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Original research article

Efficacy of nalbuphine pre-treatment in attenuation of etomidate induced myoclonus: A placebo controlled trial from Malwa region

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Abstract

Background: Propofol has been the most popular drug for induction of general anaesthesia for the past three decades due to its favourable pharmacokinetic and pharmacodynamic profile but its associated haemodynamic complications like bradycardia and hypotension are a matter of concern. On the other hand etomidate provides excellent cardio stabilityas an intra-venous induction agent but its association with myoclonusis undesirable among anaesthetists, many drugs have been tested for prevention of etomidate induced myoclonus with mixed results, keeping this background in mind we decided to test the effectiveness of 0.2mg/kg intravenous nalbuphine as a pre-treatment medication for myoclonus prevention caused by Etomidate.

Aims: Primary objective of this study is to evaluate the efficacy of nalbuphine pretreatmentin prevention of etomidate induced myoclonus, Secondary objective of this study is toevaluate the safety profile of nalbuphine.

Material and Methods: This prospective, randomized, double blind, placebo controlled study was conducted in a tertiary hospital associated with Index Medical College, 60consenting patients undergoing routine surgeries under general anaesthesia were randomly allocated to one of the two groups 10ml of normal saline was administered intravenously to group Iand 0.2mg/kg of nalbuphine in 10ml of normal saline was administered to group II intravenously, 150 seconds before injecting iv Etomidate 0.3mg/kg, administered over 20 seconds, patients were assessed for incidence and severity of myoclonus over next two minutes and side effects were observed for 24 hours, Students t test, chi square test were applied as required and a P value of <0.05 was considered statistically significant.

Result: A statistically significant, decreased incidence as well as severity of myoclonus both during the 1st and 2nd minuteswas observed with nalbuphine pretreatment compared with the control group ($P <$ 0.005). Whereas the incidence of minor side effects like hypotension, bradycardia, sedation, nausea and vomitingwere observed to be similar in both groups.

Conclusion: Both groups were similar with regards to demographic characteristics, the incidence (73.33% in group I vs. 20% in group II) and severity (1.23 at 1 minutes and 0.5 at 2 minutes in group I vs 0.17 at one minute and 0.23 at 2 minutes in group II), of myoclonus was significantly reduced in nalbuphine pre-treatment group compared to placebo group, without any significant increase in side effects.

Keywords: General anaesthesia, etomidate, myoclonus, prevention, nalbuphine, side effects

Introduction

Cardiovascular complications are the most common cause of post-operative morbidity and mortality in patients who undergo surgery [1]. Due to decreased systemic vascular resistance and cardiac contractility hypotension frequently occurs during induction of anesthesia with Propofol [2].

Whereas Etomidate is considered induction agent of choice for high-risk patients suffering from

cardiopulmonary diseases and in situations where maintaining a normal blood pressure is required [3].
Etomidate is an imidazole ring containing sedative-hypnotic induction agent which acts on gamma amino butyric acid receptors and blocks neuro excitation and produces general anesthesia. It has a stable hemodynamic profile and minimal effects on respiratory system as compared to other induction agents. Myoclonic movements and pain on drug injection are the most common side effects of this drug. Introductionof a fat emulsion preparation of etomidate has abolished the complaint of pain on injection, but myoclonus still remains a matter of concern with the newer preparation [4].
Involuntary contraction of some muscle fibres of a single muscle or of different muscles of one or more groups resulting in short visible movements of the body is defined as myoclonus [5].
The etomidate induced myoclonus seen in up to 80% of un-premedicated patients and turns out to be a very hazardous complication in patients with open globe injuries, nonfasted patients and patients with cardiac compromise it may also lead to the loss of intravenous access, displacement of the electrocardiogram electrodes and postoperative patient discomfort [6, 7]. Myocardial oxygen consumption can increase as a result ofintense muscle contractions which can prove hazardous in patients with limited cardiovascular reserve. Therefore effective measures are required to prevent such hazardous complications and to limit the incidence of myoclonus. The exact aetiology of myoclonus is still unclear, thoughit represents a seizurelike activity [6].
Many mechanisms have been proposed to explain myoclonic movements. It has been reported that myoclonic movement's results from temporal subcortical disinhibition, another theory proposes that etomidate administration depresses the inhibitory circuits earlier than the excitatory neuronal circuits causing myoclonus [8].
Many drugs have been testedin order to prevent myoclonus. Benzodiazepines opioids and muscle relaxants have shown some success in reducingthese myoclonic movements [9, 10].
Use of kappa opioid receptor agonists have demonstrateda reduction in seizure activity [11]. Nalbuphine is an opioid belonging to the agonist-antagonist group and is recommended for the management of moderate to severe pain. Intraoperative analgesia, ceiling effect to respiratory depression, low abuse potential, being free from 'controlled substances act' unlike fent any lare a few of the many advantages of nalbuphine which makes it an ideal substitute to pure opioid agonists. Keeping this background in mind our study was designed to evaluate the efficacy and safety of nalbuphine pre-treatment for prevention of etomidate induced myoclonus.

Material and Methods
After obtaining Institutional Ethical Committee approval and written informed consent from the patients, a prospective randomized placebo controlled study was conducted at tertiary health care hospital associated with Index Medical College. 60 consenting patients of American society of anaesthesiology class I and II between the age group of 20-60 years planned for routine surgeries requiring general anesthesia were randomly selected & included in the study. These patients were divided into 2 groups consisting of 30 patients each.

Inclusion criteria
Consenting patients, ASA class I and class II patients, patients aged between 20-60 years, patients undergoing routine surgeries requiring general anesthesia.

Exclusion criteria
Patient's refusal, ASA class III and above. Participants with history of allergy to any of the study drugs, anticipated, cardiac disease, pregnant or lactating females, and significant hepatic or renal insufficiency were not included in this study.

- Group I (n=30) received 10ml normal saline.
- Group II (n=30) received 0.2mg/kg nalbuphine in 10 ml normal saline.

After arriving at the operation table all routine monitors like pulse oximeter, non-invasive blood pressure, electrocardiography were attached to the patient. A 20 gauge intravenous canula was inserted at dorsum of hand and connected to a half litreringer Lactate drip and baseline readings of mean arterial blood pressure, heart rate, peripheral oxygen saturation were recorded. Patients were pre-oxygenated with 100% oxygen by facemask for 5 minutes. 10ml normal saline was administered to patients belonging to group I whereas 0.2mg/kg nalbuphine in 10ml normal saline was administered to patients belonging to group II, after waiting for 150 seconds anesthesia was induced with etomidate 0.3 mg/kg IV over 20 seconds after confirming onset of etomidate action which was established by loss of response to verbal command. The patients were ventilated for the next 2 minutes and observed for incidence and severity of myoclonus, after the two-minutes fentanyl 2mcg/kg was administered intravenously to patients belonging to group I, injection vecuronium bromide 0.1mg/kg iv was given to both the groups and were subsequently intubated with appropriately sized cuffed endo-tracheal tube. After intubation $EtCO_2$ was recorded by connecting $ETCO_2$ sensor to the endotracheal tube. The anesthesia was maintained with oxygen and nitrous oxide mixture in the ratio of 1:1, isoflurane in the concentration of

1% and maintenance dose of vecuronium bromide was given after appearance of curare notch in $EtCO_2$ monitor @ 0.01 mg/kg body weight. Patients were reversed with glycopyrrolate @ 0.01 mg/kg and neostigmine @ 0.05 mg/kg body weight and were extubated and shifted to post anesthesia care unit after following verbal commands and when neck holding for more than 5 seconds was present. All the patients were observed for a period of 24 hours for episodes of side effects like nausea, vomiting, hypotension, bradycardia sedation and respiratory depression.
Primary outcome of our study was to compare the incidence and severity of etomidate induced myoclonus and the secondary outcomes was to compare of incidence of side effects between both the groups. All patients were treated with 1gram IV paracetamol for the management of postoperative painas needed.

Result

Demographics: Patients belonging to both groups were assessed for age, weight, ASA status, gender, heart rate and mean arterial pressure and both groups were observed to be demographically comparable.

Table 1: Comparison of demographic characteristics between both the groups

Demographics	Group I (Placebo)	Group II (Nalbuphine)	P value
Age	39.80 ± 10.68	42.10 ± 9.63	0.384 NS
Weight	62.20 ± 8.07	63.50 ± 6.51	0.495 NS
ASA Status	25:5	26:4	0.718 NS
Male: Female	19:11	20:10	0.786 NS
Mean Arterial Pressure	95.77 ± 6.354	95.47 ± 6.286	0.854 NS
Heart Rate	80.43 ± 6.307	79.93 ± 4.416	0.895 NS

Chi square test is applied. The result is not significant at $p < .05$.

Incidence and severity of myoclonus

Out of 30 patients in group I,15(50%) patients showed myoclonus in the 1st minute whereas 7(23.31%) patients in the 2nd minute, whereas in group II ,3(10%) patients showed myoclonus in the 1st minute and 3(10%) patients in the 2nd minute. The severity of myoclonus in group I was as follows grade 0 in 09(29.97) grade I in 4(13.32%) patients, grade II in 7(23.31%) patients and grade III in 10(33.33%) patients whereas in group II it was grade 0 in 24(80%) patients, grade I in 2(6.66%), patients, grade II in 2(6.66%) patients and Grade III in 2(6.66%) patients.

Table 2: Cross tabulation of incidence of myoclonus between group I and II

Incidence of myoclonus at	Group I	Group II	P value
1 minute	15(50%)	03(10%)	<0.001
2 minute	06(23.33%)	03(10%)	

Chi square test significant at $p<0.05$.

Table 3: Cross tabulation of severity of myoclonus between group I and II

Severity of Myoclonus at	Group I	Group II
1 minute	1.23	0.17
2 minute	0.5	0.23

Safety profile

Out of 30 patients from group I, 6 patients developed minor side effects like bradycardia 2(6.66%), hypotension 2(6.66%), nausea vomiting 1(3.33%), sedation 1(3.33%) whereas ingroup II 8(26.64%) patients developed minor side effects like bradycardia 3(9.99%), hypotension 2(6.66%), nausea vomiting 2(6.66%), sedation 1(3.33%). None of the patients developed respiratory depression.

Table 4: Cross tabulation of safety profile between group I and group II

Side Effect	Group I	Group II	P value
Bradycardia	2(6.66%)	3(9.99%)	0.64 NS
Hypotenssion	2(6.66%)	2(6.66%)	1.00 NS
Nausea & Vomiting	1(3.33%)	2(6.66%)	0.55 NS
Sedation	1(3.33%)	1(3.33%)	1.00 NS
Respiratory Depression	0	0	-

Chi square test not significant at $p<0.05$.

Discussion

This study evaluated the efficacy of nalbuphine pre-treatment in preventing myoclonus induced by etomidate. Both the study groups were comparable demographically and these variables had no role in clinical implications of this study.

In clinical practice etomidate is widely used as induction agent for general anaesthesia. Several desirable properties, such as rapid onset, short duration of action, cardio stability and protection of intracranial pressure, makes it an attractive agent for rapid sequence intubation [12, 13, 14, 15].
However, its use is associated with etomidate induced vascular pain and myoclonus, jeopardizing its therapeutic use [4]. Vascular pain has been abolished by the new fat emulsion preparation of etomidate, but the new solvent has not reduced the incidence of myoclonus [19].
In un-premedicated patients the incidence of myoclonus has been found to be as high as 55%, 77% and 84% depending on the observation period (1, 2, and 3 min, respectively) [20].
Previous studies have showed opioids and sedatives to cause subcortical inhibition of brain stemwhich results indecreased incidence of myoclonic movements caused by etomidate [16]. Although pre-treatment with pure agonists like fentanyl and remifentanil effectively reduces Etomidate induced myoclonus, their use is associated with higher incidence of apnea, nausea, vomiting, and bradycardia compared to the placebo [17]. Although a lower dose of butorphanol (0.015 mg/kg) and high doses of fentanyl (500 µg) have proved effective in limiting the myoclonic movements caused by etomidate but they are either they fail to provide adequate analgesia or are partially effective in preventing etomidate induced myoclonus or associated with higher incidence of apnea [18].
Agonist modulation of kappa opioid receptors has been shown to limit seizure activity [11]. Nalbuphine is an opioid belonging to the agonist-antagonist group and is recommended for the management of moderate to severe pain. Intraoperative analgesia, ceiling effect to respiratory depression, low abuse potential, being free from 'controlled substances act' unlike fentanyl are a few of the many advantages of nalbuphine which makes it an ideal substitute to pure opioid agonists.
Therefore keeping the above background in mind we decided to evaluate the efficacy of nalbuphine pretreatment to prevent etomidate induced myoclonus and the doses were decided considering previous studies and the safety profile of all three drugs.
The study dose of nalbuphine was chosen to be 0.2mg/kg as its equipotent dose in providing analgesia for butorphanol (2 mg) and fentanyl (100 µg) have proved to be effective in reducing the incidence as well as severity of myoclonic movements induced by etomidate [5]. The pretreatment in our study was administered 150 s before etomidate to justify its time of onset of action of nalbuphine. Our study results indicate that intensity and severity of myoclonus was lower in patients who received 0.2 mg/kg nalbuphine intravenously 150 seconds before etomidate induction compared to the placebo group whereas the incidence of side effects were similar in both groups.

Conclusion

Based upon analysis of the data from our study we conclude that 0.2mg/kg intravenous nalbuphine pretreatment prior to induction with 0.3mg/kg etomidate significantly reduces the incidence as well as severity of myoclonus induced by etomidate without any significant increase in side effects.

References

1. Salahuddin N, Fatimi S, Huda S, Islam M. Predicting a postop cardiopulmonary complications by a test of stair climbing. J coll physicians Surg Pak. 2005;15:761-764.
2. Memtsoudis SG, Heerdt PM. Autonomic mechanism in the age-related hypotensive effect of propofol. Anesth Analg. 2005;100(1):111-5.
3. Barash PG, Cullen BF, Stoelting RK. Clinical Anesthesia, 5th Ed; Philadelphia; Lippincott Williams & Wilkins; c2006. p. 344-345.
4. Bergen JM, Smith DC. A review of etomidate for rapid sequence intubation in the emergency department. J Emerg Med. 1998;15(2):221-230. Doi: 10.1016/S0736-4679(96)00350-2. PMID 9144065.
5. Zhao X, Bao R, Zhu J, Liu Z, Meng Y, Fan X, *et al*. Pre-treatment with butorphanol reduces myoclonus after etomidate. J Anesthesiol Clin Sci. 2013;2:2.
6. Voss LJ, Sleigh JW, Barnard JP, Kirsch HE. The howling cortex: Seizures and general anesthetic drugs. Anesth Analg. 2008;107:1689-703.
7. Van Keulen SG, Burton JH. Myoclonus associated with etomidate for ED procedural sedation and analgesia. Am J Emerg Med. 2003;21:556-8.
8. Hüter L, Schreiber T, Gugel M, Schwarzkopf K. Low-dose intravenous midazolam reduces etomidate-induced myoclonus: A prospective, randomized study in patients undergoing elective cardio version. Anesth Analg. 2007;105:1298-302.
9. Hwang JY, Kim JH, Oh AY, Do SH, Jeon YT, Han SH. A comparison of midazolam with remifentanil for the prevention of myoclonic movements following etomidate injection. J Int Med Res. 2008;36:17-22. Doi: 10.1177/147323000803600103.
10. Choi JM, Choi IC, Jeong YB, Kim TH, Hahm KD. Pre-treatment of rocuronium reduces the frequency and severity of etomidate-induced myoclonus. J Clin Anesth. 2008;20:601-604. Doi: 1016/j.jclinane.2008.06.010.
11. Loacker S, Sayyah M, Wittmann W, Herzog H, Schwarzer C. Endogenous dynorphin in epileptogenesis and epilepsy: Anticonvulsant net effect via kappa opioid receptors. Brain.

2007;130(Pt 4):1017-28.
12. Morgan M, Lumley J, Whitwam JG. Etomidate, a new water soluble non-barbiturate intravenous induction agent. Lancet. 1975;1:955-956. Doi: 10.1016/S0140-6736(75)92011-5.
13. Kay B. A dose-response relationship for etomidate, with some observations on cumulation. Br J Anaesth. 1976;48:213-216. Doi: 10.1093/bja/48.3.213.
14. Harris CE, Murray AM, Anderson JM, Grounds RM, Morgan M. Effects of thiopentone, etomidate and propofol on the haemodynamic response to tracheal intubation. Anaesthesia. 1988;43:32-36. Doi: 10.1111/j.1365-2044.1988. tb09065.x.
15. Moss E, Powell D, Gibson RM, McDowall DG. Effect of etomidate on intracranial pressure and cerebral perfusion pressure. Br J Anaesth. 1979;51:347-352. Doi: 10.1093/bja/ 51.4.347.
16. Doenicke A, Roizen MF, Nebauer AE, Kugler A, Hoernecke R, Beger Hintzen H. A comparison of two formulations for etomidate, 2 hydroxypropyl beta cyclodextrin (HPCD) and propylene glycol. Anesth Analg. 1994;79:933-9.
17. Chawda PM, Pareek MK, Mehta KD. Effect of nalbuphine on haemodynamic response to orotracheal intubation. J Anaesthesiol Clin Pharmacol. 2010;26:458-60.
18. He L, Ding Y, Chen H, Qian Y, Li Z. Butorphanol pre-treatment prevents myoclonus induced by etomidate: A randomised, double-blind, controlled clinical trial. Swiss Med Wkly. 2014;144:w14-042.
19. Erdoes G, Basciani RM, Eberle B. Etomidate-A review of robust evidence for its use in various clinical scenarios. Acta Anaesthesiol Scand. 2014;58:380-9.
20. Do SH, Han SH, Park SH, Kim JH, Hwang JY, Son IL, *et al*. The effect of injection rate on etomidate-induced myoclonus. Korean J Anesthesiol. 2008;55:305-7.