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Original Research Article

A comparison of fentanyl and dexamethasone pretreatment for prevention of etomidate induced myoclonus, a randomized double blind placebo controlled study

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ABSTRACT

Background and Aims: Etomidate is used for induction of anaesthesia in haemodynamically unstable patients but its use is associated with undesirable side effects like myoclonus, incidence of which is 50-80%. This prospective, randomized, placebo controlled study is to compare the effect of dexamethasone and fentanyl for prevention of etomidate induced myoclonus.
Materials and Methods: Ninety adult patients were randomly assigned into three groups to receive Dexamethasone (group D), Fentanyl (group F) and placebo (group P) five min before injection etomidate 0.3mg/kg IV. The patients were assessed for myoclonus using a four point intensity scoring system over a period of 5 min. ANOVA and chi square test were used for statistical analysis and P<0.05 was considered as statistically significant.
Results: The incidence of myoclonus was significantly reduced in groups D and F compared with group P (p value 0.001).The incidence of pain associated with Etomidate induced myoclonus also was significantly reduced in groups D and F compared to group P (p value 0.001).
Conclusion: Dexamethasone significantly reduces the incidence of myoclonus as compared to placebo. It also significantly reduces the pain associated with Etomidate injection. However its efficacy to reduce pain and myoclonus as compared to Fentanyl is much less.

1. Introduction

Etomidate is a carboxylated nonbarbiturate imidazole derivative which is mostly used for induction of anaesthesia in haemodynamically unstable patients.[1] It has various advantages like minimal histamine release cerebral protection and haemodynamic stability. However it also has side effects like nausea, vomiting, superficial thrombophlebitis, haemolysis, adrenocortical suppression, pain on injection and myoclonus.

Etomidate induced myoclonus is an involuntary jerky movement which increases the risk of aspiration and regurgitation. It is seen in 50-80% of unpremedicated patients.[2] Various drugs including neuromuscular blocking agents (NMBA), opioids, dexmedetomidine, midazolam, propofol, gabapentin and magnesium have been used to suppress etomidate induced myoclonus.[3–7] However their use is associated with side effects like excessive sedation, delayed recovery and respiratory depression.

Dexamethasone is a type of corticosteroid medication. High dose pulsatile dexamethasone therapy has been used in children with opsoclonus-myoclonus syndrome.[8] Previous studies using Fentanyl for Etomidate induced myoclonus have been done and Fentanyl has been found to be effective. However there are no reported comparative studies comparing dexamethasone and fentanyl for prevention of etomidate induced myoclonus and pain on injection. Therefore the present study was conducted to evaluate and compare the efficacies of fentanyl and dexamethasone for prevention of etomidate induced myoclonus and pain on etomidate injection.

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2. Materials and Methods

This prospective, randomized, double blind and placebo controlled study was conducted after obtaining approval from the institutional ethics committee. After obtaining written informed consent 90 patients of age 18-50 years, ASA status of I and II scheduled for various elective surgeries under general anaesthesia were included in the study. Patients having allergy to any of the study drugs, history of seizure disorders, primary/secondary steroid deficiency, patients on steroid therapy, morbid obesity, cardiac conduction abnormalities and patients on antiarrhythmic drugs, sedatives or opioid therapy were excluded from the study.

Patients were explained about the anaesthetic technique and during preanaesthetic checkup and written and informed consent was taken. Patients were kept nil per orally 6 hrs before surgery. Premedication with tablet alprazolam 0.25 mg and tablet ranitidine 150 mg in the morning on the day of surgery with a sip of water was given.

On arrival in the operation theatre electrocardiogram (ECG), pulse oximetry and non invasive blood pressure (NIBP) were attached and baseline parameters were recorded. A 20G intravenous (IV) cannula was secured into a vein on dorsum of the hand and connected to ringer lactate drip.

The patients were randomly assigned using a random number list into one of the three groups to receive either of the following as a premedication. The first group patients received 8 mg dexamethasone (Group D) diluted to 5 ml in normal saline. The second group received 2 μg/kg fentanyl (Group F) diluted to 5 ml in normal saline. Group three (Group Placebo) received 5 ml normal saline intravenously as premedication. All drugs were prepared in 5 ml identical syringes by an independent anesthesiologist not involved further in the study. Five minutes after receiving the study drugs, patient was preoxygenated with 100% oxygen for 3 min along with anesthesia induction with 0.3 mg/kg etomidate injected intravenously over the period of 20-30 sec. The severity of etomidate induced injection pain was assessed using a 4 point scale, 0= no pain, 1= mild (pain reported only when asked), 2= moderate (pain reported without being asked or reported when asked and there were associated behavioral symptoms) and 3= severe (verbal response, grimacing, pulling the arm, tearing in the eyes).

The etomidate induced myoclonus was assessed over 5 minutes after etomidate injection and its severity was graded using a four point scale: 0= no myoclonus, 1= mild myoclonus (small movements in 1 body segment such as finger or wrist), 2= moderate (slight movements in 2 or more muscle areas such as face or shoulder) and 3= severe (intense movements in 2 or more muscle areas, sudden adduction of an extremity).

The patients and the anesthesiologists involved in assessment for etomidate induced myoclonus and etomidate injection pain were unaware of the group allocation. Five minutes after etomidate injection muscle relaxation was achieved with 0.1mg/kg vecuronium and endotracheal intubation with appropriate sized endotracheal tube performed.

Anesthesia was maintained using 1-1.5% isoflurane and 50% nitrous oxide and oxygen with target of keeping MAC value of 1. Heart rate (HR), systolic blood pressure (SBP) and diastolic blood pressure (DBP) were evaluated during the time between injection of premedication till 10 minutes after etomidate injection at an interval of 5 minutes.

The primary outcome of the study was the severity of myoclonus.The secondary outcome of the study was the severity of pain due to Etomidate injection.

Sample size of 30 patients per group was estimated based on assuming effect size of 0.8 at 80% power, 95% confidence limits with alpha error of 0.05 and beta error of 0.2.

The data were tabulated in MS Excel 2010 and statistical analysis performed using SPSS 19.0 for Windows. Statistical analysis was done using two way ANOVA with turkey with pearson chi square test. Normally distributed continuous variables were compared using ANOVA and for categorical variables Pearson Chi square test. The continous data such as patient's age, weight, heart rate, systolic blood pressure, diastolic blood pressure were expressed as mean $\pm$ standard deviation whereas categorical data such as sex, myoclonus score, pain score were expressed as frequencies (percentage). For all statistical tests, p value of less than 0.05 was considered statistically significant.

3. Results

A total of 90 patients completed this study; they were randomized into three groups of 30 patients each. The demographic variables such as age, gender and weight were comparable among the three groups. There was no statistically significant difference among the three groups regarding age, sex and weight (Table 1).

In this study majority of group F patients (86.7%) had grade 0 myoclonus while only 6.7% had grade 1 and grade 2 myoclonus while no patients had grade 3 myoclonus. In the group D 13.3% of patients had grade 1 myoclonus while 86.7% had grade 2 myoclonus while no patients had grade 3 myoclonus. In the group P 3.3% had grade 1 myoclonus and 16.7% had grade 2 myoclonus while 80% had grade 3 myoclonus. There was statistical difference in myoclonus grading in between the groups. (p value<0.05) (Table 2).

Regarding the severity of pain after etomidate injection, in group F no patients had pain after etomidate induction while group D 13.3% had mild pain while 86.7% patients had moderate pain. In group P 50% had moderate pain and 50% had severe pain. There was statistically significant difference in pain score in between the groups. (p value<0.05) (Table 3).

Table 1: Demographic characteristic of the patients

	Group D (n=30)	Group F (n=30)	Group P (n=30)	p value
Age, years (Mean + SD)	35.733 + 9.4611	37.167 + 10.222	34.167 + 6.782	D&F(0.536) D&P(0.353) F&P(0.197)
Weight (Mean + SD)	59.167 + 10.198	56.50 + 7.938	57.233 + 5.117	D&F(0.202) D&P(0.353) F&P(0.724)
Gender, n (%)				
Female	10 (33.3)	15 (50.0)	14 (46.7)	D&F(0..295)
Male	20 (66.7)	15 (50.0)	16 (53.3)	D&P(0.429) F&P(1.000)

n- Number of patients, * p value < 0.05, SD- Standard deviation

Table 2: Distribution of myoclonus in between the group

			Group n (30)			Total
			D	F	P	
Myoclonus Grade	0	Count	0	26	0	26
		%	0.0%	86.7%	0.0%	28.9%
	1	Count	4	2	1	7
		%	13.3%	6.7%	3.3%	7.8%
	2	Count	26	2	5	33
		%	86.7%	6.7%	16.7%	36.7%
	3	Count	0	0	24	24
		%	0.0%	0.0%	80.0%	26.7%
Total		Count	30	30	30	90
		%	100.0%	100.0%	100.0%	100.0%
p Value		0.001(D&F), 0.001(D&P), 0.001(F&P)				

* p value < 0.05, n- number of patients

Table 3: Comparison of pain score in between the groups

			Group (n-30)			Total
			D	F	P	
Pain score	0	Count	0	30	0	30
		%	0.0%	100.0%	0.0%	33.3%
	1	Count	4	0	0	4
		%	13.3%	0.0%	0.0%	4.4%
	2	Count	26	0	15	41
		%	86.7%	0.0%	50.0%	45.6%
	3	Count	0	0	15	15
		%	0.0%	0.0%	50.0%	16.7%
Total		Count	30	30	30	90
		%	100.0%	100.0%	100.0%	100.0%
p value		0.001 (D & F) 0.001 (D & P) 0.001 (F & P)				

* p value < 0.05, n- number of patients

Table 4: Heart rate at 0, 5 and 10 minute following etomidate injection

		n	Mean	Std. Deviation	p Value
HR 0	D	30	76.933	7.4414	0.081(D&F)
	F	30	80.533	7.4636	0.416(D&P)
		30	78.600	8.7439	0.346(F&P)
	Total	90	78.689	7.9558	
HR 5	D	30	98.133	8.5812	0.001(D&F)
	F	30	83.933	8.0427	0.001(D&P)
		30	106.333	10.5971	0.001(F&P)
	Total	90	96.133	12.9712	
HR 10	D	30	88.333	7.6309	0.001(D&F)
	F	30	77.300	7.0229	0.028(D&P)
		30	92.667	7.8139	0.001(F&P)
	Total	90	86.100	9.8620	

Table 5: SBP at 0, 5 and 10 minute following etomidate injection

		n	Mean	Std. Deviation	p Value
SBP 0	D	30	126.933	14.1102	0.121(D&F)
	F	30	121.800	10.4664	0.065(D&P)
		30	120.800	13.2207	0.761(F&P)
	Total	90	123.178	12.8383	
SBP 5	D	30	149.467	13.6021	0.051(D&F)
	F	30	143.133	14.4000	0.251(D&P)
		30	145.800	7.8142	0.403(F&P)
	Total	90	146.133	12.4325	
SBP 10	D	30	126.467	10.0025	0.932(D&F)
	F	30	126.667	11.2689	0.397(D&P)
		30	124.467	4.5994	0.351(F&P)
	Total	90	125.867	9.0482	

SBP- Systolic blood pressure, * p value <0.05, n- number of patients

Table 6: DBP at 0, 5 and 10 minute following etomidate injection

		n	Mean	Std. Deviation	p Value
DBP 0	D	30	77.000	13.1804	0.051(D&F)
	F	30	82.567	8.3612	0.731(D&P)
		30	77.600	10.4042	0.079(F&P)
	Total	90	79.056	10.9978	
DBP 5	D	30	91.200	8.9381	0.857(D&F)
	F	30	90.867	6.5323	0.172(D&P)
		30	88.667	5.4414	0.235(F&P)
	Total	90	90.244	7.1317	
DBP 10	D	30	82.133	7.8245	0.937(D&F)
	F	30	82.000	5.7054	0.256(D&P)
		30	80.200	5.9271	0.290(F&P)
	Total	90	81.444	6.5413	

DBP- Diastolic blood pressure, * p value < 0.05, n- number of patients

No significant difference was seen in heart rate at 0 min between the groups while significant difference was seen in all the groups in heart rate at 5 and 10 min (p value<0.05) (Table 4). No significant difference was seen for SBP between any group when compared to each other at (0, 5 and 10 min) (Table 5). Diastolic BP also showed no significant difference when all the groups were compared to each other at 0, 5 and 10 min. (Table 6).

4. Discussion

This study evaluated the effect of fentanyl and dexamethasone pretreatment for prevention of etomidate induced pain and myoclonus. There was no statistically significant difference among the groups with respect to demographic profile in terms of age, weight and sex and this did not have any clinical implications on the study.

Stochem et al[9] reported that patients premedicated with Fentanyl decreased Etomidate induced myoclonus in dose dependent manner but increases risk of apnea. None of the patients who received premedication of 500 μg before anaesthesia induction using etomidate had myoclonus but all developed apnea. So in our study 100 μg of Fentanyl was given and no respiratory depression was seen.

Studies using dexamethasone for etomidate induced myoclonus have not been done previously but dexamethasone has been shown to reduce incidence of opsoclonus myoclonus ataxia syndrome (OMS) by 69% reduction,[8] so we decided to include dexamethasone in our study. The dose of 8 mg was chosen as no decrease in incidence of myoclonus was seen by 4 mg dose.

The incidence of myoclonus also depends upon the speed of injection and dosage of etomidate. Doenicke et al stated that increase in dose of etomidate was associated with increased frequency of myoclonus.[10]

Vijayaragavan et al found that decrease in incidence of pain (3.33%) on injection of etomidate on pretreatment with 5 μg /kg dose of fentanyl as compared to 2 μg /kg dose for which incidence rate was 30%,[11] while in our study no pain was seen in fentanyl pretreated group with the dose of 2 μg /kg.

We took into account of heart rate, systolic blood pressure and diastolic blood pressure in this study as their values can be of significance in determining adverse effects of opioids or dexamethasone. In our study we found that there was no significant difference in HR at 0 minute in between groups. However there was significant difference between HR at 5 and 10 minutes. HR was much reduced in groups F and D as compared to group P which might be due to reduced pain and myoclonus due to etomidate injection in group F and D. (Table 4)

Isitemiz et al. observed HR and BP measurements after induction were significantly lower in fentanyl group as compared to no pretreatment group.[11] Ko et al. also found that SBP, DBP and HR to be significantly lower in case of fentanyl pretreatment group as compared to control.[12] Ko et al. also found that SBP, DBP and HR to be significantly lower in case of fentanyl pretreatment group as compared to control.[12]

The exact mechanism of myoclonus due to etomidate is still not clear. Doenicke et al. suggested myoclonus arises from subcortical disinhibition and not because of epileptic focus.[2] Disruption of the cortical GABA mediated inhibition makes skeletal muscles susceptible to spontaneous nerve transmissions thereby leading to myoclonic movements.[13]

Our study has a few limitations, first we chose to show the effect of dexamethasone on etomidate induced myoclonus on the basis of studies conducted on paediatric population. No evidence has been shown to reduce the incidence of myoclonus using dexamethasone in adult population. We chose the dose of 8mg for dexamethasone whereas in previous studies conducted in pediatric population high dose pulsatile therapy has been used. Also dexamethasone dose is not weight based in this study.

5. Conclusion

Dexamethasone significantly reduces the incidence of myoclonus as compared to no pretreatment. However it is less effective when compared to fentanyl pretreatment. Dexamethasone also reduces the pain incidence significantly but this is significantly less as compared to fentanyl.

6. Source of Funding

Nil.

7. Conflicts of Interest

Nil.

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