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Comparative Study: Impact of Propofol and Ketamine Pretreatment on Succinylcholine - Induced Myalgia

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Abstract: ***Background: Succinylcholine is still considered to be the muscle relaxant of choice for performing endotracheal intubation during general anaesthesia. Most common side effect after succinylcholine administration is postoperative myalgia which can cause significant discomfort in patients. Pretreatment with various pharmacological agents have been tried to decrease incidence of myalgia caused after the administration of Succinylcholine with varying success. We conducted the study to compare the effect of pretreatment with Propofol and Ketamine on incidence & severity of Succinylcholine induced postoperative myalgia. Methodology: After obtaining approval from the institutional ethics committee; a prospective, randomized, double blind, study was conducted in ASA Grade I, II male & female patients between age group 18 to 65 years undergoing surgeries of < 3 hours duration under general anaesthesia with endotracheal intubation after succinylcholine administration. Patients were randomly divided into 3 groups of 20 participants each; Group P – Pretreatment with Propofol (0.5 mg/kg) Group K – Pretreatment with Ketamine (0.5 mg/kg) Group N – Pretreatment with Normal Saline as control. During general anaesthesia after induction and succinylcholine administration; occurrence of fasciculations was observed and graded as nil, mild, moderate or severe. The incidence and severity of Succinylcholine induced postoperative myalgia in the patients was determined after 24 hrs& 48 hrs after surgery based on Kararmaz et al's four point scale as 0, 1, 2 & 3. Statistical analysis: Collected data was analyzed using unpaired t test, one way ANOVA & chi – square test. Probability value of < 0.05 was considered as statistically significant. Results: The demographic data (age, weight, duration of surgery) of all the 3 groups was comparable (p>0.05). We observed that the incidence & severity of fasciculation was higher in Ketamine group compared to other 2 groups with Propofol group showing least values. The incidence of post operative myalgia was significantly less (10%) at 24 hours in both Propofol and Ketamine group as compared to Normal saline group (50%) (p=0.006). None of the patients complained of moderate or severe grade myalgia in any group. There were no statistically significant changes in heart rate between Propofol and Ketamine groups. Normal saline group showed more increase in heart rate compared to other groups (p<0.05). With respect to MAP, there was statistically significant difference between Propofol, ketamine and normal saline groups with group P showing least & Group N highest values (p < 0.05). Conclusion: Incidence and severity of fasciculation and post operative myalgia is significantly reduced by pretreatment with both Propofol (0.5 mg/kg) and Ketamine (0.5 mg/kg). Although Propofol is more effective in reducing the incidence and severity of fasciculations; both Propofol and Ketamine are equally effective in reducing post - operative myalgia while maintaining haemodynamic stability.***

Keywords: Fasciculations, Ketamine, Myalgia, Propofol, Succinylcholine.

1. Introduction

Succinylcholine is considered to be the muscle relaxant of choice for performing endotracheal intubation during general anaesthesia. It provides a profound neuromuscular block of rapid onset and short duration. Though succinylcholine is associated with number of side effects, it is still considered a gold standard for rapid sequence induction and where difficulty is anticipated during intubation [1 - 6]. Most common side effect after succinylcholine administration is postoperative myalgia which can cause significant discomfort in patients; the incidence varies from 40% to 50% [1 - 8]. Pretreatment with various pharmacological agents have been tried to decrease incidence of the muscle pain caused after the administration of Succinylcholine with varying success. These agents include small dose of non depolarizing muscle relaxants, preservative free lignocaine, Benzodiazepines, magnesium sulfate, Opioids, non steroidal anti inflammatory drugs and higher dose of intravenous induction agents such as Propofol and ketamine [1 - 3, 5 - 7]. Both Propofol& Ketamine have been successfully used to decrease succinyl choline induced myalgia. We conducted the study in our hospital to compare the effect of pretreatment with Propofol and Ketamine on Succinylcholine induced postoperative myalgia. We hypothesized that both Ketamine and Propofol pretreatment are equally effective in decreasing the incidence and severity of postoperative myalgia.

2. Material and Methods

After obtaining approval from the institutional ethics committee; a prospective, randomized, double blind, study was conducted in male & female patients between age group 18 to 65 years ASA Grade I, II undergoing surgeries of< 3 hours duration under general anaesthesia with endotracheal intubation after succinylcholine administration. Pregnant patients and lactating mothers, patients with severe cardiovascular, liver or renal disease, morbidly obese (BMI > 35), patients with known allergies to the study drug and patients who has received analgesic + muscle relaxants medication in last 24 hours were excluded from the study. Informed written consent of all participants was taken for participation in the study. Patients were randomly divided into 3 groups of 20 participants each using sealed envelope method; Group P – Pretreatment with Propofol (0.5 mg/kg body weight) Group K – Pretreatment with Ketamine (0.5 mg/kg body weight) Group N – Pretreatment with Normal

Saline as control group. Patients were kept nil by mouth for 8 hours prior to surgery. After arrival of patients in operating room, routine monitoring i. e. HR, ECG, NIBP, and pulse oximetry was started and baseline parameters were noted. Patients were premedicated with Inj. Glycopyrrolate 0.005mg/kg, inj. midazolam 0.04 mg/kg and inj. Fentanyl 1.5 mcg/kg body weight. Patients were preoxygenated with 100% oxygen for 3 minutes. Thereafter study drugs were injected intravenously as per group allotment. Group P received 0.5 mg/kg Propofol diluted with normal saline up to 5 ml, Group K received 0.5 mg/kg Ketamine diluted up to 5 ml and Group N received 5 ml normal saline. The arm bearing venous access was covered with a green coloured cotton sheet to prevent the viewing of injections given. The person preparing and injecting the study drugs was different from the person who was observing the study parameters. Both the patient and observer were blind to the study drug used, making the study double blind. Two minutes after the administration of study drugs, anesthesia was induced with Inj. Propofol 2 mg/kg intravenously. After loss of eyelash reflex, 1.5 mg/kg succinylcholine was injected intravenously as a muscle relaxant. After succinylcholine administration, occurrence of fasciculations was observed and graded as nil: - no visible fasciculation, mild: - fasciculation affecting one limb without movement, moderate: - fasciculation affecting more than one limb with minimal limb movement, and severe: - vigorous sustained contraction of one or more than one limbs [1 - 3, 5, 6]. After 1 minute of positive pressure ventilation with 100% oxygen, patients were intubated with appropriate size cuffed endotracheal tube. The maintenance of anesthesia was continued using a mixture of O2, air, Isoflurane and Atracurium as muscle relaxant. Haemodynamic parameters (HR & MAP) were monitored at following intervals – baseline, after premedication, after study drug administration, after induction, after intubation (at 0, 5, 10 min of intubation). At the end of the surgery, muscle relaxation was reversed with Inj. Neostigmine 40 mcg/kg and Inj. Glycopyrrolate 10 mcg/kg. After the desired spontaneous ventilation, the patients were extubated, transferred to post - operative recovery rooms and later to wards. The patients received inj. Diclofenac sodium 75 mg 12 hourly for the treatment of surgical pain. Postoperative myalgia is defined as muscle pain not related to surgical intervention. The incidence and severity of Succinylcholine induced postoperative myalgia in the patients was determined after 24 hrs& 48 hrs after surgery based on Kararmaz et al's four point scale ([2 - 4, 6] as 0 = no muscle pain, 1 = Muscle stiffness limited to one area of the body, 2 = Muscle pain or muscle stiffness noticed spontaneously by the patient which requires analgesic treatment, 3 = Incapacitating generalized, severe muscle pain or stiffness.

Statistical analysis

The collected data was analyzed with IBM SPSS Statistics for Windows, Version 23.0. (Armonk, NY: IBM Corp). To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean & S. D. were used for continuous variables. To find the significant difference between the bivariate samples in independent groups the unpaired sample t - test was used. To find the significant difference in the multivariate analysis the one - way ANOVA was used and for categorical data Chi - Square test was used. In all the above statistical tools the probability value 0.05 was considered as significant level.

3. Results

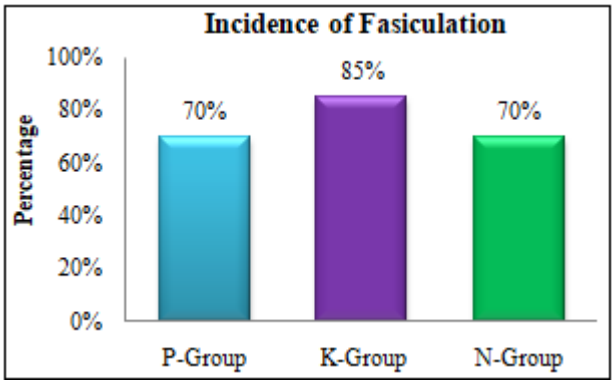
The demographic data (age, weight, duration of surgery) of all the 3 groups in our study was comparable (p>0.05) (Table 1).

Table 1: Demographic data. Results are given as mean ± SD.

Parameters	Group P (n = 20)	Group K (n = 20)	Group N (n = 20)	*P* value
Age (in years)	41.55±13.0	34.30±14.0	38.75±12.07	0.229 NS
Weight (in Kilograms)	60.30±8.15	60.55±8.88	62.85±8.90	0.593 NS
Duration of surgery (in hours)	1.5±1	1.4±1	1.6±1	0.120 NS

NS = Not significant

We observed that the incidence of fasciculation was higher in Ketamine group compared to normal saline and Propofol group (Graph 1).



Graph 1: Comparison of incidence of fasciculations between the study groups

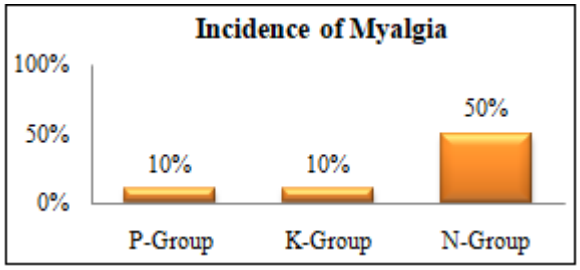
Severity of fasciculations was significantly lower in Propofol group than other groups. Moderate fasciculations were observed in 10% patients in saline group and 35% in Ketamine group. Five percent patients in both saline and Ketamine group showed severe grade fasiculations. Patients in propofol group didn't have moderate or severe grade fasiculations (Table 2).

Table 2: Comparison of grades of fasciculations between the study groups

Grade of fasciculations	Group P (N= 20)		Group K (N = 20)		Group N (N = 20)		*P* value
	No.	Percentage	No.	Percentage	No.	Percentage	
Nil	06	30	03	15	06	30	0.018S
Mild	14	70	09	45	11	55	
Moderate	00	00	07	35	02	10	
Severe	00	00	01	05	00	00	

S = Significant

The incidence of post operative myalgia was significantly less (10%) in our study at 24 hours in both Propofol and Ketamine group as compared to saline group (50%) (*p*=0.006) (Graph 2).



Graph 2: Comparison of incidence of myalgia between the study groups

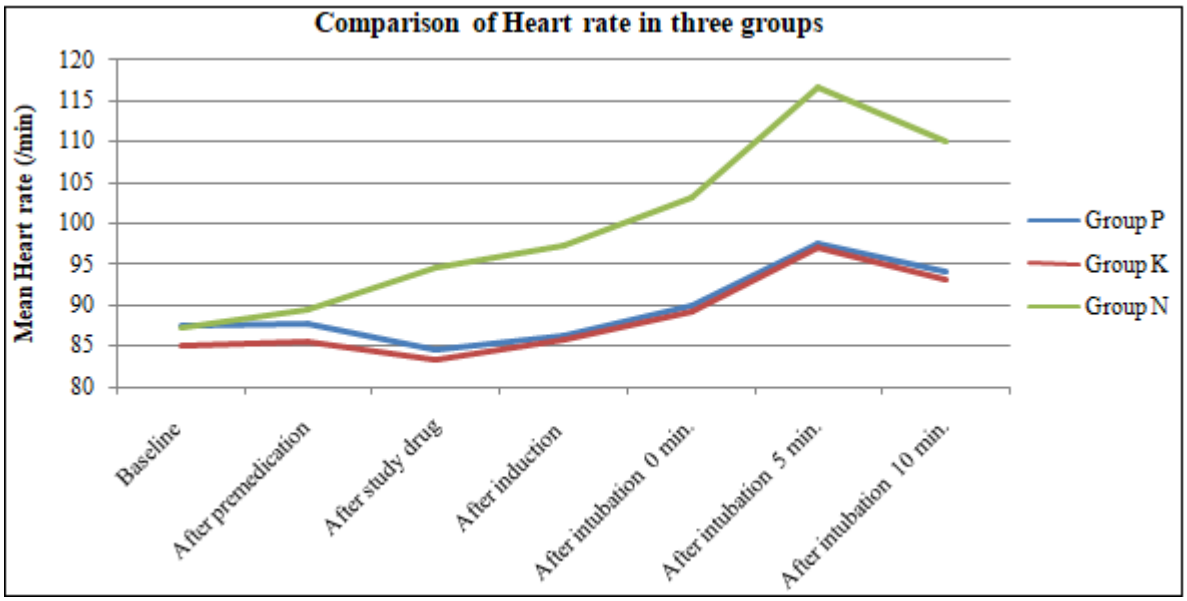
Significantly more number of patients in Normal saline group (50%) experienced mild myalgia compared to Propofol and Ketamine groups (10%). None of the patients complained of moderate or severe grade myalgia in any group (Table 3).

Table 3: Comparison of grades of myalgia between the study groups

Grade of Myalgia	Group P		Group K		Group N		P value
	No.	Percentage	No.	Percentage	No.	Percentage	
0	18	90	18	90	10	50	0.006S
1	02	10	02	10	10	50	

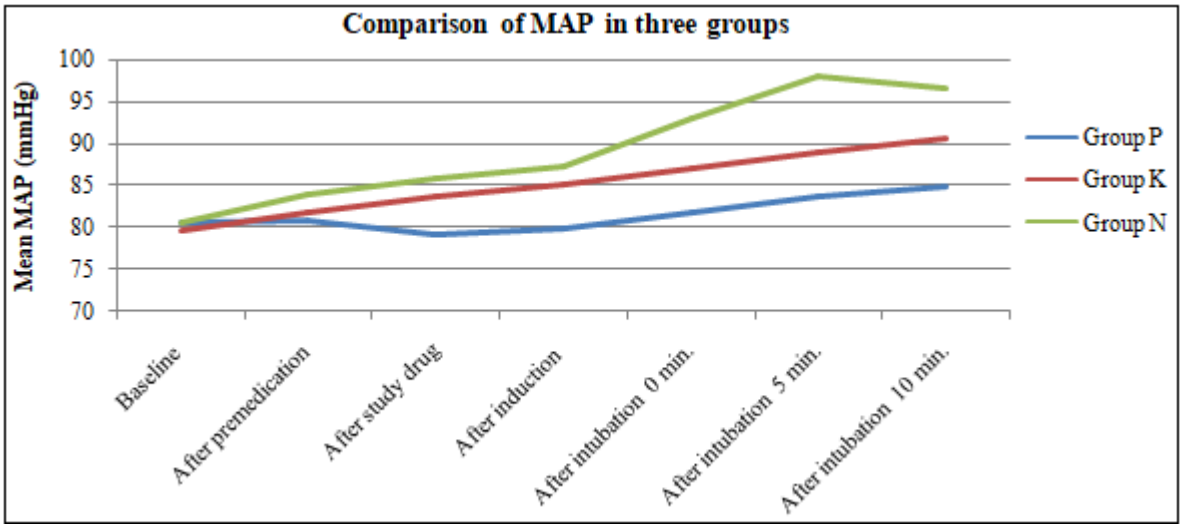
S = Significant

In our study, there were no statistically significant changes in heart rate between Propofol and Ketamine groups. Normal saline group showed more increase in heart rate compared to Propofol and Ketamine groups (p<0.05) (Graph 3).



Graph 3: Comparison of heart rate between the study groups

With respect to MAP, there was statistically significant difference between Propofol, ketamine and normal saline groups with group P showing lesser values (p < 0.05). In K and N group there was statistically significant difference (p<0.05) with Normal saline group showing higher MAP (Graph 4).



Graph 4: Comparison of mean arterial pressure (MAP) between the study groups

4. Discussion

Succinylcholine is a depolarizing muscle relaxant with rapid onset and short duration of action. Though Fasciculations are relatively benign side effect of its use, most anesthesiologists prefer to prevent them due to a possible association between fasciculations and postoperative myalgia. A prejunctional depolarizing action of succinylcholine have been considered as cause of fasiculations [3, 4, 7 - 11]. Several mechanisms have been proposed to explain the phenomenon of postoperative myalgia associated with succinylcholine administration. Fasciculations involve vigorous contraction by muscle bundles and without synchronous activity in adjacent bundles producing muscle fibre rupture or damage. Muscle damage produced by the shearing forces associated with the fasciculationsmay cause post - operative myalgia [1, 3 - 8]. The release of large amounts of lactic acid in the muscle is also one of the proposed theories for myalgia but the evidence to substantiate this view is insufficient. The reported incidence of succinylcholine – induced myalgia ranges from 1.5 to 89%. The most commonly quoted is around 50%. It usually appears on the 1st day after surgery, and is located in the neck, shoulder and upper abdominal muscles. The discomfort usually lasts for 2 or 3 days but occasionally persists for as long as a week. Although self limiting; iatrogenic postoperative myalgia is unacceptable in modern anaesthetic practice.

Different pre - treatment modalities have been attempted to reduce the incidence and severity of fasciculations and myalgia. This includes precurarization with a small dose of non - depolarizing muscle relaxant, pre succinylcholine use of lidocaine, calcium gluconate, magnesium sulphate, nonsteroidal anti - inflammatory drugs (NSAIDs), dexmedetomidine, benzodiazepines, remifentanil, phenytoin sodium, ketorolac and intravenous induction agents in higher doses. Ketamine, an intravenous anaesthetic agent, is N - methyl - D - aspartate (NMDA) receptor antagonist with good analgesic activity. Analgesic effect of Ketamine is present even with a subanaesthetic dose. Recent studies have shown the role of the NMDA receptor in facilitating the process of pain in CNS [2]. The administration of NMDA receptor antagonists prevents the development of sensitizationand hyperalgesia. Ketamine creates a combination of both antinociceptive and pronociceptive actions. It inhibits the synthesis of nitric oxide, which probably contributes to the analgesic effect. Propofol is an intravenous induction agent which acts on GABA receptors. Propofol induced potentiation of glycine receptors at the spinal level might contribute to its antinociceptive action [1, 3, 5 - 7]. It also inhibits propagation of reactions involving free radicals. This antioxidant effect of propofol according to few studies is responsible for reducing incidence and severity of postoperative myalgia caused by succinylcholine.

In our study, we compared the effect of pretreatment of Propofol (0.5mg/kg) and Ketamine (0.5mg/kg) on the incidence and severity of succinylcholine induced post - operative myalgia and fasiculations along with Normal saline as control group.

We observed that the incidence of fasciculation was higher in Ketamine group compared to normal saline and Propofol group. Kararmaz A et al [5] compared the effects of Thiopentone 5 mg/kg, Propofol 2 mg/kg and Propofol 3.5 mg/kg on succinylcholine induced fasciculations and myalgia in women who underwent laparoscopy. They found that the incidence of fasiculations was comparatively lower in Propofol (3.5 mg/kg) group, 20% of patients in this group didn't have fasiculations. Garg K et al [1] studied the effect of repeated bolus dose of Propofol (Group I no repeated bolus dose, Group II repeated bolus dose with 0.5 mg/kg, Group III repeated bolus dose with 1 mg/kg). They observed that the incidence of fasciculation was 73% and 33% in Group II and Group III respectively as against 90% in control Group ($p< 0.05$). Parmar S et al [6] studied the effect of Propofol in preventing succinylcholine induced fasciculation and myalgia. The incidence of fasiculations in their study was 75.76% and 48.48% in P1 (Propofol 2.5 mg/kg) and P2 (Propofol 3.5 mg/kg) groups respectively ($P>0.05$). All the above studies concluded that higher dose of Propofol is effective in reducing succinylcholine induced fasciculations. Our study results correlate with the above studies

In our study, severity of fasciculations was significantly lower in Propofol groupthan Ketamine group. Moderate fasciculations were observed in 10% patients in Normal

saline group and 35% in Ketamine group. Five percent patients in both Normal saline and Ketamine group showed severe grade fasiculations. Propofol group didn't have moderate or severe grade fasiculations. Kararmaz A et al ([5]) also observed that no severe fasciculations occurred in Propofol (3.5 mg/kg) group and the severity of fasciculations were significantlylower than in the other groups (p=0.01). Garg K et al ([1]) observed that the severity of fasciculation in Propofol group (1 mg/kg bolus) was significantly lower than in the other groups. No patients had severe fasiculations in this group. (p>0.05) Parmar S et al [(6)] also observed that severity of fasciculations was reduced more in group P2 (Propofol 3.5 mg/kg) than group P1 (Propofol 2.5 mg/kg) (p=0.0006). With higher dose of Propofol the severity of fasciculation was decreased. Srivastava V et al ([3]) observed more patients in placebo control group having moderate to severe fasciculations (p=0.028). Our study findings of Propofol group correlates with these studies. We did not come across any study where effects of pretreatment with ketamine on incidence & severity of fasciculation were observed.

The incidence of post operative myalgia was significantly less (10%) in our study at 24 and 48 hrs in both Propofol and Ketamine group as compared to Normal saline group (50%) (p=0.006). In the study by Kararmaz et al, ([5]) the incidence of myalgia was 30% in Propofol group (3.5 mg/kg), 60% in Propofol group (2.5 mg/kg) & 68% in control group. Garg et al ([1]) observed in their study the incidence of myalgia was 73.34% in Propofol group (0.5 mg/kg) and 60% in Propofol group (1mg/kg), in control group it was 86.67%. Parmar S et al ([6]) observed that the total incidence of myalgia was57.57% and 30.3% in group P1 (Propofol 2.5 mg/kg) and P2 (Propofol 3.5 mg/kg) respectively (p<0.001) Increasing the dose of Propofol decreased the incidence of myalgia. Nasseri K et al ([2]) studied the effect of low dose ketamine on succinylcholine induced post operative myalgia and observed that in Ketamine Group, 18.1% of the patients had myalgia, whereas 50% of patients had myalgia in Normal Saline Group (P=0.001). Our findings are similar to abovementioned studies.

We observed that 50% patients in Normal saline group had mild myalgia while in Propofol and Ketamine group only 10% of the patients experienced mild myalgia. None of the patients complained of moderate or severe grade myalgia in any group. In the study by Kararmaz et al, ([5]) none of the patients in any group complained of severe grade myalgia.20%patients had mild and 10% had moderate myalgia in Propofol (3.5 mg/kg) group which was less as compared to other 2 groups. As the dose of propofol increased; the incidence and severity of post - operative myalgia decreased. Garg et al ([1]) observed thatthe severity of myalgia at 24 hrs inpropofol groups was significantly less as compared to control group. At 48 hrs, the severity of myalgia decreased in all the 3 groups compared to severity at 24 hours with propofol groups showing further decrease in myalgia compared to control group. No patient in their study had severe myalgia at any of the time interval. Parmar S et al ([6]) observed that the severity of myalgia was reduced more in group P2 in which dose of Propofol was higher than group P1. Nasseri K et al ([2]) observed that after pretreatment with Ketamine, 81.9% of patients had no myalgia while in normal saline group 50% of patients had myalgia (P<0.001) Severity of myalgia was less in Ketamine group than in normal saline group. None of the patients in their study complained of severe grade myalgia. All of the above mentioned studies show that use of higher doses of Propofol and pretreatment with Ketamine reduce the incidence and severity of post operative myalgia. Our study results of both the groups are in accordance with above studies.

Very few studies in the literature have compared effects on haemodynamic parameters in addition to myalgia. In our study, we observed that there were no statistically significant changes in heart rate between Propofol and Ketamine groups (p>0.05). Normal saline group showed more increase in heart rate compared to Propofol and Ketamine groups (p<0.05). With respect to MAP, there was statistically significant difference between Propofol, ketamine and normal saline groups with group P showing lesser values (p < 0.05). In K and N group there was statistically significant difference (p<0.05) with Normal saline group showing higher MAP. After intubation MAP increased in all the 3 groups but more in N group. Garg K et al ([1]) observed that in controlgroup, mean HR persistently increased from baseline value throughout the study period; compared to the patients given a repeat dose of Propofol which correlates with our findings.

5. Conclusion

Incidence and severity of fasciculation and post operative myalgia is significantly reduced by pretreatment with both Propofol (0.5 mg/kg) and Ketamine (0.5 mg/kg). Although Propofol is more effective in reducing the incidence and severity of fasiculations; bothPropofol and Ketamine are equally effective in reducing post - operative myalgia while maintaining haemodynamic stability.

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