Comparison of Butorphanol with Fentanyl for reducing Etomidate-induced myoclonus: A Prospective, Randomised Clinical Trial

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Abstract

Background and Aims: Etomidate is frequently used nowadays as an inducing agent in patients with compromised cardiovascular function, but it leads to undesirable side effect like myoclonus and pain on injection during induction in unpre-medicated patients. Several drugs are considered alone and in combination, before induction to reduce the incidence of myoclonus. This prospective, randomized study was aimed to compare butorphanol and fentanyl administered before the induction of etomidate to reduce the myoclonic movements.

Material and Methods: Sixty patients of ASA I-II, aged 18-50 years undergoing surgeries in general anaesthesia were divided into two groups and pretreated either with intravenous butorphanol 0.02mg/kg and iv midazolam 1mg(Group BM) or intravenous fentanyl 1mcg/kg and iv midzolam(Group FM) followed by induction with etomidate until loss of eyelash reflex. Incidence and severity of myoclonus, pain on injection, apnoea and postoperative nausea and vomiting were noted. Induction dose of etomidate and induction time were observed and compared between the two groups.

Results: Study results showed the incidence of myoclonus of grade 1 were 6.7% and 10% in group BM and group FM respectively*(p=1.000)*. The mean dose of etomidate for induction and induction time were found to be 10.00±1.5mg and 32±4.50 seconds in group BM as compared to 12.00±1.8mg and 40±5.00seconds respectively in group FM.*(p<0.001)*

Conclusion: The incidence and severity of etomidate induced myoclonus is reduced by combination of midazolam with butorphanol or fentanyl if administered before induction. Also the dose of etomidate for induction is decreased by butorphanol in combination with midazolam.

Keywords: Etomidate, Myoclonus, Butorphanol, Fentanyl, Midazolam.

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Introduction

Propofol and etomidate are well known intravenous anaesthetic agents used for induction of anaesthesia with similar onset and duration of action. Propofol provides rapid recovery but adverse effects like hypotension due to vasodilatation are detrimental in patients suffering from coronary artery disease and compromised ventricular function. Etomidate is currently advocated as an induction agent in such haemodynamic unstable conditions. Various studies have been proved stating that Etomidate preserves haemodynamics during induction of anaesthesia as compared to propofol.[1]

The most common side effects of etomidate are myoclonus and pain on injection apart from post-operative nausea and vomiting(PONV).[2] The incidence of myoclonic jerks during etomidate induction are high as 70% in unpremedicated patients. This is a serious problem in patient either with open globe injury or emergency non fasting conditions which may lead to risk of regurgitation and aspiration. Induction with new fat emulsion of etomidate, Lipuro B Braun, Melsungen, Germany has shown to abolish pain on injection but the new solvent has not reduced the incidence of myoclonus after administering etomidate. Studies have been done in which various drugs are pre-medicated to reduce myoclonic jerks like midazolam, opioids, magnesium sulphate, dexmedetomidine, lignocaine or combination of agents. These drugs if used in high doses led to respiratory depression as well as prolonged recovery from anaesthesia[3]. So combination should be such to maintain balanced anaesthesia without causing any haemodynamic compromise.

In this study, pretreatment with fentanyl or butorphanol along with iv midazolam was given before induction with etomidate to reduce myoclonic movements. Butorphanol is a synthetic and strong analgesic with both narcotic agonist and antagonist properties. It is often used as an analgesic. Fentanyl is an opioid with agonist property frequently used in premedication.

This study was aimed primarily to compare fentanyl and butorphanol to decrease the incidence of myoclonus during etomidate induction. The secondary

aim of this study was to compare the total dose of etomidate needed for induction and induction time between the two groups. Other side effects like pain on injection, apnoea and post-operative nausea vomiting were also compared.

Materials and Methods

After approval by the ethics committee and written informed consent of each patient, a prospective, randomized clinical trial was carried out in sixty adult patients aged 18-50years, ASA I-II, scheduled for various elective surgical operations under general anaesthesia. Exclusion criteria included patients having allergy to the study drugs, history of seizure disorder, presence of primary or secondary steroid deficiency, patients on steroid therapy, patients with history of neuropsychological or neuromuscular disease, morbid obesity, pregnant patients and patients who had received sedatives and opioids within 24 hours of surgery.

On arrival at the operating room, all patients were pre-medicated with glycopyrrolate 5mcg/kg and Ondensetron 0.1mg/kg intravenously. Simultaneously, all patients were pre-oxygenation with 100% Oxygen for 3 minutes. Then the patients were randomly allocated into two groups, 30 in each group with the help of computer generated table of random numbers as below;

Group BM: Patients received iv. Butorphanol 0.02 mg/kg and iv midazolam 1 mg

Group FM: Patients received iv. Fentanyl 1 mcg/kg and iv midazolam 1mg.

After 2 minutes of administering study drug, induction was done in all patients with etomidate intravenously slowly, till the loss of eyelash reflex and this was the end point for further administration of etomidate. During the induction period, all patients were observed for pain on injection, apnoea, total dose required for induction as well as induction time. Visually presence of myoclonus as well as severity of myoclonus which was graded till 2 minutes after the end of etomidate induction were also noted. Myoclonus was defined as involuntary, short contraction of some muscle fibres, of a whole muscle, or of different muscles of one group, leading to short observable movements of the corresponding body parts. Severity of myoclonic movements were graded as (0- No myoclonic movement; 1- Mild (only mild fasciculation's involving the face and/or distal upper and/or extremities); 2- Moderate(marked movements of face and/or limbs); 3- Severe(involving limbs and trunk).

Pain on injection was graded as(0-no pain; 1-verbal complaint of pain; 2-withdrawal of arm; 3-both verbal complaint and withdrawal of arm).

Trachea was intubated in all patients by giving suxamethonium 1.5 mg/kg, which was administered after two minutes of etomidate induction. During this period, patients were supported by manual bag mask ventilation. Anaesthesia was maintained with sevoflurane in oxygen and intravenous atracurium as a muscle relaxant throughout the procedure.

All patients were monitored for Heart Rate(HR), Systolic and Diastolic blood pressure, Mean arterial blood pressure(MAP), SpO2 throughout the procedure. At the end of surgery, neuromuscular blockade was reversed and all patients were observed for postoperative nausea and vomiting.

Statistical Analysis

Sample size calculation was based on population with SD of 1.1 and 80% power with 95% confidence level and 5% alpha error. The data were analysed using SPSS version 19.0 Continuous variables were presented as Mean±SD and compared using independent t-test. Categorical data were presented as number and percentage, compared by chi-square test and analysis of variance. p value of <0.05 was considered statistically significant.

Results

There were no differences between the two groups with respect to demographic data($p>0.05$, Table 1). The Heart rate, Systolic and Diastolic blood pressure, Mean Arterial pressure were comparable in both the groups and no statistically difference were found throughout the surgery.

Out of 30 patients in each group, myoclonus of grade 1 was observed in 3(10%) patients in group FM as compared to 2 (6.7%) patients in group BM. No significant differences were found between the two groups regarding incidence and severity of myoclonus ($p>0.05$). The severity of myoclonus of grade more than 1 were not observed in any patients in both the groups(Table 2).

Bradycardia was reported in only one patient who received Fentanyl .Pain on injection, apnoea, PONV were not observed in both the groups.

The mean dose of etomidate for induction in group BM was 10.00±1.5 mg as compared to 12.00±1.8mg in group FM ($p<0.001$). The mean induction time was 32±4.5 sec and 40±5.00sec.ingroup BM and group FM respectively($p<0.001$).(Table 3).

The mean dose of fentanyl required was 58.30±12.20 mcg while but orphanol was 1.11±0.22mg.

All patients have smooth recovery and none of the patient had postoperative drowsiness and sedation.

Table 1: Showing Demographic data

	Group BM	Group FM	P Value
Age(yrs)	42±1.5	40±1.4	0.595
Sex(M:F)n=30	16:14	12:18	0.438
ASA Grade I/II	26/4	25/5	1.000
Weight(kgs)	55.6±11.2	58.3±12.2	0.376

Table 2: Showing incidence and severity of myoclonus n= number of patients

	Group BM n=30	Group FM n=30	P Value
Incidence of myoclonus	2(6.7%)	3(10%)	>0.05
Severity of myoclonus			
Grade 0	28	27	>0.05
Grade 1	2	3	-
Grade 2	0	0	-
Grade 3	0	0	

Table 3: Induction dose and induction time in both the groups

	Group BM	Group FM	P Value
Dose of Etomidate(mg)	10.00±1.50	12.00±1.80	<0.001
Induction time(sec.)	32±4.5	40±5.0	<0.001

Discussion

Etomidate is a short acting intravenous anaesthetic agent used for induction of general anaesthesia. It can evoke myoclonus movements as a side effect in unpre-medicated patients during induction. Although myoclonus does not impart any deleterious effect on patients as it is usually seen when the patient is already in a hypnotic state, it may interfere with the clinical evaluation of the depth of anaesthesia so the patient are administered additional doses of inducing agent to combat the movements thus prolonging the recovery or impairing haemodynamic stability. Myoclonic activity is investigated to be similar to restless leg syndrome during normal human sleep and is not related to any epileptic activity. The precise mechanism of etomidate-induced myoclonus is not clear and molecular theory is still ambiguous. Etomidate suppress the central reticular activating system and inhibits $GABA_A$ receptors thus sensitizing the skeletal muscle control pathways and allowing spontaneous nerve transmissions and myoclonus[2,4]. Based on this speculation, benzodiazepins are administered before etomidate to suppress myoclonus. Midazolam has been administered as low dose of 0.015mg/kg to 0.5mg/kg to suppress the myoclonus in various studies[5,6,7]. Varying effects of midazolam have been seen due to different dose regimes as well as route of administration and low doses have not much impressing results. On the other side, higher dose regimes of midazolam had led to respiratory depression and sedation.

Although opioids were administered in various studies prior to etomidate induction to reduce myoclonus, their mechanism of action is still unclear. Stochamet al[8] reported that fentanyl although decreased the incidence of myoclonus in the dose dependant manner, it increases the risk of apnoea. Remifentanil was reported to reduce the myoclonus but use was limited by its side effects like chest rigidity and bradycardia[9,10]. Sufentanil as a pretherapeutic agent might reduce (28%) the incidence of myoclonus[11].

In our study, clinical trial was carried out by pretreatment with fentanyl or butorphanol to intravenous administered 1mg midazolam. The incidence as well as severity of myoclonus were reduced to 6.7% when butorphanol was combined with midazolam as compared to 10% in reducing myoclonus during etomidate induction are limited, on the other hand various studies have been done with fentanyl. The incidence of myoclonus is reduced by one half when pretreated with 100mcg fentanyl, but incidence of apnoea is increased[8]. The requirement of mean dose of fentanyl in our study was 58.3±12.20 mcg. So it was less than 100 mcg and no patient was found to develop apnoea. Our results are consistent with the study in which butorphanol was administered in the dose of 2 mg and incidence of myoclonus to be 4%(2 out of 50 patients) following induction with etomidate[12]. In our study, we found only 2 out of 30 patients (6.7%) had shown mild form of myoclonus, but the dose requirement of butorphanol was less. The mean dose of

butorphanol in our study was found to be 1.11± 0.22mg.

In our study we have administered midazolam in the dose of 1mg intravenously in both the groups. It has been found that increasing dose of midazolam to 0.05mg/kg did not further decrease the incidence of myoclonus[5,9]. Combination of fentanyl or butorphanol to midazolam display a synergic effect to inhibit the central nervous system, although their actions are mediated by different receptors. Butorphanol have role on opioid, NMDA channels, GABA-A receptors in the anti-maximal electroshock test(MES)[13]. This action may be responsible to reduce the incidence of myoclonus after etomidate administration.

The incidence of Myoclonus also depends on speed of injection and the dosage administered during induction of etomidate[14,15]. Doenicke et al[14] stated that increased dosage of etomidate were associated with increase in frequency of myoclonus. In our study the mean dose of etomidate was 10.00±1.5mg in group BM as compared to 12.00±1.8mg in Group FM. So the dose requirement was reduced to less than 0.3mg/kg which is considered to be ideal and routinely used dose for induction. Reduction in dose might be due to synergistic action of pretreatment by midazolam and fentanyl or butorphanol. However the dose requirement of etomidate is lesser with butorphanol as compared with fentanyl as butorphanol also have sedative action, so synergistic action between midazolam and butorphanol have played a role in decreasing the etomidate dose as well as induction time. Do et al[15] investigated the effect of speed of injection at 0.3mg/kg etomidate on frequency of myoclonus to be 84% if administered over a period of 10 sec, and 28% if given slowly over a period of 2 minutes. In our study we found the incidence of myoclonus in mean induction time of 32±4.5 sec and 40±5.00sec in group BM and group FM respectively. Other side effects like apnoea, pain on injection, post-operative nausea vomiting were not found in both the groups as the dose of etomidate was not given in higher doses to cause any other side effects. One Patient developed bradycardia, it was in the fentanyl group.

Although butorphanol has sedative property, the recovery was smooth in all the patients and postoperative sedation or drowsiness was not seen in any of the patients as the dose of butorphanol, fentanyl and midazolam were adequate enough to maintain balanced anaesthesia without delay in recovery.

To conclude, pretreatment of butorphanol and fentanyl in combination with intravenous midazolam can reduce the incidence as well as severity of etomidate-induced myoclonus movements. The dose of etomidate required for induction is also reduced ifbutorphanol combined with midazolam is pretreated before induction.

References

1. Singh R, Choudhary M, Malhotra K, Kiran U. A Randomized trial of anaesthetic induction agents in patients with coronary artery disease and left ventricular dysfunction. Annals of Cardiac Anaesthesia2010;13(3):217-223.
2. Giese JL, Stockham RJ, Stanley TH, Pace NL, Nelissen RH. Etomidate versus thiopental for induction of anaesthesia. Anesth Analg 1985;64:871-876.
3. Khteishat B, Salaytah W, Qatawneh T, Alsagheer M. The effect of pre-induction with midazolam, fentanyl and ketamine on etomidate induced myoclonic muscle movements. J Res Med Sci 2011;18:38-41.
4. St Pierre M, Dunkel M, Rutherfold A, Hering W. Does etomidate increase postoperative nausea? A double blind controlled comparison of etomidate in lipid emulsion with propofol for balanced anaesthesia. Eur J Anaesthesiol 2000;17:634-641.
5. Schwarzkopf KR, Hueter L, Simon M, Fritz HG. Midazolam pretreatment reduces etomidate induced myoclonic movements. Anaesth Intensive Care2003;31:18-20.
6. Huter L, Schreiber T, Gugel M, Schwarzkopf K. Low dose intravenous midazolam reduces etomidate induced myoclonus: Aprospective, randomized study in patients undergoing elective cardioversion. Anaesth Analg 2007;105:1298-1302.
7. Iike I, Sinan U, Mehmet T, Ayse V, Yasar G, Ferda YL, Ibrahim A. Prevention of etomidate-induced myoclonus: Which is superior: Fentanyl, midazolam, or a combination? a retrospective comparative study. Med Sci Monit 2014;20:262-267.
8. Stockham RJ, Stanley TH, Pace NL, Gillmor S, Groen F et al. Fentanyl pretreatment modifies anaesthetic induction with etomidate. Anaesth Intensive Care1988;16:171-176.
9. Hwang JY, Kim J H, Oh AY, Do SH, Jeon YT, Han SH.A comparison of midazolam with remifentanil for the prevention of myoclonic movements following etomidate injection. JInt Med Res 2008;36:17-22.
10. Kelsaka E, Karakaya D, Sarihasan B, Baris S. Remifentanil pretreatment reduces myoclonus after etomidate. J Clin Anesth 2006;18:83-86.
11. Alipour M, Tabari M, Azad AM. Comparative study evaluating efficacy of sufentanil versus midazolam in preventing myoclonic movements following etomidate. Journal of Anaesthesiology Clinical Pharmacology 2016;32(1):29-32.
12. Zhao X, BaoR, Zhu J, Liu Z, Meng Y, Fan X, Li, J .Pretreatment with butorphanol reduces myoclonus after etomidate. Journal of Anaesthesiology and Clinical Science 2013,2:2.http://dx.doi.org/10.7243/2049-9752-2-2.
13. Manocha A, Sharma KK and Mediratta PK. Possible mechanism involved in the anticonvulsant action of butorphanol in mice. Pharmacol Biochem Behav 2003;74:343-350.
14. Doenicke AW, Roizen MF, Kugler J et al. Reducing myoclonus after etomidate.Anaesthesiology.1999;90(1):113-119.
15. Do SH, Han SH, Park SH et al. The effect of injection rate on etomidate- induced myoclonus. Korean J Anesthesiol. 2008;55(3):305-307.
16. Salman N, Gurbu HA, Oguzalp H, Ucar HI, Yorgancioglu C, Sakerci S. Comparison of dexmedetomidine and midazolam in prevention of myoclonus occurring due to etomidate in coronary bypass

surgery. Journal-Cardiovascular Surgery 2013;1(3):52-56.
17. Bulent U, Ceyhan D, Yelken B. Prevention of etomidate-related myoclonus in anaesthetic induction by pretreatment with magnesium. J Res Med Sci 2011;16(11):1490-1494.
18. Patel MH, Chinnachamy R, Ramani MN, Gandhi S. A comparison of dexmedetomidine and midazolam for the prevention of myoclonic movements and pain following etomidate injection. Research Journal of Pharmaceutical, Biological and Chemical Sciences 2015;6(5):161-168.