e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(4); 1137-1143

Original Research Article

Comparison between Fentanyl and Nalbuphine Pretreatment in Prevention of Etomidate Induced Myoclonus

Irfan Ahmad Siddiqui[1], Renu Dhamnani[1], Jaya Sinha[1], Prayank Mandloi[2]

[1]Senior Resident Department of Anesthesia, SSB Shyam Shah Medical College, Rewa, Madhya Pradesh

[2] Senior Registrar in Apollo Hospital, Jubilee Hills, Hyderabad, Telangana

Received: 13-02-2023 / Revised: 18-03-2023 / Accepted: 15-04-2023

Corresponding author: Irfan Ahmad Siddiqui

Conflict of interest: Nil

Abstract

Background: Etomidate is a cardio stable intra vascular induction agent associated with myoclonus, a frequent and dangerous side effect of etomidate induction, and many opioids have been studied for effectively attenuating etomidate induced myoclonus. But there is no evident literature comparing the efficacy of nalbuphine and fentanyl pretreatment on Etomidate induced myoclonus, this study was engineered to compare efficacy of 0.2mg/kg nalbuphine and 2mcg/kg fentanyl intravenous pretreatment for myoclonus prevention caused by Etomidate.

Aims: Aim of this study is to compare the efficacy fentanyl with nalbuphine in prevention of etomidate induced myoclonus.

Material and Methods: This prospective randomized double blind placebo controlled study was conducted in a tertiary hospital associated with a medical college, 60 patients undergoing elective surgeries under general anaesthesia were randomly allocated to one of the two groups 2mcg/kg of fentanyl in 10ml of normal saline(group I) or 0.2mg/kg of nalbuphine in 10ml of normal saline(group II) 150 seconds before injecting iv Etomidate 0.3mg/kg administered over 20 seconds, patients were assessed for severity of myoclonus associated with etomidate induction over next two minutes. Students t test, chi-square test were used as per the requirement and a P value of <0.05 was considered statistically significant.

Result: Out of 60 patients 30 were pretreated with fentanyl and 30 were pretreated with nalbuphine prior to etomidate induction. In our study 14(46.62%) patients from fentanyl group developed myoclonus whereas only 6(20%) patients from nalbuphine group developed myoclonus, 4(13.32%) patients from fentanyl group had pain on injection whereas only 2(6.66%) patients from nalbuphine group had pain on injection, 6(19.98%) patients from fentanyl group developed minor side effects like bradycardia 2(6.66%), hypotension 2(6.66%), nausea vomiting 1(3.33%), sedation 1(3.33%) whereas in nalbuphine group 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%).

Conclusion: Both groups were comparable with respect to demographic characteristics, the incidence(46.62% in group I vs. 20% in group II) and severity(0.4 in group I vs 0.8 in group II), of myoclonus was significantly reduced in nalbuphine pretreatment group compared to fentanyl group, whereas the safety profile of both the groups was comparable with no significant side effects; (95% confidence interval, $P < 0.05$).

Keywords: Etomidate, Myoclonus, Prevention, Opioid, Fentanyl, Nalbuphine.

Introduction

Propofol (2,6-diisopropylphenol) is a potent intravenous hypnotic drug that was developed by Imperial Chemical Industries Limited (London, UK), patented by John (Iain) Glen and Roger James in 1977 [1]. It has a favourable pharmacokinetic (PK) and pharmacodynamic profile, which has resulted in it becoming the most commonly used intravenous anaesthetic for the past three decades. [2]

The adverse effects of propofol are well-documented, with the most common being pain on injection. Other adverse effects are cardiovascular (bradycardia, hypotension) and metabolic (hyperlipidaemia secondary to infusion of lipid formulation). [3]

Etomidate was developed at Janssen Pharmaceuticals in 1964 and was introduced as an intravenous agent in 1972 in Europe and in 1983 in the United States. [4]. Etomidate is an imidazole-derived sedative hypnotic agent directly acting on gamma amino butyric acid(GABA) receptor complex, blocking neuroexcitation and producing anesthesia. It has a stable hemodynamic profile and minimal effects on respiratory system as compared to other induction agents. Pain on injection and myoclonus are the most common side effects of this drug [5]. It has been virtually abolished by the new fat emulsion preparation of etomidate, but the new solvent has not reduced the incidence of myoclonus. [4]

The etomidate induced myoclonus seen in up to 80% of un-premedicated patients is hazardous in patients with open globe injuries, nonfasted patients, and patients with cardiac compromise. [6,14] EM may also lead to the loss of intravenous (IV) access, displacement of the electrocardiogram electrodes, and postoperative patient discomfort. [7] It can lead to muscle fiber damage, myalgia, and elevated serum potassium. These adverse effects can lead to regurgitation and aspiration in nonfasting emergency patients[8] and myocardial oxygen consumption can increase due to these muscle contractions which are deleterious in cases of the limited cardiovascular reserve. These potentially hazardous sequelae warrant devising effective strategies to prevent or limit myoclonus. The aetiology of Myoclonus is unclear. It may represent a seizure-like activity. [6]

Several mechanisms have been postulated to explain myoclonus. It was reported that myoclonus resulted from temporal subcortical disinhibition, another reason could be that the inhibitory circuits are depressed earlier than the excitatory neuronal circuits after etomidate administration. [9].

Studies have been done which showed that opioids and sedatives are helpful in decreasing the incidence of etomidate-induced myoclonus by subcortical inhibition. [5]

Agonist modulation of kappa opioid receptors has been shown to limit seizure activity. [10]. With this background, we planned this study and chose to compare nalbuphine and fentanyl as a pretreatment option in the prevention of myoclonus.. However, other agonist-antagonist butorphanol [05,11] has been compared with fentanyl [5] in preventing etomidate-induced myoclonus, so we made an effort in the present study to evaluate the potency of nalbuphine versus fentanyl in terms of prevention of etomidate-induced myoclonus which is the primary outcome of this study and assessment of incidence and severity of pain on injection is the secondary objective of this study.

Material and Methods

After obtaining Institutional Ethical Committee approval from and written informed consent from the patients, a prospective randomized clinical study was

conducted at tertiary health care hospital associated with Index Medical College .60 consenting patients of American society of anaesthesiology (ASA) class I and II between the age group of 20-60 years planned for surgeries requiring general anesthesia were selected and included in the study. These patients were divided into 2 groups consisting of 30 patients each which were randomly divided.

Inclusion criteria: Consenting patients, ASA class I and class II patients, patients aged between 20-60 years, patients undergoing 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 or unanticipated difficult airway, cardiac disease, pregnant or lactating females, significant hepatic or renal insufficiency and those who received sedatives, analgesics or opioids in the 24 h preoperatively were excluded from the study.

- Group I (n=30) received 2mcg/kg fentanyl in 10ml normal saline.
- Group II (n=30) received 0.2mg/kg nalbuphine in 10 ml normal saline.

On arrival in the operation theatre all routine monitoring devices were attached. A 18G i/v canula was inserted at dorsum of hand and connected to a 500ml Ringer Lactate drip and and baseline readings of mean arterial blood pressure (MAP), heart rate (HR), peripheral oxygen saturation (SPO2) were recorded. Patients were pre-oxygenated with 100% oxygen by facemask for 3-5 minutes. In group I 150 seconds after the pretreatment with 2mcg/kg fentanyl in 10ml normal saline and In group II 150 seconds after the pretreatment with 0.2mg/kg nalbuphine in 10ml normal saline, 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 pain on injection and myoclonus, after the two-minutes 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 EtCO2 was also recorded by connecting ETCO2 sensor to the endo tracheal tube. Maintenance dose of vecuronium bromide was given after appearance of curare notch in EtCO2 monitor. The anesthesia was maintained with oxygen: nitrous oxide mixture in the ratio of 1:2, isoflurane in the concentration of 1 % and vecuronium bromide @ 0.01 mg/kg body weight every 20-45 minutes. Patient was reversed with glycopyrrolate @ 0.01 mg/kg and neostigmine @ 0.05 mg/kg body weight and was extubated and shifted to post anesthesia care unit after following verbal commands and neck holding for 5 seconds was present.

The primary outcome of our study was to compare the incidence and severity of etomidate induced myoclonus and the secondary outcomes was to compare the incidence and the severity of etomidate induced pain on injection after fentanyl pretreatment versus nalbuphine pretreatment & comparison of incidence of side effects between both the groups.

All the patients were treated with 1gram iv paracetamol for the management of postoperative pain as needed.

Result

Age distribution:

Out of 60 patients, 30 patients in group I were pretreated with fentanyl and 30 patients in group II were pretreated with nalbuphine prior to etomidate induction under general anaesthesia. The mean age in Group I was 39.80 ± 10.68 years and in Group II it was 42.1 ± 9.63 years.

Table 1: Cross tabulation of age distributions between group I and II

Group	Number	Mean Age (in years) ± SD	P value
Group I (F)	30	39.8±10.6	0.384 NS
Group II (N)	30	42.1±9.63	

Chi square test not significant at P<0.05

Incidence and severity of myoclonus:

Out of 30 patients in group I, 8(26.66%) patients showed myoclonus in the 1st minute whereas 6(20%) 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 16(53.33) grade I in 7(23.33%) patients, grade II in 4(13.33%) patients and grade III in 3(10%) 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	08(26.66%)	03(10.00%)	0.0284
2 minute	06(20.00%)	03(10.00%)	

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	0.47	0.2
2 minute	0.33	0.2

Pain on induction: Out of 30 patients in group I, 2(6.66%) patients suffered from grade I pain and 2(6.66%) patients from grade II pain whereas in group II, 1(3.33%) patient suffered from grade 1 pain and 1(3.33%) patient from grade 2 pain on induction. None of the patients suffered from grade III pain on induction.

Table 4: Cross tabulation of incidence and severity of pain on induction between group I and II

Severity of pain on induction	Group I	Group II	P value
Grade I	02	01	0.389 NS
Grade II	02	01	
Grade III	00	00	

Chi square test not significant at P<0.05

Safety profile:

Out of 30 patients from group I, 6(19.98%) patients developed minor side effects like bradycardia 2(6.66%), hypotension 2(6.66%), nausea vomiting 1(3.33%), sedation 1(3.33%) whereas in group 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 5: Cross tabulation of safety profile between group I and group II.

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

Chi square test not significant at P<0.05

Discussion

This study evaluated the efficacy of fentanyl pretreatment compared to nalbuphine pretreatment 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.

The hemodynamic stability associated with etomidate makes it the induction agent of choice in patients with compromised hemodynamic or cardiac reserves. [11] However, its use is associated with etomidate induced vascular pain and myoclonus jeopardizing its therapeutic use. [4] Seema Meena Et al 2018 established that etomidate (2mg/kg) is superior in term of hemodynamic stability compared to propofol (2mg/kg) for induction of anaesthesia for dilatation and curettage. [13]

Studies have been done which showed that opioids and sedatives are helpful in decreasing the incidence of etomidate-induced myoclonus by subcortical inhibition. [5]

Although pretreatment with pure agonists like fentanyl and remifentanil effectively reduces Etomidate induced, their use is associated with higher incidence of apnea, nausea, vomiting, and bradycardia compared to the placebo.[18].A dose-response decrease in the incidence of EM has been established with increasing doses of fentanyl and dexmedetomidine by previous authors. [15]

Namrata Natraj et al 2018-established that nalbuphine (0.3mg/kg) can be used to attenuate pressure response of laryngoscopy and tracheal intubation. Similarly can be used as sole anesthetic agent that gives intraoperative and perioperative analgesia without side effects. [16]

Stockham RJ et al 1988-established that increasing pre-induction doses of fentanyl are more effective at preventing increases in systolic arterial blood pressure and heart rate due to etomidate induction. [15] The results suggest that 500 micrograms of fentanyl is an ideal pretreatment dose in fit patients prior to anaesthetic induction with etomidate. Although a lower dose of butorphanol (0.015 mg/kg) and higher doses of fentanyl (up to 500 µg) have been found to be effective in reducing etomidate induced myoclonus, they are either sub-analgesic doses, partially effective for etomidate induced myoclonus or associated with higher incidence of apnea respectively. [17]

Therefore we decided to compare the efficacy of fentanyl pretreatment with nalbuphine pretreatment to prevent etomidate induced myoclonus and pain on injection and the doses were decided considering previous studies and the safety profile of all three drugs.

The pretreatment in our study was administered 150 s before etomidate to justify its time to onset of action of 2–3 min. [20] Our study results indicate that 0.2 mg/kg nalbuphine pretreatment 150 s before etomidate effectively reduces the intensity and severity of etomidate induced myoclonus compared to 2mcg/kg fentanyl. We chose 0.2 mg/kg as the study dose of nalbuphine as its equianalgesic dose of butorphanol (2 mg) and fentanyl (100 µg) have been shown to effectively reduce the incidence as well as severity of Etomidate induced myoclonus. [4,12]

The incidence of myoclonus 20% found in the nalbuphine group lies in between that reported with butorphanol 2 mg (4%) and fentanyl 100 µg (24%). The varying affinity and intrinsic activity on κ-opioid receptors might be responsible for this observed variation in the inhibitory effect of equianalgesic doses of different opioids on the Etomidate induced myoclonus. [4,12]

Whereas incidence of myoclonus in fentanyl group was found to be 46.66%

which lies between the incidence of myoclonus observed in nalbuphine group 20% versus. In unpremeditated patients has been found to be 55%, 77%, and 84% depending on the observation period (1, 2, and 3 min, respectively). [19]

Pain on injection and myoclonus are the most common side effects of this drug [5]. It has been abolished by the new fat emulsion preparation of etomidate, but the new solvent has not reduced the incidence of myoclonus. [11] which was confirmed by this study only 13.32% patients in fentanyl group suffered from etomidate induced pain on injection whereas 6.66% patients in nalbuphine group complained of etomidate induced injection pain which was statistically not significant. [20]

The safety profile of both the drugs was observed to be statistically comparable at the doses chosen for this study.

Conclusion

Based upon analysis of the data from our study we conclude that pretreatment with 0.2mg/kg nalbuphine prior to induction with 0.3mg/kg etomidate was found to be more effective in decreases the incidence and severity of myoclonus compared to pretreatment with 2mcg/kg fentanyl prior to induction with 0.3mg/kg etomidate without any significant increase in side effects whereas the incidence and severity of Etomidate induced vascular pain was found to be comparable in both the groups.

References

1. Glen JB, James R. 2,6-Diisopropylphenol as an anaesthetic agent. London: United States Patent and Trademark office; 1977; 1-10.
2. Fulton B, Sorkin EM. Propofol. An overview of its pharmacology and a review of its clinical efficacy in intensive care sedation. Drugs. 1995; 50:636–657.
3. Marik PE. Propofol: therapeutic indications and side-effects. Curr Pharm Des. 2004; 10:3639–3649.
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.
5. 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.
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. Luan HF, Zhao ZB, Feng JY, Cui JZ, Zhang XB, Zhu P, et al. Prevention of etomidate-induced myoclonus during anesthetic induction by pretreatment with dexmedetomidine. Braz J Med Biol Res. 2015; 48:186–90.
9. Hüter L, Schreiber T, Gugel M, Schwarzkopf K. Low-dose intravenous midazolam reduces etomidate-induced myoclonus: A prospective, randomized study in patients undergoing elective cardioversion. Anesth Analg. 2007; 105:1298–302.
10. 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.
11. 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. [PubMed] [Google Scholar]
12. Zhao X, Bao R, Zhu J, Liu Z, Meng Y, Fan X, et al. Pretreatment with butorphanol reduces myoclonus after etomidate. J Anesthesiol Clin Sci. 2013; 2:2.
13. Seema Meena et al. Evaluation of safety and efficacy with propofol and

etomidate for induction of Anaesthesia in dilatation and curettage. Indian Journal of Clinical Anaesthesia.
14. Berry JM, Merin RG. Etomidate myoclonus and the open globe. Anesth Analg 1989;69:256‑9.
15. Stockham RJ, Stanley TH, Pace NL, Gillmor S, Groen F, Hilkens P. Fentanyl pretreatment modifies anaesthetic induction with etomidate. Anaesth Intensive Care 1988;16:171‑6.
16. Namrata Natraj and Seema Shripad. Efficacy of Preoperative Nalbuphine Hydrochloride and Pentazocine Lactate on Hemodynamic Response to Tracheal Intubation and Postoperative Analgesia.2018.
17. 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:w14042
18. Chawda PM, Pareek MK, Mehta KD. Effect of nalbuphine on haemodynamic response to orotracheal intubation. J Anaesthesiol Clin Pharmacol 2010; 26: 458‑60
19. 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.
20. Chakdoufi S., & Guerboub P. A. Kyste De La Neurohypophyse: À Propos D'un Cas. Journal of Medical Research and Health Sciences, 2023; 6(3): 2484–2489.