, and only justifies the attenuation in total dosages of analgesic agents. Clearly, more studies must be conducted on the interaction between Mg and propofol as excluded factors.

In another study, Telci et al. showed that Mg, reduces demand to anesthesia drugs during operation. The study group received bolus dose of Mg (30 mg/kg) and 10mg/kg/h infusion, both groups received the same volume of isotonic crystalloids. Anesthesia was maintained by propofol and infusion remifentanil. At the end of study, it was specified that prescribing Mg, apparently led to lowering the need to anesthesia drugs during total intravenous anesthesia (TIVA) with Propofol, Fentanyl and Vecuronium [21].

Seyhan et al. studied the effects of different dosages of Mg, on reducing the amount of propofol demand, hemodynamic and relieving pain after gynecology surgeries. In their study, 80 women were divided into four equal groups [22]. The control group received normal saline and in other groups, one received bolus dosage 40mg/kg, bolus dose plus infusion 10 mg/kg/h and 20mg/kg/h in 4 hours, respectively.

. The results showed that the group 2 and 3 showed significant reduction in taking Propofol, Atracorium and Morphine sulfate during and after surgery and increase in Mg dosage, did not lead to improvement of results [14].

Most studies which were performed on laparoscopic surgery focus on hemodynamic changes during pneumoperitoneum [23]. In laparoscopic surgery in which, the cardiovascular changes are among the prevalent side effects, and usually shows itself as hypertension, drugs that affect hemodynamic, causing hypotension might prove useful in such operations. As mentioned, the pneumoperitoneum by CO2, causes rapid increase in plasma catecholamines which is due to increase in internal peritoneum pressure and peritoneum stimulation via CO2 gas (sympathoadrenal stimulation) [24]. The studies reported that serum Mg concentrations of 2-4 mmol/l, are needed to exert these effect [11].

It is shown that bolus dose of Mg (50 mg/kg) increases the serum concentration of Mg, in this range and this serum level of Mg, blunts the increase of catecholamines level of the plasma, during pneumoperitoneum, and effectively, prevents the sympathoadrenal hemodynamic stress responses emerging form pneumoperitoneum [15]. Moreover, the vasopressin hormone is one of the effective and basic factors in the pneumoperitoneum-caused hemodynamic variations [25].

In the present study, we observed that in control group, the MAP increased suddenly upon initiation of pneumoperitoneum and similar to previous observations, the increase in blood pressure remained during pneumoperitoneum course [26]. On the other hand, in magnesium group, more hemodynamic stability was observed and the amount of increase, was less than 20 mmHg rather than baseline MAP of the same group; while in the control group, that increase was more than 20 mmHg rather than MAP of the baseline of the same group.

The first RCT research was carried out by Jee et al. to study the effects of Mg in cholecystectomy in laparoscopic method. In that study, 50 mg/kg of Mg was prescribed exactly prior to pneumoperitoneum [20]. In present study, prescribing 50 mg/kg injection of Mg, prior to anesthesia induction effectively reduced the side effects caused by hypertension, prior to pneumoperitoneum and also, after pneumoperitoneum and in this way, it might be suitable for patients under laparoscopy surgery.

Conclusion

Prescribing magnesium sulfate prior to induction of anesthesia, decrease pneumoperitoneum induced hypertension caused by the pneumoperitoneum by CO2, in patients undergoing laparoscopic cholecystectomy. Our results showed that magnesium sulfate, could induce significant hemodynamic stability during pneumoperitoneum in laparoscopic operations. In our study, we did not measure the effectt of Mg on duration of muscle relaxation, and more important the level of Mg, during operation, to keep the effective dosage of Mg in plasma; because the Mg level was prepared in long time, at our center. In future, and in presence of spectrophotometry in operation rooms, this shortcoming could be addressed.

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