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Comparative evaluation of clonidine and magnesium sulfate infusions upon intraoperative hemodynamics and anesthetic consumption, and postoperative recovery profile in lumbar spine surgery : a prospective, randomized, placebo controlled, double-blind study

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Abstract : *Background and aims* : General anesthetic drugs are increasingly associated with neurotoxicity and post-operative cognitive dis-turbances. This has led to more frequent use of adjuvants to facilitate the use of lower anesthetic dose, while ensuring adequate anesthetic depth. This study aimed to analyse the effects of clonidine and magnesium sulfate on anesthetic consumption during total intravenous anesthesia while main-taining intraoperative hemodynamic stability in lumbar spine surgeries with a secondary aim to assess their effects on postoperative recovery profile.

Material and methods : Patients were randomly divided into three groups. Group A patients received clonidine 2 µg/kg intravenously over 20 minutes followed by 1 µg/kg/h maintenance infusion. Group B patients received magnesium sulfate 30 mg/kg over 20 minutes followed by 10 mg/kg/h infusion. Group C patients received 0.9 % normal saline in the same volume. Anesthesia was maintained using propofol infusion. Fentanyl was given for analgesia and vecuronium for muscle relaxation. Intraoperative hemodynamics, recovery times and anesthetic consumption were recorded.

Results : Both drugs reduced the propofol induction and maintenance doses significantly ($P<0.001$). Clonidine reduced fentanyl maintenance dose most significantly while magnesium sulfate reduced vecuronium consumption more. The MAP and HR both were reduced in clonidine and magnesium groups compared to preoperative values and also in comparison to control group ($P<0.05$). The recovery parameters were significantly prolonged in patients receiving magnesium ($P<0.05$).

Conclusion : Clonidine and magnesium sulfate both are effective in maintaining hemodynamic stability in patients undergoing lumbar spine surgeries. Both reduce intraoperative anesthetics consumption significantly. Magnesium delays the postoperative recovery in comparison to clonidine and control group.

Keywords : Clonidine ; Magnesium sulfate ; Anesthesia adjuvants ; General anesthesia.

Introduction

The term *Balanced anesthesia* was introduced by Lundy in 1926 (1). Lundy suggested to use anesthetic agents and techniques in balance to produce the different components of anesthesia (i.e., analgesia, amnesia, muscle relaxation, and abolition of autonomic reflexes with maintenance of homeostasis). It describes the concurrent administration of several anesthetic drugs so that no single drug is given in a dosage sufficient to produce toxicity during or after surgery.

Evidence suggests that some anesthetic drugs have a neurotoxic effect that continues beyond the exposure time, altering genes and protein expression (2,3). Harmful effects have been recorded following exposure to ketamine, midazolam, propofol, isoflurane, sevoflurane, and desflurane (2). It is unknown whether it is related to the drug used, the dose of anesthetic, or the depth of the anesthesia, or whether it derives from characteristics that are inherent to the patient. However, promising strategies attribute a neuroprotective effect to lithium, melatonin, xenon, alpha -2 agonists and magnesium sulfate (3).

Clonidine, the prototype of alpha-2 agonists, has been extensively studied as anesthetic adjuvant and has sedative, anxiolytic and analgesic properties. It has also shown to provide improved intraoperative hemodynamic stability, attenuated

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sympathoadrenal responses to laryngoscopy, reduced intraoperative requirement of volatile and intravenous anesthetics and less postoperative pain, postoperative nausea vomiting and shivering (4-7). Parenteral Magnesium sulfate has also been studied as an anesthetic adjuvant and has found to cause overall reduced consumption of intravenous anesthetics, opioids and muscle relaxants (8-10).

So this study was designed to compare and assess the effects of intravenous clonidine and intravenous magnesium sulfate on anesthetic consumption, hemodynamics and postoperative recovery when used as adjuvant agents in patients undergoing lumbar spine surgeries under general anesthesia.

Material and methods:

The present study was carried out over a period of one year from April 2014 to May 2015. Approval from the Institutional Ethics Committee was obtained and informed consent from all participating patients was taken for the study. Sample size was calculated on the basis of previously done studies (11,12). PASS 14 Power Analysis & Sample Size Software was used for calculation of sample size. It was calculated that a sample size of 20 patients per group would be needed to detect an intergroup difference of at least 20% (between groups A and C, or between B and C) as well as a difference of at least 10% between groups A and B, in the propofol consumption as the primary goal, keeping a two sided type I error of 0.01% ($\alpha = 0.01$, two-sided) and statistical power level as 90%, with two sample t-test. A total of 100 patients were assessed for eligibility out of which 90 patients fulfilled the required criteria of ASA grade I-II, aged 20-60 years of either sex, scheduled to undergo elective lumbar spine surgeries under general anesthesia. They were randomly allocated to one of the thee study groups of 30 each in order to avoid the data loss due to possible drop-outs (Fig. 1). The group allocation was done according to the numerical order of a computer generated randomization list. Allocation concealment was ensured with sealed opaque envelopes.

Group A - received clonidine 2 µg/kg over 20 minutes before induction followed by intraoperative 1 µg/kg/h infusion

Group B - received magnesium sulfate 30 mg/kg over 20 minutes before induction followed by intraoperative 10 mg/kg/h infusion

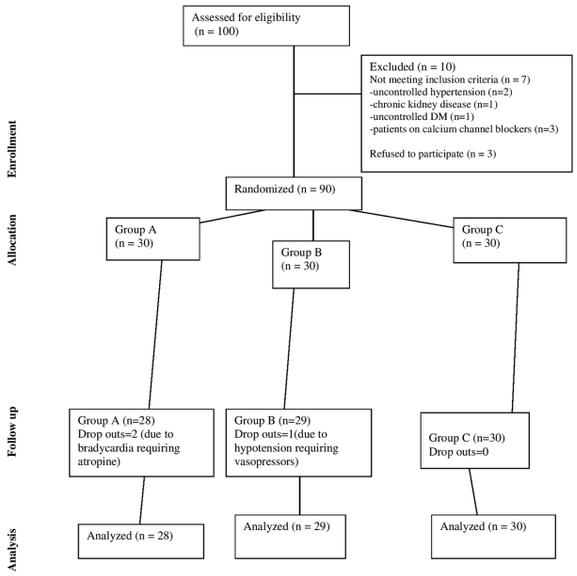

Fig. 1. — Study design.

Group C - Control group received normal saline in equal volumes (50 ml) over 20 minutes before induction followed by intraoperative normal saline infusion

Exclusion criteria were as follows:

Age>60years
Uncontrolled Hypertension
Uncontrolled Diabetes mellitus
Severe cardiopulmonary, hepatic, renal or endocrine dysfunction
Morbid obesity
Pregnancy
Drug or alcohol abuse
Prior treatment with calcium channel blockers
Known allergy to study drugs

During preanesthetic check up a thorough clinical examination was done along with routine laboratory investigations for each patient. In all patients' pre-operative serum magnesium value was recorded to compare it with an end of surgery value. All patients were kept in an NPO status for 8 hours before surgery. In the operation theatre standard monitoring such as pulse oximeter, electrocardiogram, non invasive blood pressure, BIS (Bispectral index) and NMJ monitors (TOF, Train of four) were applied. An 18 gauge intravenous cannula was put and preloading was done with 10 ml/kg Ringer's lactate drip. Before starting the induction, they received the study drug prepared in 50 ml normal saline via syringe pump over 20 minutes. Since this was a double blind study, neither the patient nor the attending anesthetist was aware of their exact composition, which was known only

to an independent anesthetist who prepared the infusions in coded syringes.

Fentanyl 2 µg/kg intravenously given for analgesia. Slow intravenous induction done with propofol 10 mg every 5 seconds until the BIS below 60 and after cheking adequate mask ventilation, vecuronium 0.1 mg/kg iv given for muscle relaxation, followed by endotracheal intubation after 3 minutes. Correct tube placement was confirmed with bilateral chest auscultation and capnography. Anesthesia was maintained using intravenous propofol infusion and 50:50 oxygen:air mixture to achieve a target BIS between 40 and 60. Muscle relaxation was maintained using vecuronium 0.01 mg/kg intravenous top-ups when TOF (Train of four) counts exceeded 2 until 10 minutes prior to end of surgery.

HR, MAP and BIS were monitored thoughout the intra operative period at 5 minute intervals and were recorded pre operatively, after bolus infusion of study drug, one minute after induction, just after intubation, at 5th, 15th and then at every 15 minute interval in the observation sheet. Other monitoring included electrocardiogram, Spo2, Etco2 and duration of surgery. TOF was measured at 5 minutes interval till the end of surgery.

All patients received propofol infusion titrated to the clinical situation, while keeping BIS between 40 to 60. Signs of inadequate analgesia, defined as an increase of heart rate and MAP of more than 20% of baseline, were to be managed by a bolus dose of fentanyl 0.5 µg/kg [if BIS was within 40-60]. BIS score > 60 indicated an insufficient depth of anesthesia; in that case, propofol infusion rate was increased by 10 µg kg-1 min-1. Hypotension, defined as SBP below 90 mm Hg or MAP below 60 mm Hg for more than 5 minutes, was treated by reducing propofol infusion by 10 µg kg-1 min-1. Additional intravenous fluids were given as deemed appropriate. Unresponsive hypotension was managed with ephedrine 5 mg boluses up to a maximum of 15 mg, after which phenylephine or dopamine were added. Symptomatic bradycardia, defined as HR < 60/minute associated with hypotension, was treated with atropine 0.5 mg bolus, up to a maximum of 3 mg. In all cases, response was reassessed at 5 minute intervals and the above measures continued until stabilization.

At the end of the surgeries all the infusion were stopped and BIS was allowed to rise to 80. Blood samples were taken and sent to laboratory at this point to analyze serum magnesium levels. The residual neuromuscular block was antagonized with neostigmine 0.05 mg/kg and glycopyrrolate 0.01 mg/kg when T4/T1 ratio reached 70% or higher followed by tracheal extubation. The following times were recorded from the end of anesthetic infusions as recovery parameters :

Time to tracheal extubation

Time to response to verbal commands (spontaneous eye opening)

Orientation time (for the patients to give their name and place)

Total consumption of propofol, fentanyl and vecuronium were recorded.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) for Windows, version 16.0. Patient characteristic data were analyzed with one way analysis of variance (ANOVA) for continuous variables and Chi square test for categorical variables. Comparisons between groups for demographic data, total anesthetic consumption, recovery parameters and hemodynamic variables were performed by one-way ANOVA. In case of statistical significance, post hoc comparisons were made by unpaired samples t-test with Bonferroni correction. In order to evaluate the changes in hemodynamics, intra-group comparisons were made by repeated measures ANOVA. Post hoc comparisons were made by Tukey HSD and Dunnet's t-test. The results are presented as mean (SD). Statistical significance was assumed for $P<0.05$.

Results

A total of 100 patients were assessed for the eligibility and 90 patients were included in the study. Two patients from group A developed symptomatic bradycardia requiring atropine and one patient from group B developed hypotension which needed vasopressor support. Their data is only included in comparison of demographic profile; but they were not subjected to further statistical analysis (Fig. 1). The three groups were comparable with respect to the demographic profile ($P > 0.05$) (Table 1).

There was no significant difference in pre-operative hemodynamic parameters amongst the groups. A significant fall in MAP and HR was seen after the bolus infusion of study drugs in groups A and B, greatest being in group A. HR in group A and group B were significantly decreased ($P<0.05$) during the whole intraoperative period, however, this decrease was not seen in group C, compared to preoperative values. There was no rise in HR in

Table 1. — Demographic Data

	Group A (n=30)	Group B (n=30)	Group C (n=30)	*P* - value
Age (years)	32.43 (10.09)	33.67 (10.24)	33.87 (9.25)	0.829
Sex(male/female)	21/9	21/9	19/11	0.816
Weight (kg)	57.9 (6.74)	57.6 (6.49)	56.93 (5.29)	0.826
Height (centimetres)	161.5 (6.76)	161.2 (7.25)	161.73 (6.18)	0.955
Duration of surgery (minutes)	127.33 (16.71)	134.5 (17.09)	130.53 (15.36)	0.243

Data are presented as either mean values (SD) or by absolute numbers

Table 2. — Intraoperative anaesthetics consumption

Variable	**Group A (n=28)**	**Group B (n=29)**	**Group C (n=30)**	***P* -value**		
				A vs B	**A vs C**	**B vs C**
Propofol induction dose (mg)	72.70 (14.23)	94.11 (16.18)	117.14 (17.65)	0.000	0.000	0.000
Propofol maintenance dose (mg/hr)	180.44 (26.28)	200.79 (28.42)	225.52 (25.14)	0.007	0.000	0.001
Fentanyl maintenance dose (µg/hr)	23.50 (5.96)	35.68 (6.88)	41.89 (8.35)	0.000	0.000	0.003
Vecuronium maintenance dose (mg/hr)	1.94 (0.40)	1.26 (0.48)	2.3 (0.57)	0.000	0.008	0.000

Data are presented as mean values (SD)

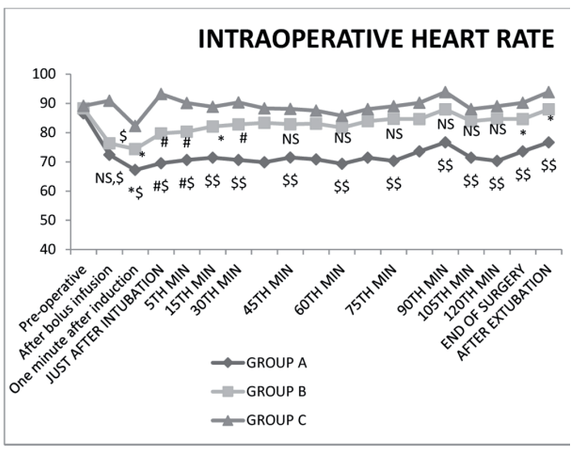

Fig. 2. — Intraoperative HR.

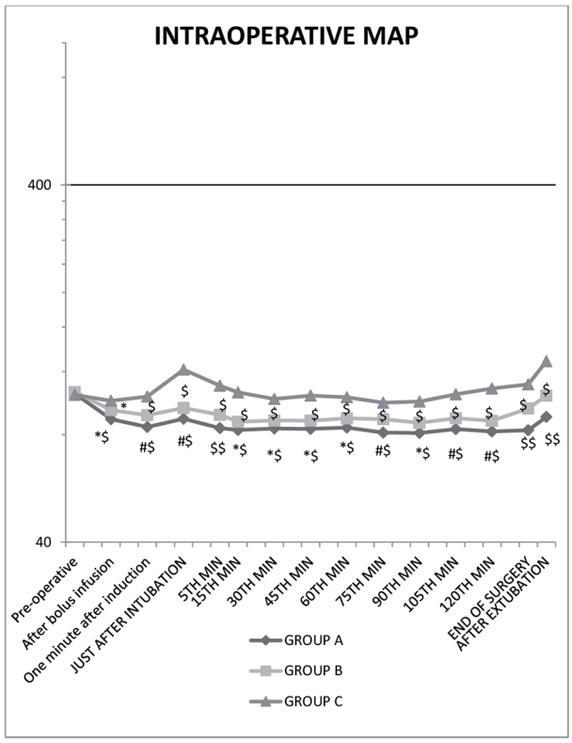

Fig. 3. — Intraoperative MAP..

groups A and B, after intubation, while in group C significant rise was seen. This difference was significant even between group A and B (P<0.05). A significant difference in HR (A<B<C) was seen upon inter group comparisons, throughout the whole intra operative period. Even after extubation HR remained stable in group A with group B showing some rise and groub C showing the maximum increase (Fig. 2).

MAP values were statistically significantly lower in the group A and group B compared to group C after intubation and all time observations of surgery (P<0.05). There was a significant decrease in MAP in all groups, compared to preoperative values at all time intervals of surgery (P<0.05). There was also significant difference in intraoperative MAP

Table 3. — Recovery parameters

RECOVERY PARAMETERS	Group A (n=28)	Group B (n=29)	Group C (n=30)	P-Value		
				A vs B	B vs C	A vs C
Extubation time	5.88 (0.38)	8.74 (0.47)	6.05 (0.32)	0.000	0.000	0.070
Response to verbal commands	7.33 (1.48)	9.79 (1.61)	7.78 (1.26)	0.000	0.000	0.221
Time for orientation	9.47 (1.55)	10.96 (1.30)	8.97 (1.49)	0.000	0.000	0.220

Data are presented as mean values (SD)

between group A and B (P<0.05). MAP values difference were more when comparing the group A with group C (P<0.001) and group B with group C than group A with group B (P<0.05) (Fig. 3).

Symptomatic bradycardia was observed in two patients of group A, which received atropine 0.5 mg i.v., while one patient from group B developed severe hypotension which failed to respond to ephedrine and fluid infusion and was managed with phenylephine 50 µg top ups.

Significantly greater propofol induction dose was required by group C than by A and B groups, (P<0.001) as seen in the Table 2. The difference was also significant between groups A and B (P<0.05), with a lesser consumption in the former group. Maintenance dose of propofol was also significantly decreased in group A and B when compared to group C (P<0.05). Significantly reduced fentanyl maintenance dose was needed in group A compared to group B and C (P<0.001). The difference was also significant between group B and C (P<0.05). Vecuronium maintenance dose was significantly less in group B compared to Group A and C (P<0.001). This difference was also significant between group A and C (P<0.05).

When the groups were compared for the parameters of recovery; extubation time, time to response to verbal commands and time for orientation; all were significantly delayed in group B (P<0.001). The difference was not significant between group A and group C (P>0.05) (Table 3).

All patients were also analyzed for the end of surgery serum Magnesium levels and compared to their preoperative values. While in group A and C, there was no difference in these values; group B patients demonstrated a significant rise from preoperative value of 1.51 ± 0.15 to 1.68 ± 0.20 mEq/L at the end of surgery (P<0.001). However, serum magnesium stayed within the normal range (1.5 to 2.0 mEq/L) even in group B.

Discussion

Clonidine and magnesium sulfate have attracted increased attention as adjuncts to both regional as well as general anesthesia in many studies. Reduced anesthetic consumption while maintaining hemodynamic stability has been the most desired feature of an anesthetic adjuvant, and few studies have used clonidine and magnesium sulfate to fulfill this aim (11,12). The theoretical benefit of reduced anesthetic consumption is less neurotoxicity (2,3). In spine surgeries sudden hemodynamic changes are associated with bleeding and blurring of surgical field. So, agents providing controlled hypotension and total intravenous anesthesia have emerged with the purpose of surgical field clarity in these surgeries (13). Therefore we compared clonidine and magnesium sulfate in a placebo controlled study for maintaining hemodynamic stability while studying their effects on total anesthetic consumption in patients undergoing lumbar spinal surgeries under general anesthesia.

Ibrahim et al reported greater hemodynamic stability after an intravenous bolus of clonidine 2 µg/kg before induction of anesthesia, compared to patients treated with esmolol in patients undergoing laparoscopic cholecystectomy (14). The attenuation of stress related sympathetic out flow by clonidine has been reported to result in better perioperative hemodynamic stability.

When discussing role of clonidine in general anesthesia, it is important to emphasise that, clonidine is only capable of reducing BP that is dependent on sympathetic tone (15). Important protective physiological reflexes are left intact since clonidine does not interfere with catecholamine metabolism and ganglion transmission and a full range of clinically useful vasoactive drugs remain effective in the clinical setting (15). Altan et al used clonidine 3 µg/kg intravenously over 15 minutes,

before induction and 2 µg/kg/hour by continuous infusion intraoperatively. They observed significant incidences of bradycardia and hypotension in their study (11). Ray et al administered clonidine 3 µg/kg intravenously over 15 minutes, before induction and reduced the infusion to 1 µg/kg/hour intraoperatively but still observed significant incidences of bradycardia and hypotension (12). In our study, we lowered the bolus of clonidine to 2 µg/kg, given over 20 minutes, a significant reduction in intraoperative HR and MAP was observed. However, symptomatic bradycardia developed in 2 patients which responded to iv atropine 0.5 mg.

Khafagy et al (16) reported that 3 µg/kg intravenous clonidine before induction followed by 2 µg/kg/h reduced the requirement of target controlled infusion administered propofol by 33% when anesthetic depth was assessed by bispectral index (BIS). Higuchi et al (17) demonstrated that 5 µg/kg oral clonidine premedication reduced propofol and fentanyl requirements by 25% and 15%, respectively, when assessed by hemodynamic responses. In our study also, both induction and maintenance doses of propofol and fenanyl maintenance dose were reduced in patients receiving clonidine. The interaction of α2-adrenoreceptors and opioids lead to decrease in the dose of fentanyl. The α2 adrenoceptor agonists like clonidine produce analgesia via descending pain pathways at both spinal and supra spinal levels leading to 30% to 50% reduction in the requirements of opioids with a consequent reduction in opioid related side effects (18).

Anjum et al (19) reported that, when co-administered with propofol, both clonidine, and dexmedetomidine cause delay in the recovery from anesthesia. With the dose of clonidine used in our study (2 µg/kg over 20 minutes followed by 1 µg/kg/h), the recovery was comparable to the control group (P>0.05). Jabbary Moghaddam M et al, also reported a faster recovery in elderly patients undergoing fractured leg surgeries under general anesthesia when premedicated with 5 µg/kg clonidine compared to placebo group (20). Paris A et al too found no delay with the use of clonidine in comparison to midazolam (21). Such discrepancy in results among studies might arise due to different clonidine doses administered and the presence or absence of premedication.

Sameenakousar et al demonstrated that clonidine was superior to fentanyl in the attenuation of the pressor response (7). Mesbah kiee et al found that magnesium sulfate attenuated the hemodynamic response to tracheal intubation better than lignocaine in patients undergoing coronary artery bypass grafting (22). In our study also, both clonidine and magnesium sulfate blunted the hemodynamic response to laryngoscopy and intubation, but clonidine was more effective.

Telci et al (23) demonstrated significant reductions in hourly infusion rates of propofol titrated to maintain bispectral index (BIS) between 45 and 60 by using 30 mg/kg bolus and 10 mg/kg/h magnesium infusion throughout spinal operations. Gupta et al (24) also reported that magnesium reduced the requirements for propofol, rocuronium and fentanyl in spinal surgical patients. Their findings are similar to our study. The role of magnesium for perioperative analgesia has been investigated by many authors. Magnesium sulfate has been reported to be effective in perioperative pain management and in blunting somatic, autonomic and endocrine reflexes provoked by noxious stimuli (8,9).

It is hard to speculate on the exact mechanism of magnesium's contribution to anesthesia in our study. Theoretically, magnesium could modulate anesthesia by several mechanisms. Magnesium sulfate is an antagonist of the NMDA receptor. Inhibition of NMDA-mediated excitatory neurotransmission may contribute to the anesthetic, amnesic, and anticonvulsant properties of propofol (Reves et al) (25). Therefore, it is suggested that magnesium sulfate when co-administered with propofol potentiates anesthetic effects and NMDA antagonism of propofol. Another mechanism could involve reduction of catecholamine release though sympathetic stimulation, by which magnesium might decrease peripheral nociceptor sensitization or the stress response to surgery. However, these mechanisms do not explain the reduction in propofol requirements. Clearly, further studies of the interaction between magnesium and propofol as a sole agent are needed. Magnesium sulfate prolongs and potentiates neuromuscular block by non-depolarizing neuromuscular blocking agents. Our study also showed lower vecuronium requirements with magnesium use, consistent with previous studies (26,27). Wang H et al (28) has demonstrated in vitro enhancement of non-depolarizing muscle relaxant vecuronium action at adult muscle type nicotinic acetylcholine receptor by magnesium sulfate.

It is known that magnesium might induce hypotension directly by vasodilation, as well as indirectly by sympathetic blockade and inhibition of catecholamine release. In our study, 1 of the patients receiving magnesium sulfate developed hypotension, responded only to iv phenylephine.

None of the patients developed symptomatic bradycardia. Magnesium sulfate infusion dose used in our study is same as used by many other researchers since higher doses have resulted in more side effects (11,12,23). as was the findings of Elsharnouby and Elsharnouby (29), who used magnesium sulphate 40 mg/kg over 15 minutes followed by 15 mg/kg/h infusion and observed more severe episodes of hypotension. Seyhan et al (30) studied effect of thee different dose regimens on propofol consumption in comparison to control group receiving normal saline. They did not notice any serious hypotensive episodes requiring ephedrine, even in the higher infusion rate group. They also demonstrated that 'response to verbal commands' and 'extubation time' was significantly longer in Magnesium groups than control group. In our study also, all the recovery parameters were significantly prolonged in magnesium group in comparison to clonidine and control group patients (P<0.0001). Few studies also observed that there was no significant increase in the recovery parameter in magnesium sulfate treated patients when monitored though TOF (26,27). We also monitored TOF, but we have given vecuronium until 10 min. prior to the end of surgery, because most of the lumbar spinal surgeries were done in prone position and change of position in the absence of adequate relaxation would have resulted in hemodynamic derangements.

There are some limitations of our study. First is use of fixed doses of study drugs, so effects of higher or lower doses are not studied. Second is we only assessed the reduced intraoperative analgesic requirements in the study, reduction in postoperative analgesic requirements was not studied among groups.

Conclusion

To conclude both, clonidine and magnesium sulfate are useful anesthetic adjuvants and reduce intraoperative consumption of propofol, fentanyl and vecuronium. Both set the hemodynamics to the lower level and prevent sudden changes during lumbar spinal surgeries. Magnesium delays the postoperative recovery when compared to clonidine and control group patients.

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