ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

A Comparison of Dexmedetomidine and Midazolam for the Prevention of Myoclonic Movements and Pain Following Etomidate Injection.

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ABSTRACT

Etomidate is increasingly used for anesthesia induction because of rapid onset, cerebro-protective properties, lack of respiratory depression and minimal changes in hemodynamic status. Two undesirable side effects of etomidate are pain on injection and myoclonus. We designed a placebo-controlled study to investigate the effects of pretreatment with IV midazolam or dexmedetomidine on incidence and severity of myoclonus and injection pain due to etomidate. 90 patients posted for elective surgery were given Inj Dexmedetomidine 1µg/kg(Group-A), Inj Midazolam 0.05mg/kg(Group-B) or Normal Saline(control group-C). Sedation was assessed using the Ramsay Sedation Scale 90 seconds after the study drugs administration and just before induction with etomidate. Pain and myoclonus were recorded after etomidate administration and graded with 4-point scoring systems. The dose of etomidate required to produce a loss of eyelash reflex was recorded. Incidence of myoclonus is less in dexmedetomidine(33%) and midazolam(40%) compared to control(86.7%)(p=0.002). Injection pain was less with midazolam(36.7%) and dexmedetomidine (33.3%) compared with placebo(86.7%)(p=0.001). The average doses of etomidate for induction was 10.40±1.33, 11.00±1.64, 18.20±2.67 mg for groups A, B and C respectively (p=0.006). The average time to loss of eyelash reflex was 31.03±4.66, 41.00±5.58, 72.97±9.45 seconds for groups A, B and C respectively (p=0.004). Dexmedetomidine is superior to midazolam in reducing the myoclonus and injection pain. Dexmedetomidine significantly reduced the induction dose and the time to induction with etomidate as compared to midazolam. Dexmedetomidine effectively achieved a state of conscious sedation, whereas midazolam achieved deep sedation.

Keywords: etomidate, myoclonus, midazolam, dexmedetomidine, sedation, pain.

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ISSN: 0975-8585

INTRODUCTION

Etomidate is a carboxylated imidazole compound that was introduced in Europe in 1972. It has been used increasingly for anaesthesia induction because of its rapid onset of anaesthesia, cerebral protective properties, and lack of respiratory depression [1,2] Also, etomidate causes no significant change in hemodynamic status [3,4] and consistently shows a superior hemodynamic profile compared with thiopentone [5]. Two undesirable side effects of etomidate are pain on injection and myoclonus [6-9]. The problem of pain on injection has been reduced by new lipid formulations for etomidate. Myoclonus may be of clinical significance in a variety of patients during induction of general anaesthesia.

Various agents have been investigated for suppression of etomidate-induced myoclonus. Opioids such as fentanyl, sufentanil and remifentanil, and benzodiazepines or magnesium sulfate can effectively reduce myoclonic movement [6, 10-14]. Drugs for preventing myoclonic movements should be short-acting, not have significant effects on respiration and hemodynamics, and recovery from anaesthesia. Myoclonus after Etomidate may not necessarily be hazardous in terms of EEG changes [6] but, it can be problematic in cases of open globe injury or those at risk of aspiration [15].

We designed a placebo-controlled study to investigate the effects of pretreatment with IV midazolam or dexmedetomidine on the incidence and severity of myoclonus and injection pain during induction of anaesthesia with etomidate in elective unpremedicated patients. Our study also assessed and compared the degree of sedation and etomidate dose reduction achieved by these drugs.

MATERIAL AND METHODS

The study was conducted after approved by the Institutional Ethics Committee. A written and informed consent was obtained from the patients before being enrolled into this study. Exclusion criteria are, having psychiatric illness, mental retardation, on anxiolytic or sedative drugs, having neuromuscular disorders, intake of enzyme inducers within the 24 hours preceding the study, any medication likely to cause cardiovascular changes.

Ninety Patients of ASA I and II, posted for elective surgery were randomly allocated into 3 groups of 30 patients each, Group A – Inj. Dexmedetomidine 1 µg/kg over 10 min diluted in 50 ml NS, Group B – Inj. Midazolam 0.05 mg/kg, Group C – Inj. Normal Saline 10ml (Placebo control group). Patients were not pre-medicated. All patients were infused 2-3ml/kg 0.9% normal saline pre-induction. Heart rate, non invasive arterial blood pressure (Systolic Blood Pressure, Diastolic Blood Pressure) and oxygen saturation (SPO_2) were recorded every minute of the study. Sedation was assessed using the Ramsay Sedation Scale after pretreatment with the study drugs. Scoring was done after a 90 seconds period after the administration of the study drug. After that, induction of anaesthesia with sleep doses of Etomidate started. During the intravenous injection of etomidate, the patients were requested to inform the anaesthesiologist spontaneously and on request about their sensations at the injection site.

Pain was graded as 0 = none, 1 = mild (reported only in response to questioning and without any behavioural signs), 2 = moderate (reported in response to questioning and accompanied by behavioural signs or reported spontaneously without questioning), 3 = severe (strong vocal response or response accompanied by facial grimacing, arm withdrawal or tears).

During the injection of intravenous etomidate and for up to 60 seconds thereafter, before administering injection vecuronium bromide, patients were observed continuously for occurrence of myoclonus and the intensity of myoclonus was graded as 0 = no myoclonus, 1 = mild myoclonus (only mild fasciculations involving the face and/or distal upper and/or lower extremities), 2 = moderate myoclonus (marked movements of face and/or limbs), 3 = severe myoclonus (involving limbs and trunk). Heart rate(HR), systolic blood pressure(SBP), diastolic blood pressure(DBP) and peripheral oxygen saturation(SPO_2) were recorded before pretreatment (Tb; baseline), after pretreatment (Tt), 1 minute after induction of etomidate anaesthesia (T1), 3 minutes(T3) and 5 minutes(T5) after induction.

The duration from the beginning of anaesthesia to the disappearance of eyelash reflex was measured. The dose of etomidate required to produce a loss of eyelash reflex was also recorded.

Statastical Analysis

In our study, quantitative data are presented in terms of mean, SD or range. One way anova was used for analysis of differences in age, weight, hemodynamic variables. ASA physical status, sex, number of patients, myoclonic movements and injection pain were analyzed with chi-squared test. Significance was defined as $P < 0.05$. All statistical comparisons were accomplished with EpiInfosoftware(version 3.5.3 , CDC Atlanta).

RESULTS

There were no significant differences among the groups regarding age, weight, height, sex and ASA physical status. (Table 1)

Table 1: Demographic Data

Parameter	Group A	Group B	Group C	P value
Age(years)	34.8±11.16	34.0±11.24	38.43±11.85	0.9
Weight(kg)	62.0±8.99	63.23±9.21	60.3±7.94	0.7
Height(m)	1.64±0.08	1.62±0.28	1.64±0.07	0.4
Sex ratio(Male: Female)	20/10	19/11	19/11	0.7
Heart Rate(beats/min)	82.77±10.2	82.73±10.87	77.07±9.98	0.7
ASA grade(I/II)	21/9	20/10	19/11	0.5

Values are mean±2SD or in numbers

We found that pretreatment with midazolam and dexmedetomidine significantly reduced the incidence and the severity of myoclonic movements after etomidate induction as compared to control group (p=0.002). Myoclonus developed in 10(33.3%) out of 30 patients in the dexmedetomidine group, 12(40%) out of 30 patients in the midazolam group and 26(86.7%) out of 30 patients in the placebo group within 60 seconds after induction of anaesthesia with etomidate. The severity of myoclonus in these groups is given in Table 2.

Table 2: Myoclonus –Incidence and Severity

Degree of myoclonus	A(n=30)	B(n=30)	C(n=30)	P value
No myoclonus	20 (66.7%)	18 (60%)	4 (13.3%)	0.02
Mild myoclonus	7 (23.3%)	9 (30%)	11 (36.7%)	0.1
Moderate myoclonus	3 (10%)	3 (10%)	8 (26.7%)	0.6
Severe myoclonus	0 (0%)	0 (0%)	5 (16.7%)	0.2

In groups A and B, the incidence of injection pain after etomidate induction was significantly lesser compared to group C (P = 0.01). Immediately after injection of etomidate intravenously, 10(33.3%) out of 30 patients in group A, 11(36.7%) out of 30 patients in group B and 26(86.7%) out 30 patients in group C developed injection pain. The distributation of severity of injection pain is given in Table 3.

Table 3: Injection Pain± Incidence and Severity

Severity of pain	A(n=30)	B(n=30)	C(n=30)	P value
No pain	20 (66.7%)	19 (63.3%)	4 (13.3%)	0.01
Mild pain	8 (26.7%)	5 (16.7%)	15 (50%)	0.04
Moderate pain	2 (6.7%)	6 (20%)	11 (36.7%)	0.002
Severe pain	0(0%)	0(0%)	0(0%)	0.7

The dose of etomidate required for induction is 10.40 ± 1.33mg, 11.00 ± 1.64mg and 18.20 ± 2.67mg in group A, B and C respectively. The time to loss of eyelash reflex following etomidate is 31.03 ± 4.66 seconds, 41.00 ± 5.58 seconds and 72.97 ± 9.45 seconds in group A, B and C respectively..There is significant reduction in induction time (p=0.006) and induction dose (p=0.004) following dexmedetomidine or midazolam as compared to placebo.

ISSN: 0975-8585

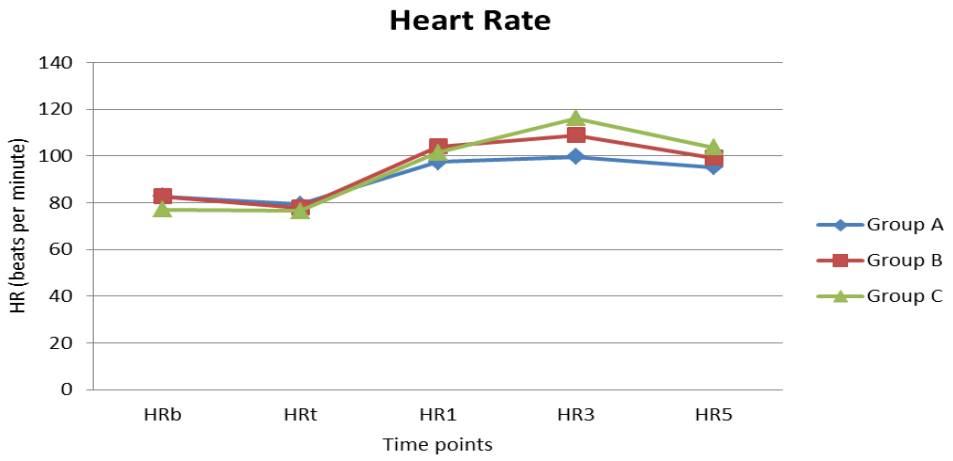
Sedation following study drugs is recorded and given in table 4. Majority of patients [27] with dexmedetomidine had level 2 or 3 sedation while with midazolam, majority [24] had deeper level of 4 or 5 sedatation.

Table 4: Sedation Score

Ramsay Sedation Score	A(n=30)	B(n=30)	C(n=30)	P value
1	0 (0%)	0 (0%)	21 (70%)	0.001
2	7 (23.3%)	0 (0%)	9 (30%)	0.02
3	20 (66.7%)	2 (6.7%)	0 (0%)	0.001
4	3 (10%)	8 (26.7%)	0 (0%)	0.04
5	0 (0%)	18 (60%)	0 (0%)	0.006
6	0 (0%)	2 (6.7%)	0 (0%)	0.8

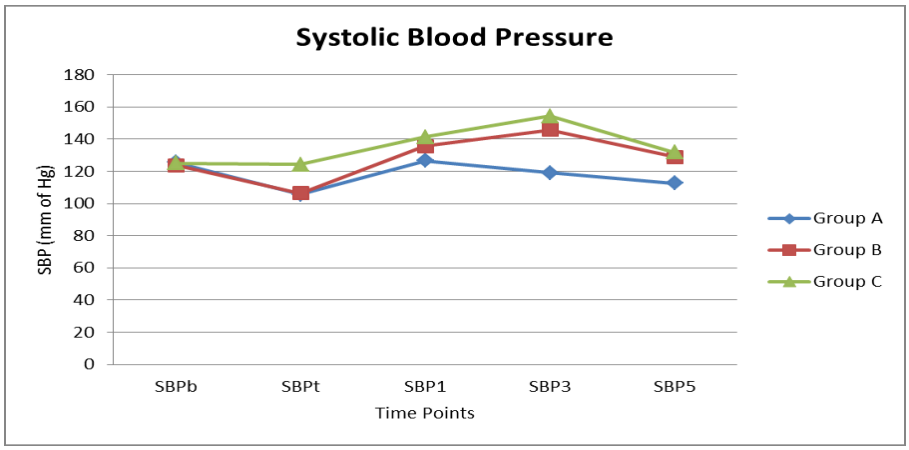
Baseline heart rate, systolic and diastolic blood pressure were comparable in all three groups. The mean systolic and diastolic blood pressure in group A after premedication and during the period of observation were significantly lower than the SBP and DBP in groups B and C(chart 1, 2 and 3).

Chart 1 Heart Rate Comparisons



HRb- basal heart rate, HRt-after pretreatment with study drug, HR1,3 and 5- at 1,3 and 5 minutes after induction with etomidate.

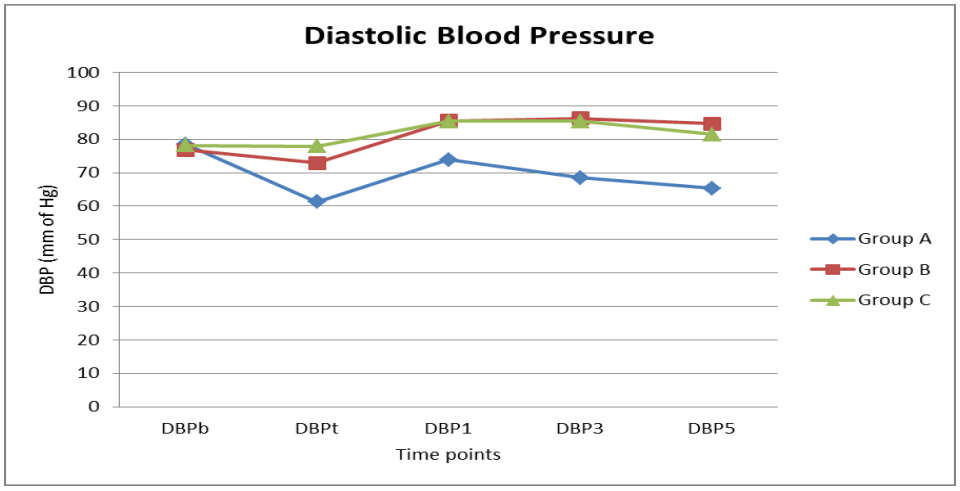
Chart 2 Systolic Blood Pressure Comparisons



SBPb- basal systolic blood pressure, SBPt-after pretreatment with study drug, SBP1,3 and 5- at 1,3 and 5 minutes after induction with etomidate.

ISSN: 0975-8585

Chart 3 Diastolic Blood Pressure Comparisons



DBPb- basal diastolic blood pressure, DBPt-after pretreatment with study drug, DBP1,3 and 5- at 1,3 and 5 minutes after induction with etomidate.

We did not encounter the known side effects of dexmedetomidine, namely, hypotension and bradycardia in any of the patients in group A. In group B, two patients became apnoeic after intravenous midazolam 0.05 mg/kg, which was effectively managed by intermittent positive pressure ventilation with a Bain's circuit and mask with 100% oxygen.

DISCUSSION

Dexmedetomidine is a relatively selective alpha2-adrenoceptor agonist with centrally mediated sympatholytic, sedative and analgesic effects. Dexmedetomidine infusions are used for sedation in the treatment of mechanically ventilated patients in an intensive care setting or as premedication for anaesthesia and surgery.

Midazolam is a very short-acting benzodiazepine. It is used for conscious sedation, anxiolysis, and amnesia during minor surgical or diagnostic procedures, as an anaesthesia induction agent, or as an adjunct to regional anaesthesia. Benzodiazepines exert their effects through enhancement of the gamma-aminobutyric acid (GABA)-benzodiazepine receptor complex. GABA-A is the primary receptor subtype in the CNS and is thought to be involved in the actions of anxiolytics and sedatives. Of three subtypes, activation of the BNZ1 receptor is thought to mediate sleep while the BNZ2 receptors present in cerebral cortex and spinal cord affects muscle relaxation, anticonvulsant [16] activity, motor coordination, and memory. The BNZ3 receptors are found in peripheral tissues.

Several studies have reported myoclonic activity in 50% to 80% of patients receiving etomidate [12,17]. Despite the variety of drugs potentially reducing the incidence of myoclonic movements after etomidate administration, the mechanism by which this effect is achieved remains unclear [12,15]. Doenicke et al reported that myoclonus after etomidate is caused by subcortical disinhibition [12].Etomidate interacts with GABA-A receptors suppressing the central nervous reticular activating system. With interruption of GABA neurons, pathways associated with skeletal muscle control can become more sensitive, allowing spontaneous nerve transmissions to occur. These events can ultimately lead to myoclonic contractions [18]. Kugler et al postulated that inhibitory circuits can be depressed earlier and at lower concentrations than excitatory neuronal circuits. We hypothesized that the excitatory phenomenon of myoclonus was caused by disequilibrium of the drug at the various effect sites in the central nervous system (CNS). Differences in local cerebral blood flow or affinity might produce a temporary disequilibrium of effect, resulting in more rapid inhibition of cortical depression. If over time, inhibitory and excitatory neural circuits are both depressed by etomidate, but the inhibitory are depressed sooner, then pretreatment could reduce the incidence of myoclonus. Conversely, larger initial bolus doses (upto a point), increase the incidence of myoclonus [19]. Our findings support this hypothesis as the patients in group A showed the least incidence of myoclonus as

compared to the groups B and C. Also, the overall incidence of myoclonus was significantly lower in groups A and B, which correlates to a significant dose reduction of etomidate to achieve a loss of eyelash reflex in groups A and B, further substantiating our hypothesis.

Benzodiazepines pretreatment has also been investigated to reduce myoclonus associated with etomidate. Schwarzkopf et al reported that the incidence of myoclonic movements was significantly less in patients pretreated with 0.05mg/kg midazolam (37%) compared with placebo (90%) [20]. We did not find any research about dexmedetomidine and myoclonus in the literature; therefore, we chose the dose of loading dose dexmedetomidine (1µg/kg). In our study, we showed that the incidence of myoclonic movements was significantly less in patients pretreated with 1µg/kg dexmedetomidine (33.3%) and 0.05mg/kg midazolam (40%) compared with placebo group (86.7%). Also, reducing the incidence of myoclonic movements in group midazolam and dexmedetomidine may be explained in both groups as the total dose of etomidate used for induction was lesser than that in the placebo group.

Injection Pain

A problem with previous preparations of etomidate was that the solvent used caused pain on injection. Ganta et al showed that the overall incidence of pain on injection was 60% with two formulations of etomidate (propylene glycol or etomidate in ethanol) [21]. Etomidate is now available as a lipid emulsion (Etomidate-Lipuro, B. Braun AG, Melsungen Germany) and is a registered drug in a number of European countries. Nyman et al reported that the use of Etomidate –Lipuro was found to significantly reduce the incidence of pain on injection compared with propofol-lidocaine (5% vs 47.5%) [22]. In our study, we used lipid formulation of etomidate and we observed incidence of pain on injection was 86.7% in group C. The incidence of injection pain was significantly less in patients pretreated with 0.05mg/kg midazolam (36.7%) and 1µg/kg dexmedetomidine (33.3%) compared with placebo. Clinical trials reveal that a2 agonists produce significant analgesia in humans when administered by the intrathecal or epidural routes; however, the analgesic action of systemically administered a2 agonists, assessed by a reduction in the requirement for postoperative opioids, is modest at best and may be confounded by the coexistent sedative effect [23]. The combination α-adrenoceptor agonists to etomidate may provide reducing injection pain because dexmedetomidine acts at a different site. Also, as shown by Cortinez and Hsu et al, reduction of the etomidate related injection pain may be explained with the sedative effects of midazolam [23], in our study, we have further substantiated this finding.

Reduction in injection pain of etomidate can be attributed to the reduced dose of etomidate required to induce anaesthesia in both groups. Dexmedetomidine by its inhibitory action on the Locus ceruleus and midazolam by its interaction with various GABA receptor sub-types producing sub-cortical neuronal inhibition may have acted as an adjuvant to etomidate [20,24]. Thus, producing a loss of eyelash reflex in a significantly lesser time and with a lesser dose of etomidate in patients in group A and B than in patients of group C in conjunction with the results of Schwartzkopf et al.

Haemodynamic Response

In most studies, etomidate causes no significant change in hemodynamic status [10,25,26]. Johnson et al prospectively observed the hemodynamic effects of etomidate and they didn't find any significant changes in non-invasive blood pressure, respiratory rate, or oxygen saturation [27]. The cardiovascular stability of etomidate during induction of anaesthesia even in patients with cardiac disease and during bolus application might be related to an interaction of etomidate with peripheral α2B adrenoceptors. The α2B mediated vasoconstriction may oppose hypotensive effects of other coadministered agents during induction of anaesthesia, and thus be responsible for the known beneficial hemodynamic profile of etomidate. In the present study, hemodynamic variables were significantly lower in the dexmedetomidine group than that in the midazolam and the placebo group. The reduced heart rate and systolic and diastolic blood pressure in Group A compared to Groups B and C can be attributed to the well-established sympatholytic effects of dexmedetomidine [14].Alpha-2 receptors are located on blood vessels, where they mediate vasoconstriction, and on sympathetic terminals, where they inhibit norepinephrine release [29].Dexmedetomidine, on binding to α2 receptors, reduces the sympathetic outflow and an augmented cardiac vagal activity resulting in decreases heart rate and cardiac output [16].

Sedation

Locus Ceruleus of the brainstem is the principal site for the sedative action and the spinal cord is the principal site for the analgesic action of dexmedetomidine, both acting through α2A receptor agonistic action [24]. The result of this action is the attainment of sedation without cortical suppression and hence respiratory depression, culminating into a state of sedation called conscious sedation, which is unique to dexmedetomidine. This conscious sedation was further elucidated in our study where we found 66.7% of patients in group A displayed a sedation score of 3 on the Ramsay sedation scale as compared to 6.7% of patients in group B, where they were adequately sedated but responded to verbal commands on arousal and instantaneously went into a state of sedation after the cessation of stimulus for arousal, thus demonstrating a truly unique and desirable property of dexmedetomidine. Sixty percent of the patients in group B displayed a sedation score of 5.

CONCLUSION

In conclusion, this clinical study shows that dexmedetomidine administered before etomidate induction reduces myoclonic muscle movements and injection pain without any hemodynamic side effects. Moreover, dexmedetomidine was significantly superior to midazolam in reducing the myoclonus and injection pain, but either dexmedetomidine or midazolam caused sedation administered before etomidate induction. Dexmedetomidine pretreatment significantly reduced the induction dose and the time to induction of anaesthesia with etomidate as compared to midazolam. Dexmedetomidine effectively achieved a state of conscious sedation, whereas midazolam achieved deep sedation. Thus, Dexmedetomidine may become a good alternative for preventing undesirable effects of etomidate.

ACKNOWLEDGEMENT

- Department of anesthesiology, BJ Medical College and civil hospital, Ahmedabad, for allowing the study to be conducted under departmental guidance.
- Ethical committee, BJ Medical College, Ahmedabad for granting permission for the study.

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