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Comparison between pre-treatment with nalbuphine *vis-a-vis* dexmedetomidine for prevention of etomidate induced myoclonus

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ABSTRACT

Background: Etomidate is considered as an excellent drug for induction in anesthesia, although it has an undesirable side effect like myoclonus. **Aims and Objectives:** The aims of this study were to compare the effect between pre-treatment with nalbuphine and dexmedetomidine for attenuation and severity of etomidate induced myoclonus and to assess their adverse drug reaction. **Materials and Methods:** A prospective, randomized, and single-blinded study was conducted on patients undergoing elective surgery under general anesthesia. After selection of patients according to inclusion/exclusion criteria, nalbuphine (0.2 mg/kg) and dexmedetomidine (0.5 μg/kg) were infused 10 min before the induction of anesthesia. The vital parameters and any incidences of myoclonus during operation were observed at fixed interval. **Results:** A total of 102 patients in the age group of 18–60 years of either sex were assessed. In Group D 7, out of 51 patients (13.7%) were found to have myoclonus, whereas, in Group N, it was observed in 21 out of 51 patients (41.2%). Difference between the two was found to be statistically significant ($P<0.001$). In Group D, grade 3 myoclonus was observed in 0% patients. About 2% patients had grade 2 and 11.8% had grade 3 myoclonus. In Group N, grade 3, 2, and 1 myoclonus was recorded as 3.9%, 11.8%, and 25.5%, respectively. The difference between the two groups is statistically significant ($P<0.001$). **Conclusion:** Incidence and severity of etomidate induced myoclonus were less in patients who received pre-treatment with dexmedetomidine than those who underwent pre-treatment with nalbuphine. Furthermore, more hemodynamic stability was achieved with use of dexmedetomidine as the agent for pre-treatment.

Key words: Anesthesia; Etomidate; Nalbuphine; Myoclonus

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INTRODUCTION

Etomidate is an imidazole-derived sedative-hypnotic agent directly acting on gamma-amino butyric acid receptor complex, blocking neuroexcitation, and producing anesthesia. The advantages of using this drug for induction include excellent pharmacodynamics, protection from myocardial and cerebral ischemia, minimal histamine release, and a stable hemodynamic profile, along with minimal effects on the respiratory system.[1] The hemodynamic stability offered by this drug makes it the induction agent of choice in patients with compromised hemodynamic and cardiac reserve.[2] However, two undesirable side effects often associated with etomidate are vascular pain on injection (EP) and myoclonus (EM), which are defined as sudden, involuntary, short either irregular, or rhythmic contraction of some muscle fibers of a whole muscle or of different muscles of one group, leading to short observable movements of the corresponding body part. All these jeopardize therapeutic use of this drug.[3]

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Although mechanism of etomidate-induced myoclonus is still not clear, a number of drugs have been investigated by researchers due to their ability to suppress these myoclonic movements.[4] Drugs for preventing myoclonic movements need to be short-acting, which should not have significant effect on respiration and hemodynamic, along with smooth recovery from anesthesia.[5] Various pharmacological studies with different pharmacological agents have given variable success in attenuating EM, those include pre-treatment with fentanyl, morphine, lignocaine, nalbuphine, and dexmedetomidine.[1,2,6-9] Different agents have been evaluated for their ability to attenuate etomidate-induced myoclonus, opioids being most prominent of them all. A meta-analysis was published by Wang et al., in 2018,[7] which evaluated effects of pre-treatment with opioids for preventing etomidate induced myoclonus. Although morphine has often been the standard opioid analgesic for pain control and has been used widely, certain drug induced adverse effects have been reported as intolerable and needed to be addressed. A study by Zeng et al.,[10] in 2010, revealed that in comparison with morphine, nalbuphine has much lesser side effects such as pruritus, nausea, vomiting, and respiratory depression with equal efficacy.

Nalbuphine is a synthetic opioid belonging to the agonist-antagonist group[10,11] and is recommended for the management of moderate-to-severe pain. Nalbuphine in analgesic dosage (0.2 mg/kg body weight) has been found to be effective in reducing the intensity and severity of EM.[2] On the other hand, pre-treatment with dexmedetomidine, a highly selective alpha-2 adrenoceptor agonist acts by presynaptic activation of the α2A adrenoceptors in the locus ceruleus and inhibits the release of norepinephrine. Such pharmacological action resulting in sedative and hypnotic effects[1] and thus probably helping in prevention of myoclonus as well as stabilization of hemodynamic responses. These findings have been reported in several studies with insignificant adverse effects of the drug.[4,12,13] Thus, this study was conducted to compare the efficacy and safety of these two promising molecule when administered as a pre-treatment to control etomidate-induced myoclonic seizure.

Aims and objectives

The primary aim of the study was to comparison between pre-treatment with nalbuphine and dexmedetomidine for attenuation of etomidate-induced myoclonus and comparison of severity of myoclonus between pre-treatment with nalbuphine and dexmedetomidine in affected patients. The secondary objective was to assess any adverse drug reaction due to administration of the study drugs.

MATERIALS AND METHODS

A prospective, randomized, and single-blinded study was conducted on patients undergoing elective surgery under general anesthesia with orotracheal intubation at Calcutta National Medical College and Hospital, Kolkata, India, for 14 months (June 2020–July 2021) after obtaining prior approval from the Institutional Ethics Committee. With a power of study of 90%, considering type 1 error of 5%, difference in treatment effect of 30%, and a dropout rate of 10%, a total of n=102 patients of either sex aged between 18 and 60 years belonging to the American Society of Anesthesiologists physical Status I or II undergoing elective general anesthesia were recruited. Those with history of allergy to any of the study drugs, anticipated difficult airway, cardiac disease (if any), pregnant or lactating mothers, having significant hepatic or renal insufficiency, receiving sedatives, analgesics, or opioids in the 24 h preoperatively and known patient of epilepsy or seizure disorder were excluded from the study. The recruited patients were taken into the operating room. Intravenous (IV) cannulation with 18 G needle done. IV fluid ringer lactate started at the rate of 6 ml/kg/h. Multichannel monitors attached and vitals recorded in the form of heart rate (HR), mean blood pressure (MBP), and SpO_2. Patients were assigned to two groups by computer generated randomization of n=51 each, namely, Group N (n=51) received 0.2 mg/kg of nalbuphine in 10 ml of normal saline 150 s before induction and Group D (n=51) received injection dexmedetomidine infusion (0.5 μg/kg) 10 min before the induction of anesthesia. In the next step, Injection Glycopyrrolate (0.2 mg) followed by induction of anesthesia with Etomidate 0.3 mg/kg IV over 20 s was carried out. The patients were observed visually by an observer unaware of the group allocation for another 2 min for recording the occurrence of myoclonus (if any). During the 2-min observation, the ventilation was assisted with 100% oxygen. After the 2-min observation period, Injection Vecuronium bromide 0.1 mg/kg IV was given to both the groups. The patients were intubated with an appropriately sized endotracheal tube followed by a standardized anesthesia and analgesia protocol. The HR, MBP, and SpO_2 were monitored continuously and any episode of intraoperative bradycardia (HR <60 mmHg), tachycardia (HR >100/min), or hypertension (MBP >85 mmHg) were recorded and managed appropriately.

The severity of myoclonus graded as follows: 0: no myoclonus, 1: mild (short movements of a body segment), 2: moderate (mild movement of two different muscles), and 3: severe (clonic movements in two or more muscle groups or fast adduction of a limb).[2] If a patient had >1 episode of myoclonus during the 2 min observation period; then, the episode with the highest severity grading was recorded for statistical analysis. The time to first onset of myoclonus in seconds was recorded. The sedation achieved was assessed by Ramsay sedation score (RSS), where 1: anxious and agitated, 2: cooperative, oriented, 3: asleep and responding

to verbal commands, 4: asleep but brisk response to light stimulus, 5: sluggish response to stimulus, and 6: asleep without response to stimulation.[14] Incidences of adverse effects due to administration of the study drugs were also assessed during the study period.

Statistical analysis

At the end of all the relevant data collection, the demographic data clinical parameters and post-operative status of the patients were statistically analyzed by standard statistical software Microsoft Excel 2010 and expressed as mean and standard deviation and percentage. P<0.05 was considered as statistical significant.

RESULTS

A total of 102 adult patients were randomly allocated into two groups of 51 each receiving either nalbuphine or dexmedetomidine. The demographic prolife and pre-operative parameters of the study participants were comparable and were not statistically significant, that is, P>0.05 (Table 1).

There was significant changes (increase) in the HR observed in Group N when compared with Group D with P<0.0001 during intraoperative and immediate post-operative phases, although it was not significant during the pre-medication and pre-induction phase (P>0.05) (Table 2).

The mean arterial blood pressure was also found to be statistically significant in Group N before induction, intraoperative, and immediate post-operative phases with P<0.05 when compared to Group D (Table 3).

Incidence of myoclonus was observed to be more in Group N (41.2%) than Group D (13.7%). Statistically significant association was found between the groups in incidence of myoclonus, with P=0.003 (Figure 1).

The severity of myoclonus was observed more in Group N as compared to Group D, as depicted in Figure 2. Grade 3 severity was observed more in Group D as compared to Group N.

The average timing of onset of myoclonus was found to be 47.33±5.465 s in Group D and 30.20±6.346 s in Group N which was highly significant (P<0.0001). No statistically significant difference (P>0.05) of SpO_2 noted between the two study groups before premedication and in the immediate post-operative period. The Ramsay sedation scoring is depicted in Figure 3 and the association between the two study groups was found to be statistically significant with P=0.001.

Table 1: Demographic profile and other parameters of the study participants

Parameters	Group D (n=51)	Group N (n=51)	P-value
Age (years)	37.59±11.970*	37.53±10.992*	0.979
Body weight (kg)	58.90±8.132*	61.33±7.025*	0.109
Male	26 (51%)#	27 (52.9%)#	0.843
Female	25 (49%)#	24 (47.1%)#	
ASA-1	39 (76.5%)#	41 (80.4%)#	0.630
ASA-2	12 (23.5%)#	10 (19.6%)#	
Duration of surgery (min)	114.80±16.522*	113.73±17.744*	0.751

*Mean±SD #n (%), ASA: American society of anesthesiologists

Table 2: Variation in heart rate among the study participants in the two study group

Heart rate at different time interval	Group D (n=51)	Group N (n=51)	P-value
	Mean±SD		
Before premedication	79.08±9.090	79.80±9.342	0.692
Before induction	86.51±10.691	83.92±10.560	0.222
Intraoperative	87.82±5.039	94.22±7.978	<0.0001
Immediate post-operative	79.10±10.251	93.59±8.925	<0.0001

Table 3: Variation in mean arterial blood pressure among the study participants in the two study group

Mean arterial blood pressure (mmHg) at different time interval	Group D (n=51)	Group N (n=51)	P-value
	Mean±SD		
Before premedication	77.12±7.972	78.49±8.334	0.397
Before induction	67.71±4.785	84.76±6.501	<0.0001
Intraoperative	68.31±4.764	86.22±6.031	<0.0001
Immediate post-operative	76.57±7.595	86.35±8.715	<0.0001

Incidence of adverse events in the form of nausea and vomiting observed more in Group N 39.2% in comparison to Group D 19.6% which was statistically significant between the two groups with P=0.03.

DISCUSSION

In this randomized, prospective, and single-blind clinical study, our primary objective was to compare the effects of dexmedetomidine and nalbuphine pre-treatment on the incidence and severity of etomidate-induced myoclonus and our secondary objective was to assess the effect of the two drugs on hemodynamic stability as well as incidence of adverse effects in the form of post-operative nausea, vomiting, and cough. To the best of our knowledge, there is paucity of the literature comparing pre-treatment with dexmedetomidine and nalbuphine for etomidate-induced

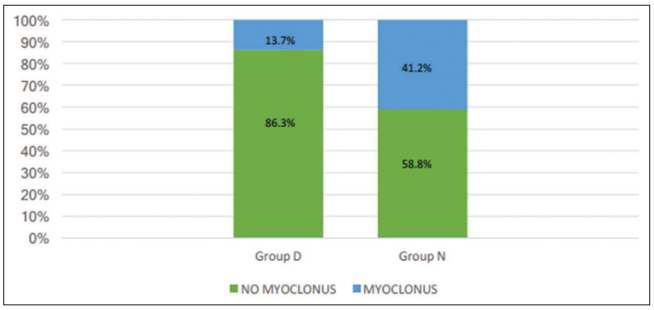

Figure 1: Incidences of myoclonus among the two study group

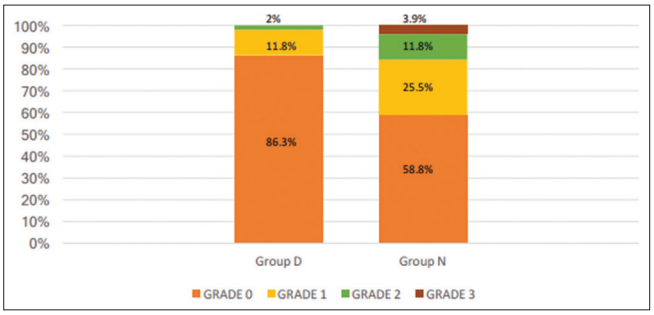

Figure 2: Distribution of severity of myoclonus among the study participant

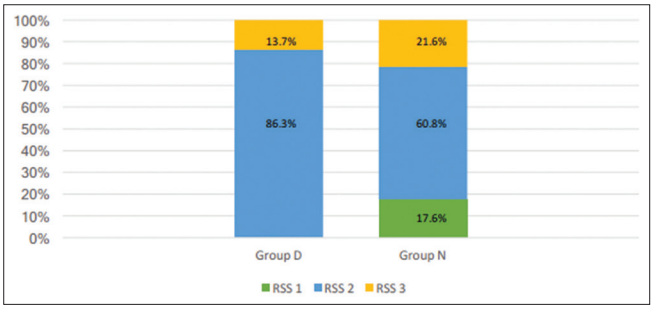

Figure 3: Ramsay sedation score as observed in both the study group

myoclonus. In our study, the incidence of myoclonus was found to be 13.7% in Group D compared to 41.2% in Group N. The result of the study of Dey and Kumar[1] also found to conclude dexmedetomidine to be an effective agent in controlling etomidate-induced myoclonus. In the present study, the severity of myoclonus was found to be statistically significant lesser (P<0.001) with pre-treatment with dexmedetomidine as compared to nalbuphine. In the study conducted by Mizrak et al.,[9] they concluded similar outcome when they compared dexmedetomidine with thiopentone sodium. Even the onset timing in (seconds) of myoclonus was delayed in the dexmedetomidine group when compared to nalbuphine group and this finding was also statistically very significant (P<0.001) in the present study. Again this findings corroborated with observations noted in the study conducted by Du et al.,[15] and Ghodki and Shetye,[16] where they found that the onset of myoclonus was much delayed in the dexmedetomidine group.

The secondary objective of our study was to assess the hemodynamic stability as well as incidence of post-operative nausea-vomiting and cough after premedication by dexmedetomidine and nalbuphine. Observations were made in terms of HR, oxygen saturation, and MBP before premedication, before induction, intraoperative, and immediate post-operative phases. HR in the two groups was comparable before premedication and before induction. In the intraoperative period, a mean HR (bpm) with SD of 87.82±5.039 was noted in Group D, whereas, for Group N, it was 94.22±7.978. In the immediate post-operative period, the values were 79.10±10.251 and 93.59±8.925, respectively, for Group D and Group N. Thus, in both intraoperative and immediate post-operative phases, the difference between the two groups were found to be statistically significant with P=0.001 in both the situations.

Group D and Group N were comparable in terms of oxygen saturation of the patients before premedication. In immediate post-operative period, mean and SD in Group D was found to be 93.59±8.925, compared to 95.47±1.837 in Group N. The difference between them being not statistically significant. 66 As for MBP, the two groups were comparable before premedication. In Group D, the observation values (mean±SD) were noted as 67.71±4.785, 68.31±4.764, and 76.57±7.595, respectively, in before premedication, before induction, and immediate post-operative phases, respectively. In Group N, the recorded values in the three aforementioned phases were 84.76±6.501, 86.22±6.031, and 86.35±8.715, respectively. The difference between the two groups was found to be statistically significant in all three phases with P=0.000 for each phase. Thus, dexmedetomidine was found to achieve better hemodynamic control in at least two of the attributes. RSS was recorded in all patients to find out the more suitable drug between the two to obtain optimum post-operative sedation and analgesia. In Group D, no patients had RSS 1, 86.3% had RSS 2, and 13.7% had RSS 3. In Group N, they were 17.6%, 60.8%, and 21.6%, respectively. P=0.001, and the difference between the two groups were statistically significant. Incidence of adverse events was noted in terms of post-operative nausea, vomiting, and cough. In Group D, 19.6% patients had adverse events, whereas, in Group N, it was 39.2%. Thus, incidence of adverse events in Group D was lower compared to Group N with statistically significant difference between the two (P=0.03).

Limitations of the study

The outcome of the study is single centric on a small cohort of patients and need further evaluation by doing large sample studies to establish the findings. Second, only single doses of nalbuphine (0.2 mg/kg) and dexmedetomidine (0.5 μg/kg) were used and the effect of escalating dose of these study drugs were not established.

CONCLUSION

The incidence of etomidate-induced myoclonus was significantly decreased among patients who underwent pre-treatment with dexmedetomidine in comparison to nalbuphine. The severity of myoclonus was also lesser with use of dexmedetomidine as the pre-treatment agent. Onset of myoclonus was observed to be delayed in pre-treatment with dexmedetomidine. In addition, pre-treatment with dexmedetomidine was observed to achieve greater hemodynamic stability during intraoperative and immediate post-operative period. Dexmedetomidine was found to be superior in post-operative pain management as was indicated by the RSS. Incidence of adverse effects in the form of post-operative nausea, vomiting, and cough was also observed to be lesser by premedication with dexmedetomidine.

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MKS, PB- Concept, design of study and literature search, experimental studies; **MKS, SM-** Data acquisition, data analysis, statistical analysis; **AB, SB:** Manuscript preparation; **MKS, AB, SB, PB-** Manuscript editing and manuscript review.

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