A Comparision of Two Different Doses of Butorphanol-Pretreatment to Establish A Minimum Effective Dose for Etomidate Induced Myoclonus - A Prospective Randomized Study

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ABSTRACT

Introduction: Etomidate is often used for induction of general anaesthesia because of its very stable hemodynamic profile. myoclonus is common problem with induction of anaesthesia with etomidate, which may be a problem in non fasting patients, open eye injury and epileptic patients. Incidence of myoclonus shown to be reduced by variety of opioid agents. Butorphanol is strong analgesic with both narcotic agonistic and antagonistic properties. This prospective randomized study was aimed to compare two different doses of butorphanol to establish minimum effective dose for prevention of myoclonus.

Material and methods: A total of 90 patients,ASA I and II undergoing elective surgery were randomized into three groups comprising of 30 patients each. Group B and Group C received butorphanol 0.04 mg/kg and 0.02 mg/kg respectively and group A received normal saline. Two minutes after pretreatment patients received etomidate 0.3 mg /kg. Assessment of myoclonus after etomidate was done using four point scale:0= no myoclonus, 1 = mild myoclonus, 2= moderate myoclonus and 3= severe myoclonus.

Results: The incidence of myoclonus in Group A is 76.67% and Group B and Group C is 3.3% and 10% respectively. The difference among Group A to Group B and Group C is highly significant ($P < 0.001$) and Group B and Group C is statistically insignificant ($P = 0.296$).The difference in severity of myoclonus in Group A in compared to Group B and C is statistically significant($p < 0.001$) and between Group B and C is insignificant(($P = 0.552$).

Conclusion: Butorphanol 0.02 mg/kg is as effective as 0.04 mg/kg in reducing etomidate induced myoclonus.

Keywords: Etomidate, Butorphanol, Myoclonus, Pretreatment

INTRODUCTION

Choosing the induction agent is a very vital step in commencing general anesthesia. Etomidate, a carboxylated imidazole compound, is an anesthetic induction drug with a very favourable hemodynamic character[1] Etomidate was selected as an ideal induction agent because of its many desirable properties like rapid onset of profound hypnosis, minimal histamine release, hemodynamic stability, minimal respiratory depression, and favourable cerebral effects. Despite problems such as pain on injection, decreased cortisol secretion and myoclonus, the positive pharmacologic attributes of etomidate have contributed toward its continued use. There is transient adrenal suppression but it is not clinically significant after a single bolus injection. Because most of side effects associated with etomidate induction were related to the vehicle propylene glycol, the vehicle has been changed to a fat emulsion (Etomidate-Lipuro). With the new solvent, pain on injection, venous irritation, and hemolysis were virtually abolished.[2] However, the incidence of myoclonus during induction was not affected by the solvent. When anesthesia is induced with etomidate, 50-80% of patients who are not premedicated experience myoclonus.[3] Myoclonus is a common problem during induction of anesthesia with etomidate, up to 80% of non-premedicated patients develop myoclonic movements, which may be a problem in the non-fasting patients, in patients with an open globe injury, myoclonus after etomidate raises the risk of prolapse of vitreous material as a result of high intraocular pressure.[4] In patients with epilepsy, myoclonus can enhance focal epileptogenic activity.[5,6] The neurologic mechanism of myoclonus after etomidate administration is still unclear, but it may represent a type of seizure.[7–9] Agonistic modulation of κ opiate receptors limits seizures[10, 11], and butorphanol acts mainly in this manner.[12] Ideally a pretreatment drug for preventing myoclonic movements should be short-acting, should not have significant effects on respiration and hemodynamics, and should not prolong recovery from anesthesia. Despite different agents including opioids or benzodiazepines have been chosen for inhibiting etomidate induced myoclonus, the mechanism by which this effect is achieved is still unclear. Etomidate is a ligand of γ-amino-butyric-acid (GABA) receptors, which suppress the reticular activating system of central nerves. It has been postulated that it is a disinhibition phenomenon, presumably because large doses of etomidate depress cortical activity before they depress subcortical activity. Butorphanol is a synthetic, strong analgesic with both narcotic agonist and antagonistic properties. As an agonist butorphanol mainly binds to and modulates κ opiate receptor, which are involved in anti-seizure activity. It is likely that the effects of butorphanol on these receptors are responsible for the reduction of myoclonic movements. Since the effectiveness

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How to cite this article: Rashmi Pal, Parul Jain, K.K. Arora, Bharathi B. A comparision of two different doses of butorphanol-pretreatment to establish a minimum effective dose for etomidate induced myoclonus - a prospective randomized study. International Journal of Contemporary Medical Research 2018;5(3):C7-C11.

of pre-treatment with different doses of butorphanol on myoclonic activity has not been previously investigated, the aim of the present study was to compare effectiveness and the side effects of the two different doses of butorphanol pretreatment in reduction of etomidate induced myoclonus, so as to find a lowest dose which has lesser side effects as well.

MATERIAL AND METHODS

After approval from instituitional ethic committee and consent from participating patients

A total of 90 patients of ASA grade I and II of age 20-60 years of both sex undergoing elective surgery under general anaesthesia were randomized by computerization in three different groups comprising of 30 patients each. Patients who have received analgesic, sedative and opioids within 7 days, patients with neurological disease, significant cardiac disease, significant acute and chronic pulmonary disease, patients with drug allergies and hemodynamically unstable patients were excluded from study. Group A (placebo) received normal saline, Group B given butorphanol – 0.04mg/kg and Group C butorphanol – 0.02 mg/kg. Each vial of Butorphanol contains 2 mg/ml and was diluted to 10 ml so that each ml has 0.2mg. The day before the surgery night all patients were given oral alprazolam 0.25 mg. Next day, before anaesthesia, patients were cannulated (with 20-gauge needles) intravenously on the forearm. Inj. Glycopyrolate 0.004mg/kg was given intramuscularly 30 minutes before surgery as premedication. Standard monitors, including those for electrocardiography, non-invasive blood pressure measurement and SpO2, were applied, and Ringer lactate was infused 10 ml/ kg/ hr. After pre-oxygenation for 3 minutes, the pre-treatment drug was infused over 30 seconds. Two minutes after infusion, patient was induced with etomidate (0.3mg/kg) infused over 30 sec. The patient was observed for myoclonus with its intensity for next 2 minutes. Thereafter injection atracurium (0.5mg/kg) was administered iv slowly and after 3 minutes endotracheal intubation was done using adequate size endotracheal tube. Meanwhile positive pressure ventilation with mask will be maintained using O2:N2O 50%: 50% and isoflurane (0.6% – 1.0%). Once correct placement of ETT was confirmed by auscultation, Inj fentanyl 1ug/kg were given. Anaesthesia was maintained as per standard protocol. For the group A (placebo), normal saline in the same volume was given in place of pretreatment drug. Patients were observed continuously for myoclonus by an anaesthesiologist who were blinded to the pre-treatment drug. The patients were also not aware of the pre-treatment drug. The intensity of myoclonus was scored as: Grade 0= no myoclonus, Grade 1= mild myoclonus (small movements in one body segment, such as fingers or wrist.),Grade 2= moderate myoclonus (mild movements of two different muscles such as face, arm, shoulder or elbow),Grade 3=severe myoclonus (clonic movements in two or more muscle groups or fast adduction of a limb).[3] Side effects, Including sedation, bradycardia, headache, dizziness, and nausea, were checked by another anaesthesiologist who was blinded to the groups in order to avoid bias of the investigators who had observed myoclonus. Heart rate (HR), non-invasive arterial blood pressure (NIBP), and oxygen saturation (SpO2) were recorded at regular intervals during the study period. Primary outcome was the incidence and grade of myoclonic movements after etomidate injection. Secondary outcomes were the side-effects of pre-treatment drugs like bradycardia, hypotension, nausea, headache, dizziness and sedation.

STATISTICAL ANALYSIS

The data were analysed using one-way analysis of variance ANOVA and pearson chi-square test for continuouse and categorical variables respectively. p value < 0.05 were considered statistically significant and p value < 0.001 were considered highly significant. All statistical analyses were performed using mini tab version 17.

RESULTS

All three groups were comparable in demographic profile. (Table 1). The incidence of myoclonus in Group A (76.67%) is more compared to Group B (3.3%) and Group C (10%). The difference in incidence of myoclonus among Group A to Group B and Group C is statistically highly significant. ($P < 0.001$). The difference in incidence of myoclonus in Group B (3.3%) and Group C (10%) is statistically insignificant, ($P = 0.296$) (Table 2). The severity of myoclonus is more in Group A in compared to Group B and Group C which is statistically highly significant ($p < 0.001$).The difference in

parameter	Group A (n= 30)	Group B (n=30)	Group C (n=30)	*P* value
Age (in years) Mean ± SD	41.62 ± 11.07	40.06 ± 11.75	43.35 ± 10.63	0.523
Weight (in kg) Mean ± SD	62.67 ± 9.53	61.23 ± 11.69	62.01 ± 10.72	0.873
Ratio (M:F)	14:16	13:17	11:19	0.801

Table-1: Demographic distribution of patients

	Group A	Group B Butor 0.04 mg/kg	Group C Butor 0.02 mg/kg
Incidence of myoclonus	76.67%	3.3%	10%
group A to group B and C ($p < 0.001$), group B and group C ($p = 0.296$)			

Table-2: Incidence of myoclonus in three groups

	Mild myoclonus	Moderate myoclonus	Severe myoclonus
Group A (Placebo)	35.46%	55.46%	8.63%
Group B (0.04 mg/kg)	3.3%	0%	0%
Group C (0.02 mg/kg)	6.6%	3.3%	0%
group A to group B and C ($p < 0.001$), group B and group C ($p = 0.552$)			

Table-3: Severity of myoclonus among three groups.

	Group A placebo%		Group B Butor 0.04 mg/kg%		Group C Butor 0.02mg/kg%	
Sedation	0	0%	0	0	0	0%
Dizziness	0	0%	4	13.3%	1	3.3%
Bradycardia	0	0%	0	0%	0	0%
Nausea	0	0%	2	6.6%	1	3.3%
Headache	0	0%	1	3.3%	0	0%

Table-4: Incidence of side effects among three groups.

severity of myoclonus in Group B and Group C is statistically not significant (*P*=0.552) (Table 3). Incidence of side effects shown in Table 4.

DISCUSSION

We observed that pre-treatment with both the doses of butorphanol, 0.02 mg/kg and 0.04 mg/kg reduce the incidence and severity of myoclonic movements significantly during induction of anaesthesia with etomidate.

Sung et al. found that the butorphanol was a good opioid analgesic for balanced anaesthesia.[13] The authors suggested that butorphanol was a better choice than morphine for balanced anaesthesia technique because of its comparable analgesic efficacy and amnesia along with lesser respiratory depression and a short stay in recovery room.

The neurologic mechanism of myoclonus after etomidate is not clear. Kugler et al.,[14] postulated that inhibitory circuits can be depressed earlier and at lower etomidate concentrations than excitatory neuronal circuits.

Doenicke et al., observed that myoclonus due to etomidate is due to subcortical disinhibition like restless legs during normal human sleep and is not due to an epileptic focus[3].

Incidence of myoclonus is influenced by dose of etomidate. The dosage as much as 0.05 mg/kg etomidate did not induce myoclonic activity, but a dosage above 0.075 mg/kg caused myoclonic activity in men. Various methods have been used for attenuating myoclonus during IV injection of etomidate. Pretreatment with diazepam or flunitrazepam did not reduce myoclonus[15] but midazolam reduced the incidence because of fast onset of action.

Doenicke et al., found that pretreatment with three different dosages (etomidate 0.03, 0.05 or 0.075 mg/kg IV) of etomidate reduced myoclonus in a trial (n=20) without a control group in premedicated patients.[3] Other agents have been used to reduce etomidate-induced myoclonus in placebo-controlled clinical trials. Dexmedetomidine (0.5 µg/kg) and thiopental (1.0 mg/kg) reduced the incidence of myoclonus from 64% to 34% and 36%, respectively. Pretreatment with fentanyl 100µg reduced the incidence of myoclonus to 8%.[16] The use of larger fentanyl dosages, however, increased the incidence of apnea during induction.[17] The incidence of myoclonus after pretreatment with alfentanil 5µg/kg was found to be 25%.[18] Hueter et al.,used sufentanil 0.3 µg·kg-1 for prevention of myoclonus after etomidate in female patients and found that none of patients experienced myoclonus in sufentanil group, but 80% patients experienced myoclonus in placebo group.[19] 60% of the patients treated with sufentanil showed some degree of sedation from mild to severe, whereas only 15% in the placebo group. Although it was found that fentanyl, alfentanil, or sufentanil are effective in reducing myoclonus, these agents are more suitable for longer surgical procedures. Opioid with very short onset time, remifentanil (1 µg/kg), was very effective in reducing myoclonus after etomidate from 70% in the placebo group to 6.7% in the remifentanilgroup.[20] However, remifentanil can cause severe bradycardia.

Klausen showed that buprenorphine has no effect on the incidence of myoclonus.[23]

Guleret et al reported that Magnesium 2.48 mmol administered 90s before the induction of anaesthesia with etomidate was effective in reducing incidence and severity of etomidate-induced myoclonus[24] and that ketamine did not reduce the incidence of myoclonus.

He Liang, 2014, compared 0.015 mg/kg of butorphanol with saline and observed that the incidence of myoclonus was significantly lower in Butorphanol group than in Saline group (13.0% vs 79.6%), Which correlates with our study with 10% incidence of myoclonus in group B (butorphanol 0.02 mg/kg) and 3.3% in Group C (butorphanol 0.04 mg/kg). Also the severity levels of myoclonic movement in Butorphanol group were significantly lower than in Saline group ($p<0.001$) of He Liang, which correlates with our study ($p<0.001$). Our study go in hand with the side-effects in two groups with regard to headache, dizziness, and nausea, done by He Liang, 2014., as one patients experienced headache, and only a few patients dizziness (4 patients) and nausea (1 patient) in Butorphanol group. None of the patients experienced these side-effects in Saline group.[22] which go in hand with our study too as none of the patients experienced any side effects in control group (GroupA)

Xiaohong Zhao, 2013, observed that pretreatment with butorphanol 2 mg or fentanyl 100µg reduced the incidence and severity of myoclonus associated with IV injection of etomidate ($p <0.001$). Butorphanol pretreatment was more effective in attenuating the incidence and severity of myoclonus ($p <0.001$),[21] which go in hand with our study

Butorphanol tartrate is a mixed agonist–antagonist with intrinsic activity at receptors of the mu opioid type (morphine like). It is also an agonist at kappa opioid receptors. Its interactions with these receptors in the CNS mediate most of its pharmacological effects, including analgesia. Butorphanol has 5-8 times more analgesic action than morphine with less respiratory depression,nausea and vomiting, no undesirable psychomimetic effects and perioperative amnesia.

Buorphanol has fast onset of action (within 1-2 minutes) with peak effect in 4-5 minutes after intravenous administration.[25] The site of action of butorphanol in reducing the myoclonus of etomidate injection is not clear. Manocha et al., 2003 study the effect of butorphanol on convulsive behavior using maximal electroshock (MES) test.[26] Their results implicated a role for multitude of neurotransmitter systems, i.e., opioid (mu, kappa, delta), NMDA channel, BZD–GABAA chloride channel complex, and GABA B receptors in the anti-MES action of butorphanol. The analgesic and sedative effect of butorphanol may be responsible for reduction in incidence and severity of myoclonus after etomidate administration. Further study is suggested for confirming the mechanism of action of butorphanol in prevention of etomidate-induced myoclonus.

We used alprazolam in all patients as premedication on the night before surgery for ethical reasons. In spite of alprazolam premedication, the incidence of myoclonus was high in the placebo group. Butorphanol has very good sedative effect alone and especially in combination with other agents such as promethazine. The combination of butorphanol and etomidate may cause excessive sedation, but delayed awakening was not observed in all of our patients.

This study shows that butorphanol in a dose of 0.02 mg/kg is as effective as a dose of 0.04mg/kg in reducing incidence and severity of etomidate induced myoclonus, since the difference is statistically insignificant between the two drug groups.

So we conclude that pretreatment with butorphanol 0.02 mg/kg before induction with 0.3 mg·kg-1 etomidate reduces the incidence and severity of myoclonus with lesser side effects such as dizziness, headache compared with the butorphanol 0.04 mg/kg. Butorphanol can be a good choice for prevention of myoclonus after etomidate administration. However, it is believed that independent studies will prove further demonstration of its efficacy and tolerability.

There are some limitations for this clinical trial. First, the main outcome measure (rating of myoclonus) was subjective. Second, we did not investigate the optimal clinical dose of butorphanol on etomidate-induced myoclonus, since there are few previously reported studies on the relationship between butorphanol and myoclonus. Whether higher doses of butorphanol exert stronger inhibitory effects without adverse side effects will be tested in future studies.

CONCLUSION

we conclude that butorphanol 0.02 mg/kg is as effective as butorphanol 0.04 mg/kg in suppressing etomidate induced myoclonus with lesser side effects.

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Source of Support: Nil; **Conflict of Interest:** None

Submitted: 25-03-2018; **Accepted:** 29-03-2018; **Published:** 05-04-2018