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A STUDY TO ASSESS THE EFFECT OF PRETREATMENT WITH ROCURONIUM BROMIDE IN REDUCTION OF ETOMIDATE INDUCED MYOCLONUS DURING ANESTHETIC INDUCTION

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ABSTRACT

Introduction: Induction agents are drugs that, when given intravenously in an appropriate dose, cause rapid loss of consciousness. They are also used to maintain anesthesia by intravenous infusion, as the sole drug for short procedures done under local anesthesia and to provide conscious sedation in intensive care unit.

Materials and Methods: This study is a prospective, randomized, double blind study conducted in hospitals attached to Bangalore medical college & Research Institute, Bangalore. A written informed consent was obtained from all patients included in the study. As per protocol, clearance was taken from institutional ethical clearance. The incidence of myoclonus in the non pretreatment group was estimated to be 80% based on previous studies. To detect a 50% difference in the incidence of myoclonus at a confidence interval of 95% and keeping a power of 80%, a minimum of 35 patients in each group was required.

Results: In the Rocuronium group, 40% had Myoclonus and in Saline group, 75% had Myoclonus. There was significant difference in Myoclonus incidence between two groups. Odds ratio was 4.5. I.e. Incidence of Myoclonus was 4.5 times higher in Saline group than in Rocuronium group. For Grade 1 Myoclonus, odds ratio was 1.92. There was no significant difference in Grade 1 Myoclonus between two groups. For Grade 2 Myoclonus, odds ratio was 3.733. I.e. Grade 2 Myoclonus was 3.733 times higher in Saline group compared to Rocuronium group. There was significant difference in Grade 2 Myoclonus between two groups. For Grade 3 Myoclonus, odds ratio was 14.4. I.e. Grade 3 Myoclonus was 14.4 times higher in Saline group compared to Rocuronium group. There was significant difference in Grade 3 Myoclonus between two groups.

Conclusion: Pretreatment with priming dose (0.06mg/kg) of rocuronium bromide modifies the induction of anaesthesia with etomidate by reducing the incidence of myoclonic movements and preserves the advantages of etomidate: cardiovascular stability, minimal respiratory depression and cerebro-protective effects.

KEYWORDS : Induction agents, Rocuronium, Myoclonus, etomidate.

INTRODUCTION

Induction agents are drugs that, when given intravenously in an appropriate dose, cause rapid loss of consciousness. They are also used to maintain anesthesia by intravenous infusion, as the sole drug for short procedures done under local anesthesia and to provide conscious sedation in intensive care unit.[1]

Etomidate is an intravenous anaesthetic, a carboxylated imidazole derivative widely used for induction and maintenance of anaesthesia. It is characterized by hemodynamic stability, minimal respiratory depression and cerebro-protective effects. The effect of increased coronary perfusion along with negligent sympathetic response makes it an ideal induction agent of choice in all ischemic heart disease patients.[2]

Etomidate as a hypnotic agent was introduced into clinical practice in 1972 and is still widely used due to its several advantages, extremely stable hemodynamic profile, minimal histamine release, cerebral protection, and pharmacokinetics enabling rapid recovery after either a single dose or a continuous infusion. The effect of etomidate on cardiac output, myocardial oxygenation and its wide therapeutic index is approximately 6 fold greater than thiopentone and propofol.[3]

However, it is associated with some disturbing side effects, such as pain on injection, postoperative nausea and vomiting, adrenal suppression, superficial thrombophlebitis and myoclonus.[4]

Pain on injection, superficial thrombophlebitis and hemolysis associated with etomidate induction were related to the vehicle propylene glycol[2], 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, however, the incidence of myoclonus during induction was not affected by the solvent and 50-80% of patients who did not receive premedication experience myoclonus.The mechanism of etomidate induced myoclonus appears to be disinhibition of subcortical structures that normally suppress extrapyramidal motor activity.[5]

There are few studies which have evaluated the effects of rocuronium on myoclonus after etomidate injection.[6]

This study is aimed to investigate the effects of pretreatment with priming dose of rocuronium on the incidence and severity of myoclonus during anesthesia induction with etomidate.

MATERIALS AND METHODS

This study is a prospective, randomized, double blind study conducted in hospitals attached to Bangalore medical college & Research Institute, Bangalore. A written informed consent was obtained from all patients included in the study. As per protocol, clearance was taken from institutional ethical clearance.

Study Group:

The incidence of myoclonus in the non pretreatment group was estimated to be 80% based on previous studies. To detect a 50% difference in the incidence of myoclonus at a confidence interval of 95% and keeping a power of 80%, a minimum of 35 patients in each group was required.

To increase the validity of the study, we included 40 patients in each group with total sample size of 80.

Inclusion Criteria:

· ASA physical status classes I and II.

· Age between 18 and 60 years
· Patients who gave written informed consent

Exclusion Criteria:
· Patient not willing to participate in the Study.
· Patients with cardiovascular and respiratory disease.
· Patients with chronic abuse of alcohol and psychotropic agents.
· Patients with hepatic, renal disease and epilepsy.
· Patients with adrenal disease.
· Pregnant and lactating women.

Data collection was undertaken during the period December 2017 and May 2019.

A thorough pre anesthetic assessment was done for all patients the day before surgery. No special investigations were done pertaining to study. Patients were evaluated for any systemic diseases. Basic investigations like hemoglobin, total and differential count, ECG, chest X-ray, urine routine were carried out for all patients. The procedure for general anaesthesia and study was explained to the patients. After obtaining informed written consent from the patients, participation consent and surgeon's consent, 80 patients were randomized using numbers generated from www. Random . org website and assigned to one of the two groups.

Control Group: Group S [Saline group]-40 patients

Study Group: Group R [Rocuronium group]-40 patients

Patients were advised to fast from night before the day of surgery. They were given tablet alprazolam 0.5mg and tablet ranitidine 150mg previous night.

On the day of surgery, anaesthesia workstation and monitors were checked. Appropriate size endotracheal tubes, working laryngoscope with medium and large sized blades, stylet and working suction apparatus were kept ready before the induction of general anesthesia. Emergency drug tray consisting of atropine, adrenaline, ephedrine were also kept ready for any eventuality.

Once the patients "nil peroral status was confirmed, patients were shifted to operating room (OR). After placing patient in supine position on OR table, an intravenous line was secured. Standard monitoring devices like pulse oximeter (SpO_2), non-invasive blood pressure (NIBP),echocardiogram (ECG),Neuromuscular junction (NMJ) and end tidal carbon dioxide ($ETCO_2$) monitors were connected. Baseline hemodynamic parameters were assessed.

All patients were pre-oxygenated with 100% oxygen for 3 minutes before induction of anaesthesia and all patients were premedicated with Inj glycopyrrolate 0.01mg/kg IV. The study syringes were prepared by an anaesthetist not involved in the procedure. Patient and anaesthesia provider were not aware of the study drug. Thus both the observer and the patient were blinded. Group R patients received 0.06mg/kg of Rocuronium Bromide diluted to 5ml IV over 30 seconds and the group S patients received 5ml of normal saline over 30 seconds. Oxygen supplementation through mask was given during this period. After 3 minutes of the study drug, Inj etomidate 0.3mg/kg was administered over 30 seconds. Immediately pain on injection and myoclonus evaluation was done. After 2 minutes of etomidate induction, Inj. fentanyl 2µg/kg and inj midazolam 0.05mg/kg was administered, and tracheal intubation facilitated with inj. vecuronium 0.1mg/kg. Anesthesia is maintained as per institutional protocol.

After the surgery, residual neuromuscular block was reversed using inj. Neostigmine 0.05mg/kg and inj glycopyrrolate 0.01mg/kg. Trachea was extubated after adequate recovery of muscle power.

Patients were monitored post-operatively.Patients with nausea or vomiting in the postoperative period received inj. Ondanseton 4mgIV as rescue antiemetics.

Parameters Measured:-
1) Heart rate (HR), oxygen saturation (SpO2), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), end tidal carbon dioxide (ET CO_2), before premedication, before pretreatment, after premedication, after pretreatment and after etomidate at 5 minutes interval till the completion of surgery.

2) Pain evaluation, myoclonus evaluation, time to extubation (from stoppage of inhalational agent to extubation of trachea) and recovery profile (from stoppage of inhalational agent to opening of eyes) were evaluated accordingly.

3) Immediate post-operative HR, SpO2, SBP, DBP, MAP, RR, nausea and vomiting will be monitored every half hourly for 2 hours.

4) Adverse effects such post-operative nausea , vomiting (PONV) if any were observed.

Statistical Analysis:
In our study, all the data needed was extracted onto the paper case information proforma and then converted into electronic data base in excel software. The variables were checked for accuracy and completeness before entry. Results on continuous measurements are presented on Mean±SD(Min-Max) and results on categorical measurements are presented in number (%). Significance is assessed at 5% level of significance.

RESULTS

The present study was undertaken in 80 ASA 1 and ASA 2 patients of both sex aged between 18-55 years, scheduled for elective surgeries under general anaesthesia. The patients were divided into 2 groups, Group S (saline) and Group R (rocuronium).

Table 1: General Profile Of Subject's Comparison Between Two Groups

	Group			
	Rocuronium		Saline	
	Mean	SD	Mean	SD
Age (yr)	35.22	11.16	37.10	9.60
Weight (kg)	56.61	10.80	56.55	9.80
Height (cm)	157.87	7.44	156.52	8.50
BMI	22.77	4.36	23.13	3.72

In our study, Mean age of subjects in Rocuronium group was 35.22 ± 11.16 years, in saline group was 37.10 ± 9.60 years

Mean weight of subjects in Rocuronium group was 56.61 ± 10.80 Kgs, in saline group was 56.55 ± 9.80 Kgs.

Mean Height of subjects in Rocuronium group was 157.87 ± 7.44 cms, in saline group was 156.52 ± 8.50 cms.

Mean BMI of subjects in Rocuronium group was 22.77 ± 4.36, in saline group was 23.13 ± 3.72.

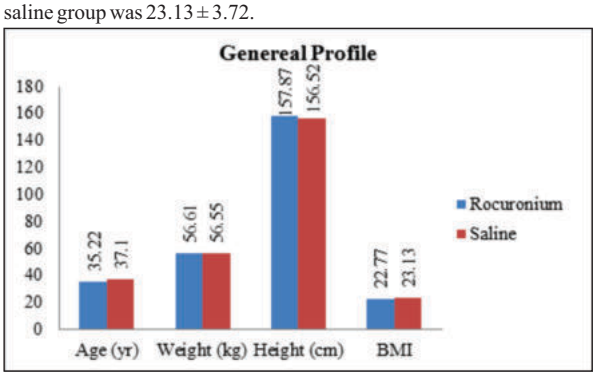

Figure 1: Bar Diagram Showing General Profile Of Subjects Comparison Between Two Groups

Table 2: ASA Grade Comparison Between Two Groups

		Group			
		Rocuronium		Saline	
		Number	%	Number	%
ASA grade	1	36	90.0%	28	70.0%
	2	4	10.0%	12	30.0%

$\chi 2 = 5$, df = 1, p = 0.025*

In Rocuronium group, 90% had ASA grade 1 and 10% had ASA grade 2, in Saline group, 70% had ASA grade 1 and 30% had ASA grade 2.

Table 3: MP Grade Comparison Between Two Groups

		Group			
		Rocuronium		Saline	
		number	%	number	%
MP grade	1	8	20.0%	10	25.0%
	2	29	72.5%	27	67.5%
	3	3	7.5%	3	7.5%

$\chi 2 = 0.294$, df = 2, p = 0.863

In Rocuronium group, 20% had MP grade 1, 72.5% had grade 2 and 7.5% had grade 3, in Saline group, 25% had MP grade 1, 67.5% had grade 2 and 7.5% had grade 3. There was no significant difference in MP grade between two groups.

Table 4: Duration Of Surgery Comparison Between Two Groups

	Group				p value
	Rocuronium		Saline		
	Mean	SD	Mean	SD	
Duration of surgery	97.37	37.19	111.94	33.34	0.084

Mean duration of surgery in Rocuronium was 97.375 ± 37.192 min and in saline group was 111.94 ± 33.34 min. There was no significant difference in duration of surgery between two groups.

Table 5: Myoclonus Grading Comparison Between Two Groups

		Group					
		Rocuronium		Saline		Total	
		number	%	number	%	number	%
Myoclonus grading	0	24	60.0%	10	25.0%	34	42.5%
	1	5	12.5%	4	10.0%	9	11.2%
	2	9	22.5%	14	35.0%	23	28.7%
	3	2	5.0%	12	30.0%	14	17.5%

$\chi 2 = 14.106$, df = 3, p = 0.003*

In Rocuronium group, 60% had grade 0, 12.5% had grade 1, 22.5% had grade 2 and 5% had grade 3. In Saline group, 25% had grade 0, 10% had grade 1, 35% had grad 2 and 30% had grade 3. There was significant difference Myoclonus grading between two groups.

Table 5: Incidence Of Myoclonus Comparison Between Two Groups

		Group				p value
		Rocuronium		Saline		
		number	%	number	%	
Myoclonus grading	Total Incidence	16	40%	30	75%	0.0015*
	Absent	24	60.0%	10	25.0%	
	Grade 1	5	12.5%	4	10.0%	0.3921
	Grade 2	9	22.5%	14	35.0%	0.018*
	Grade 3	2	5.0%	12	30.0%	0.0003*

In the Rocuronium group, 40% had Myoclonus and in Saline group, 75% had Myoclonus. There was significant difference in Myoclonus incidence between two groups. Odds ratio was 4.5. I.e. Incidence of Myoclonus was 4.5 times higher in Saline group than in Rocuronium group.

For Grade 1 Myoclonus, odds ratio was 1.92. There was no significant difference in Grade 1 Myoclonus between two groups.

For Grade 2 Myoclonus, odds ratio was 3.733. I.e. Grade 2 Myoclonus was 3.733 times higher in Saline group compared to Rocuronium group. There was significant difference in Grade 2 Myoclonus between two groups.

For Grade 3 Myoclonus, odds ratio was 14.4. I.e. Grade 3 Myoclonus was 14.4 times higher in Saline group compared to Rocuronium group. There was significant difference in Grade 3 Myoclonus between two groups.

In Rocuronium group, 77.5% had grade 0, 20% had grade 1 and 2.5% had grade 2. In Saline group, 57.5% had grade 0, 30% had grade 1 and 12.5% had grad 2. There was no significant difference Pain on injection grading between two groups.

Table 6: Pain On Injection Grading Comparison Between Two Groups

		Group					
		Rocuronium		Saline		Total	
		Count	%	Count	%	Count	%
Pain on injection grading	0	31	77.5%	23	57.5%	54	67.5%
	1	8	20.0%	12	30.0%	20	25.0%
	2	1	2.5%	5	12.5%	6	7.5%

$\chi 2 = 4.652$, df = 2, p = 0.098

Table 7: Time For Loss Of Palpebral Reflex Comparison Between Two Groups

	Group				p value
	Rocuronium		Saline		
	Mean	SD	Mean	SD	
Time for loss of palpebral reflex(sec)	42.03	18.25	45.22	8.58	0.319

Mean Time for loss of palpebral reflex in Rocuronium group was 42.03 ± 18.25 min and in saline group was 45.22 ± 8.58 sec. There was no significant difference in Time for loss of palpebral reflex between two groups.

Table 8: Intraoperative Heart Rate (HR) Comparison Between Two Groups At Different Time Intervals

	Group				p value
	Rocuronium		Saline		
	Mean	SD	Mean	SD	
Baseline	91.68	19.77	85.65	13.03	0.112
After Premed	88.88	16.79	85.83	11.75	0.349
After Pretreatment	88.90	20.69	83.87	10.98	0.183
5min	92.23	18.97	91.32	18.03	0.828
10min	95.20	22.89	87.80	11.73	0.073
15min	89.62	16.12	85.38	12.72	0.198
20min	90.64	16.41	85.05	13.07	0.098
25min	89.54	17.56	85.35	12.37	0.223
30min	90.23	17.00	84.15	11.91	0.069
35min	92.62	16.68	83.90	10.81	0.007*
40min	89.82	16.21	84.40	12.31	0.100
45min	89.13	16.16	83.80	12.77	0.109
50min	88.24	15.89	84.13	13.23	0.221
55min	88.16	16.34	82.90	12.55	0.118
60min	87.36	15.81	81.97	12.69	0.107
1hr5min	83.70	14.21	82.23	12.55	0.643
1hr10min	84.90	16.28	84.54	12.88	0.917
1hr15min	80.58	14.54	85.20	11.90	0.187
1hr20min	81.65	15.89	86.20	13.69	0.250
1hr25min	80.65	15.24	83.67	13.86	0.456
1hr30min	81.74	12.86	83.74	12.72	0.584
1hr35min	83.25	11.77	87.07	13.30	0.312
1hr40min	86.35	13.62	89.32	13.74	0.473
1hr45min	83.06	17.80	86.91	11.68	0.426
1hr50min	84.85	14.89	89.53	11.98	0.333
1hr55min	83.64	13.76	87.06	13.61	0.523
2hr	81.33	12.87	88.76	11.48	0.145
2hr5min	80.56	14.66	86.79	13.64	0.311
2hr10min	81.11	14.98	90.57	15.45	0.162
2hr15min	80.43	18.38	88.40	8.88	0.250
2hr20min	84.40	22.80	85.00	7.84	0.946
2hr25min	84.20	24.25	85.63	10.07	0.884
2hr30min	80.40	19.55	85.50	10.21	0.545
2hr35min	81.75	23.07	84.63	10.13	0.764
2hr40min	75.50	25.68	91.50	13.43	0.177
2hr45min	77.50	25.09	94.00	17.56	0.252

In the study there was significant difference in mean Intraoperative Heart rate between two groups at 35 min. At this interval mean HR was significantly higher in Rocuronium group compared to saline group.

There was no significant difference in mean HR between two groups at other intervals.

In our study there was significant difference in mean Intraoperative SpO2 between two groups at 50min and 60 min. At these intervals mean SpO2 was significantly higher in Saline group compared to Rocuronium group.

There was significant difference in mean Postoperative SpO2 between two groups at 1hr and 2hr. At these intervals mean SpO2 was significantly higher in Saline group compared to Rocuronium group. Mean SpO2 maintained above 99% at all times.

There was no significant difference in mean SpO2 between two groups at other intervals.There was no significant difference in mean SBP between two groups at all intervals.

In the study there was significant difference in mean Intraoperative DBP between two groups at Baseline, after premed, after pretreatment, 5min, 10 min, 15 min and 25min. At these intervals mean DBP was significantly higher in Saline group compared to Rocuronium group. Mean DBP maintained above 70 mmHg at all times.

There was no significant difference in mean DBP between two groups at other intervals.

In the study there was significant difference in mean Intraoperative MAP between two groups at after premed, after pretreatment, 5min, 10min, and 15 min. At these intervals mean DBP was +significantly higher in Saline group compared to Rocuronium group. Mean MAP maintained above 85mmHg at all intervals.

There was no significant difference in mean MAP between two groups at other intervals.

In the study there was significant difference in mean Intraoperative EtCo2 between two groups at 5 min to 25 min, 40 min, 50 min, 1hr10min, 1hr15min and 1hr20min. At these intervals mean EtCo2 was significantly higher in Saline group compared to Rocuronium group.

There was no significant difference in mean EtCo2 between two groups at other intervals.

In the study there was no significant difference in mean RR at Postoperative respiratory rate (RR) between two groups.

Mean Time taken for onset (TOF-0) in Rocuronium group was 3.75±0.776 and in Saline group was 4.1±0.777 min. There was significant difference in mean time for onset between two groups.

Mean Duration (TOF-3) in Rocuronium group was 51.35±4.179 and in Saline group was 50.55±4.361 min. There was no Significant difference in mean duration between the two groups.

Mean recovery profile in Rocuronium group was 351.20 ± 187.21 min and in Saline group was 245.23 ± 119.38 sec. There was significant difference in mean recovery profile between two groups.

Mean Time To Extubation in Rocuronium group was 368.88 ± 189.77 min and in Saline group was 265.77 ± 123.30 sec. There was significant difference in mean Time To Extubation between two groups. Post operative nausea grade was significantly higher in Rocuronium group at ½ hr and 1½hr compared to Saline group. At other intervals there was no significant difference in Post operative nausea between two groups.

In the study there was no significant difference in post operative vomiting grade between two groups from 0 hr to 2 hrs.

Table 9: Drugs Comparison Between Two Groups At Different Time Intervals

		Group			
		Rocuronium		Saline	
		Count	%	Count	%
Drugs	Nil	30	75.0%	31	77.5%
	Ondansetron	10	25.0%	9	22.5%

$\chi 2 = 0.069$, df = 1, p = 0.793

In Rocuronium group, Ondansetron was used in 25% of subjects and in Saline group, Ondansetron was used in 22.5%. There was no significant difference in drugs used between two groups.

DISCUSSION

Induction of general anesthesia initially began with gases or vapours, which was an unpleasant experience for patients. The introduction of intravenous anaesthetic agents was a milestone in the development of anesthesia[1]. Etomidate is an intravenous anaesthetic, a carboxylated imidazole derivative widely used for induction and maintenance of anaesthesia. The beneficial properties of etomidate include hemodynamic stability, minimal respiratory depression, cerebral protection, rapid recovery after a single dose or continuous infusion[2]. However it has limitation of inducing myoclonus. Myoclonus is observed in 50-80% of patients after etomidate administration. Etomidate could induce myoclonic movements as a side effect in unpremedicated patients during induction of anesthesia with unknown mechanism. Myoclonus has made etomidate an undesirable drug to many anesthesiologists[3,4,5,6].

Our study was a prospective randomized double blind controlled study carried out at hospitals attached to Bangalore Medical College and Research Institute, Bengaluru. 80 ASA I and II patients undergoing elective surgery were randomized into 2 groups of 40 patients in each.Group R patients received 0.06mg/kg of Rocuronium Bromide diluted to 5ml IV over 30 seconds and the group S patients received 5ml of normal saline over 30 seconds as pretreatment.

Patients in our present study were middle aged (42.5 ± 17.3 years old) and not very sick (ASA I–II). Although it is speculated that a young age could influence the incidence of myoclonus, we have found no such influence of age on the incidence of myoclonic movements after etomidate administration. As the power analysis of the present study was based on the assumption that 50% of patients would experience myoclonic movements, the finding of such movements in almost half of the patients in the control group implies that the present investigation is well designed and reflects the estimate of a population parameter. In the light of the observation of a 30% reduction in the incidence of myoclonus in our study, we assume that our results could be of clinical value.

In our study, the demographic data were comparable for age, sex, weight. BMI, ASA grade, type of surgeries and duration of surgeries in both the groups.

A study conducted by Salman N and group to compare the efficacy of pretreatment with dexmedetomidine 0.5µg/kg IV over 60s and midazolam 0.25mg/kg on etomidate induced myoclonus, it was observed that both agents did not cause severe myoclonus. There was no statistically significant difference in mild and moderate myoclonus between the two groups.[16]

In our study no significant difference in recovery profile and time to extubation was observed between the two groups.

Low-dose priming with rocuronium could effectively suppress etomidate-induced myoclonus. This study provides valuable clinical data to be used in many hospital settings. By using low-dose rocuronium as premedication, etomidate as a valuable drug could be properly used in induction of anesthesia without myoclonus as a prominent adverse effect.

CONCLUSION

Pretreatment with priming dose (0.06mg/kg) of rocuronium bromide modifies the induction of anaesthesia with etomidate by reducing the incidence of myoclonic movements and preserves the advantages of etomidate: cardiovascular stability, minimal respiratory depression and cerebro-protective effects.

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