Original Research Article

Comparative evaluation of efficacy and safety of Atracurium besylate and different doses of Cisatracurium besylate using peripheral nerve stimulator

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Abstract

Background and Aims: Neuromuscular blockers have become essential part of anaesthesiologist armamentarium. They aid endotracheal intubation, mechanical ventilation, reduce anaesthetic requirement, prevent patient movement and facilitate surgery. The ideal neuromuscular relaxant is an agent which has a quick onset time and short duration of action. We compare the efficacy of Atracurium besylate and different doses of Cisatracurium besylate in patients undergoing elective abdominal surgeries under general anesthesia, Considering onset time, intubating conditions and duration of action. **Material and methods:** Randomized trial was conducted in ninety patients of ASA grade I and II ,posted for elective abdominal surgeries were randomly allocated into three groups, of 30 patients each, depending on muscle relaxant and its doses used for intubation. **Results**: In present study, we found that cisatracurium with the dose of 0.2 mg/kg B.W. is better neuromuscular blocking agent for intubation than cisatracurium 0.1mg/kg B.W. and atracurium 0.5 mg/kg B.W. **Conclusion**: Faster onset, longer duration of action with larger doses of cisatracurium and with good to excellent intubating conditions makes cisatracurium a more promising alternative muscle relaxant agent for tracheal intubation in clinical practice.

Keywords: Atracurium besylate , Cisatracurium besylate, Intubating conditions, neuromuscular blockers.

Introduction

The introduction of neuromuscular blocking drugs revolutionized the practice of anaesthesia. After the introduction of muscle relaxants, anaesthesia underwent a conceptual change. Anaesthesia was redefined as a triad of narcosis, analgesia and muscle relaxation, specific drugs being used to produce each of these effects[1].The ideal neuromuscular relaxant is an agent which has a quick onset time and short duration of action. The ideal drug should not accumulate when given during a continuous infusion, has no active metabolites with neuromuscular blocking properties, and is free of toxic adverse effects[2].The elimination of such a drug should be through spontaneous breakdown within the plasma, rather than relying on an organ system for removal.Curare was first introduced in clinical anaesthesia by Griffith Jhonson et al[3]. (1942), it changed the pattern of anaesthetic practice. This drug is eliminated unchanged in the urine or bile. Prolonged activity can be expected with renal or hepatic disease. Doxacurium chloride is a long acting bis-benzylisoquinolinium. It has a high potency (ED95=0.03 mg/kg) and is devoid of dose related cardiovascular effects[4].

Succinylcholine was used to facilitate endotracheal intubation due to early onset and short duration of action, but its use is either hazardous or contraindicated in some conditions like burns, hyperkalemia, severe muscle trauma and myopathies. These side effects of succinylcholine causes search of new nondepolarizing muscle relaxant and promoting their use. Pancuronium introduced in anaesthesia by Baird et al[5]. (1967) was tried in higher doses for intubation, but it was also found to be associated with profound cardiovascular side effects e.g. tachycardia and hypertension[5].Pipecuronium is an aminosteroid neuromuscular blocking agent that has an onset time and duration of action similar to pancuronium. Unlike pancuronium however, it has no significant effects on the cardiovascular system.Rocuronium, an intermediate acting nondepolarizing neuromuscular blocking agent has replaced succinylcholine, because it has a more rapid onset of action and is gold standard for intubation[6]. Atracurium, an intermediate acting nondepolarizing neuromuscular blocking agent, is primarily metabolized by ester hydrolysis and has extra safe guard of metabolism by non-enzymatic Hoffmann degradation[7], so can be safely used in patients with hepatic and renal diseases, but histamine release in higher doses limit its use in the patients of asthma. Cisatracurium is a newer nondepolarizing neuromuscular blocking agent with intermediate action. It is the isomer of atracurium, and has the neuromuscular blocking potency approximately three fold that of atracurium.Cisatracurium, is devoid of histamine induced cardiovascular effects in the range of clinical doses. Also, cisatracurium is metabolized by Hoffmann elimination to laudanosine and a monoquaternary acrylate such as atracurium[8]. Laudanosine is dependent on the liver and kidney for its elimination and its concentration is elevated in patients with hepatic or renal disease[9]. Unlike atracurium, about five times less laudanosine is produced with cisatracurium, and accumulation of this metabolite is not thought to be of any consequence in clinical practice[10]. This made cisatracurium an appealing alternate to older agents for muscle relaxation. Mellinghoff et al[11]. (1996) studied 80 patients randomized to receive either cisatracurium (n=40) or atracurium (n=20)and compared the time course of neuromuscular block. They estimated that onset times were 3.1±1.0min with cisatracurium and 2.3±1.1min with atracurium (*P*=0.008).**Kirov kel et al[12].** (2004) compared the neuromuscular blocking effect of cisatracurium and

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atracurium and concluded that cisatracurium is slower in onset with higher potency than atracurium.Magdy omera et al[13]. (2005) compared rocuronium with cisatracurium and they found that rocuronium has rapid onset and both are potent and safe without apparent histamine release.These above studies inspired us to conduct a study to compare the efficacy and safety of cisatracurium in doses of 0.1mg/kg B.W. and 0.2mg/kg B.W. to compare with standard dose of atracurium 0.5 mg/kg B.W. in patients undergoing elective abdominal surgeries under general anesthesia.

Material and Methods

The present study was carried out in the "Department of Anaesthesiology", Shyam Shah Medical College & associated Sanjay Gandhi and Gandhi Memorial Hospitals, Rewa (M.P.) from April 2018 to March 2019.After getting clearance from Institutional Ethics Committee (IEC), 90 patients of 18-60 years of age of either sex, ASA grade I-II and mallampatti grade I-II, posted for elective abdominal surgeries under general anaesthesia, were selected for the study.Patients who refused to give consent for the study, with psychological disorders, with neuromuscular, cardiovascular, renal and hepatic disease,on medication known to interact with neuromuscular blocking drugs e.g. antibiotics (aminoglycosides and tetracycline), antidepressants, anticonvulsants, antiarrhythmics (calcium channel blockers and quinidine) and magnesium sulphate, history of COPD, asthma and allergy were excluded from the study.

A detailed history of all selected patients were taken. A thorough pre-anaesthetic evaluation including the airway assessment was performed. The patients were explained about the entire procedure and informed consent was taken, in a language of their understanding.

The patients were randomised using a computer based randomisation software, "Random Allocation Software 1.0" in 3 groups of 30 patients each, depending on muscle relaxant and its doses used for intubation as under:

Group A: Patients received atracurium with initial dose of 0.5 mg/kg.

Group B: Patients received cisatracurium with initial dose of 0.1 mg/kg.

Group C: Patients received cisatracurium with initial dose of 0.2 mg/kg.

All patients were kept nil by mouth for atleast 6 hours prior to surgery. The patients were shifted to the operation theatre. Monitor was attached and preoperative baseline parameters like heart rate, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), oxygen saturation (SPO_2), end tidal CO2 ($EtCO_2$) and electrocardiographic (ECG) tracings were observed and carefully recorded. Intravenous line was secured. All the patients were pre-medicated with Inj. Midazolam 0.05mg/kg B.W. and Inj. Fentanyl 2mcg/kg B.W. given intravenously. Preoxygenation was done with 100% oxygen for 3 min. Anaesthesia was induced with Inj. Propofol 2.5mg/kg B.W. intravenously.Neuromuscular blockade was measured by twitch height in response to ulnar nerve stimulation. For monitoring of neuromuscular transmission, two surface electrodes of peripheral nerve stimulator were fixed over the path of ulnar nerve. The distal electrode was placed at the level of the wrist on the ulnar surface at the flexor crease, as close to the nerve as possible. The second electrode was placed 1-2cm proximal to the first, parallel to the flexor carpi ulnaris tendon. The negative (black) lead wire was attached to the distal electrode and the positive (red) lead wire was attached to the proximal. The transducer fixed on corresponding thumb and response was to see the thumb twitching.After a stable base line period of at least 5 min, calculated dose of neuromuscular blocking agent in coded syringes (drug prepared and coded by fellow resident) was injected intravenously. After 2 min, endotracheal intubation was attempted using proper size tube. Time from injection of muscle relaxant to > 90 % suppression of single twitch height was noted and considered as onset time. If intubation unsuccessful, it was reattempted after 30 seconds, but for all practical purposes the intubating conditions at first attempt were taken in to consideration and the condition of intubation was assessed clinically and recorded by a score as used by R. Cooper et al[14]. (1992).

Intubating condition

	Jaw relaxation	Vocal cords	Response to intubation
0	Poor(impossible)	Closed	Severe coughing or bucking
1	Minimal(difficult)	Closing	Mild coughing
2	Moderate(fair)	Moving	Slight diaphragmatic movement
3	Good(easy)	Open	None

Overall intubating condition

Intubating condition	Score	Remarks
Excellent	8-9	Clinically Acceptable
Good	6-7	
Fair	3-5	Clinically not Acceptable
Poor	0-2	

Correct placement of endotracheal tube was confirmed by auscultation and end tidal carbon dioxide ($EtCO_2$) values. After confirmation and fixation of endotracheal tube all patients were maintained on 70% N2O+ 30%O2 and Isoflurane. Time from injection to reappearance > 25% of twitch height or any respiratory movement in breathing bag and notch in capnography whichever is earlier was noted and considered as duration of action. Further dose of neuromuscular blocking agent was given if needed.

At the end of surgical procedure, the reversal of residual neuromuscular block was done by administration of neostigmine 0.05mg/kg B.W. and glycopyrrolate 0.01mg/kg B.W. mixture through slow IV injection. Patient were extubated after orotracheal suction and then oxygenated for 5 min and shifted to post anaesthesia care unit (PACU) for observation.

Statistical analysis: Statistical analysis was performed by using SPSS version 20. Quantitative data were expressed as the means ± SD, while qualitative data were expressed as numbers and percentages (%). ANOVA test was used to test significance of difference for quantitative variables (HR, BP) that follow normal distribution and chi square was used to test the significance of difference for qualitative variables(sex). A probability value (*P*-value)<0.05 was considered statistically significant.

Results

Table 1: Demographic Distribution of age of patients between groups

Parameter (Mean ± SD)	Group A	Group B	Group C	P value	Group A vs Group B (P value)	Group A Vs Group C (P value)	Group B vs GroupC (P value)
Age (in years) (Mean ± SD)	39.07 ± 12.758	44.10 ± 14.366	37.67 ± 12.631	0.149	0.437	1.000	0.192

Table 1 shows that there is no statistically significant difference regarding age of patient . Mean age og group A, B & C patients was 39.07 ± 12.758, 44.10 ± 14.366 & 37.67 ± 12.631 respectively.

Table 2: Comparative evaluation of onset of time between groups.

Parameter (Mean ± SD	Group A	Group B	Group C	P value	GroupAvsGroupB (P value)	GroupAvs Group C (P value)	GroupBvs Group C (P value)
Onset Time (min)	2.917 ± 0.302	3.857 ± 0.320	2.55 ± 0.294	< 0.001	< 0.001	<0.001	< 0.001

Table 2 shows the mean onset time was 2.917 ± 0.302 min in group A, 3.857 ± 0.320 min in group B and 2.55 ± 0.294 in group C. Time of onset was found to be significantly lower with group A than group B. Group C showed onset time that was significantly lower than with group A and group B (P <0.001).

Table 3: Comparative evaluation of duration of action between groups

Parameter (Mean ± SD	Group A	Group B	Group C	P value	Group A vs Group B (P value)	Group A vs Group C (P value)	Group B vs Group C (P value)
Duration of Action (Minutes)	42.93 ± 0.333	44.162 ± 5.114	59.69 ± 2.07	< 0.001	0.477	<0.001	< 0.001

Table 3 shows the duration of action was 42.93 ± 0.333 min in group A, 44.162 ± 5.114 in group B and 59.69 ± 2.07 in group C. Duration of Action was longer in group C as compared to group A and group B. The difference of duration of action between group A, group B and group C is statistically significant (p <0.001).

Table 4: Condition of jaw relaxation (laryngoscopy) among groups.

Jaw Relaxation (J R)	Group A		Group B		Group C		Total
	N	%	N	%	N	%	
Poor (Impossible)	-	-	-	-	-	-	-
Minimal (Difficult)	-	-	-	-	-	-	-
Moderate (Fair)	7	23.3	7	23.3	3	10	17
Good (Easy)	23	76.7	23	76.7	27	90	73
Total	30	100	30	100	30	100	90

Table 4 shows ease of laryngoscopy and condition of jaw relaxation at the time of intubation. Jaw relaxation was good in 27 patients of group C, 23 patients of group B and 23 patient of group A. Moderate degree of jaw relaxation was present in 3 patients of group C, 7 patients of group B and 7 patients of group A.

Table 5: Condition of vocal cords among groups

Vocal cords		Group A		Group B		Group C		Total
		N	%	N	%	N	%	
VC	Closed(0)	-	-	-	-	-	-	-
	Closing (1)	-	-	-	-	-	-	-
	Moving (2)	14	46.7	26	86.7	6	20.0	46
	Open (3)	16	53.3	4	13.3	24	80	44
Total		30	100	30	100	30	100	90

Table 5 shows the condition of vocal cords at the time of intubation. Vocal cords were wide open in 24 patients of group C, 4 patients of group B and 16 patients of group A. Vocal cords are moving in 6 patients of group C, 26 patients of group B and 14 patients of group A.

Table 6: Response to intubation among groups.

Response to intubation	Group A		Group B		Group C		Total
	N	%	N	%	N	%	
Severe coughing or bucking (0)	-	-	-	-	-	-	-
Mild coughing (1)	-	-	-	-	-	-	-
Slight diaphragmatic movement (2)	16	53.3	22	73.3	7	23.3	45
None (3)	14	46.7	8	26.7	23	76.7	45
Total	30	100	30	100	30	100	90

Table 6 shows that there was no response to intubation in 23 patients of group C, 8 patients of group B and 14 patients of group A, but there was slight diaphragmatic movement visible in 7 patients of group C, 22 patients of group B and 16 patients of group A.

Table 7: Comparison of overall intubating condition between groups

Parameter		Group A		Group B		Group C		Total
		N	%	N	%	N	%	
Overall Intubating condition	Excellent	14	46.7	9	30	24	80	47
	Good	16	53.3	21	70	6	20	43
	Fair	-		-		-		-
	Poor	-		-		-		-
Total		30	100	30	100	30	100	90

(P value- <0.001)

Table 7 shows group C was statistically significant versus group A and group B. Group C (80% excellent and 20% good) had higher percentages of patients with excellent condition of intubation than group B (30% excellent and 70% good) and group A (46.7% excellent and 53% good). So group C were significantly better than group B and group A. No one of the studied patients in the three groups been reported as not possible intubation.

Discussion

Cisatracurium has many advantages, compared with other neuromuscular blocking agents. Cisatracurium is a non depolarizing neuromuscular blocking agent with an intermediate duration of action. It is the cis isomer of atracurium, and is approximately 3 to 4 fold more potent than the mixture of isomers that constitute the parent

drug.The present study was conducted in order to compare the onset time, duration of action, intubating conditions in terms of vocal cords assessment, jaw relaxation and response to intubation after two different doses of cisatracurium and a standard intubating dose of atracurium. All the three study groups were comparable in terms of demographic profile which included age and gender. This rules out the possibility of differences in the dosages based on age group.

Onset time and Duration of action

In our study, time from injection of muscle relaxant to > 90 % suppression of single twitch height was considered as onset time. Time from injection of muscle relaxant to reappearance of > 25 % of twitch height or any respiratory movement in breathing bag or notch in capnography whichever is earlier was considered as duration of action.Group A with 2×ED95 dose of atracurium had more rapid onset of action (2.917 ±0.302 min) with statistical significance than the group B with equivalent dose of cisatracurium (3.857±0.320min) 2×ED95. But higher doses of cisatracurium (4×ED95) in group C were found to be statistically significant more rapid onset of action (2.55 ± 0.294 min) than 2×ED95 dose of both atracurium and cisatracurium.Regarding the duration of action, higher doses of cisatracurium (4×ED95) in group C showed statistically significant longer duration of action (59.69±2.07min) than lower doses of cisatracurium in group B (44.162 ± 5.114 min) and atracurium (2×ED95) in group A (42.93 ± 0.333min). A study conducted by El kasaby AM et al[15]. (2010) the efficacy of atracurium was compared with different doses of cisatracurium for general anaesthesia. They found that the time of onset with 0.5 mg/kg atracurium (3.24±0.55 minutes) was significantly lower than that with 0.1 mg/kg of cisatracurium (4.37±0.46 minutes), resonating similar results as our study.Bluestein et al[16]. (1996) studied 80 ASA physical status I or II, 18–70 years of age whom were randomly assigned to four groups (A-D). Group A received cisatracurium 0.1 mg/kg (2×ED95), group B received atracurium 0.5 mg/kg (2×ED95). Patients in group C and group D were treated with cisatracurium 0.2mg/kg (4×ED95) and 0.15 mg/kg (3×ED95), respectively.. They reported that increasing the initial dose of cisatracurium (from 0.1 to 0.15 and 0.2 mg/kg), decreased the mean time of onset (from 4.6 to 3.4 and 2.8 min, respectively) and increased the mean time of clinically effective duration (45 to 55 and 61 min, respectively). Mellinghoff et al[11]. (1996) studied 80 patients randomized to receive either cisatracurium (n=40) or atracurium (n=20)and compared the time course of neuromuscular block. Results obtained by Mellinghoff *et al* were similar to our results. They estimated that onset times were 3.1±1.0 min with cisatracurium and 2.3±1.1 min with atracurium (*P*=0.008). Rochana G Bakhshi et al[17]. (2016) compared neuromuscular blockade and recovery characteristics of cisatracurium and atracurium in adult patients and found mean onset of action in cisatracurium group was 3.75 minutes, which was faster as compared to 4.79 minutes in atracurium group but difference was not statistically significant. Results obtained by Rochana *et al* were similar to our study results.M. T. Carroll et al[18]. (1998) compared neuromuscular blocking effects and the reversibility of cisatracurium 0.1 or 0.15 mg/kg with atracurium 0.5 mg/kg. The median times to maximum block were 2.7, 2.2 and 1.5 min following cisatracurium 0.1 and 0.15 mg/kg and atracurium 0.5 mg/kg, respectively. Results obtained by M. T. Carroll *et al* were not similar to our results.

Intubating conditions

In our study the intubating conditions are graded using a method described by R.Cooper et al[14]. (1992). This takes into consideration the Jaw relaxation (ease of laryngoscopy), condition of vocal cords and response to tracheal intubation. These are scored on four point scale (0-3) and total score added together to give an overall intubating score for each patient. A score of 8-9 was considered excellent, 6-7 as good, 3-5 as fair and 0-2 as poor. Good and excellent intubating conditions were taken as clinically acceptable.In our study, jaw relaxation was good in 27 patients of group C, 23 patients of group B and 23 patient of group A. Moderate degree of jaw relaxation was found in 3 patients of group C, 7 patients of group B and 7 patients of group A. So, jaw relaxation (laryngoscopy) was similar in group A and group B, while group C was better than group A and group B.Vocal cords were wide open in 24 patients of group C, 4 patients of group B and 16 patients of group A. Vocal cords are moving in 6 patients of group C, 26 patients of group B and 14 patients of group A. There was no response to intubation in 23 patients of group C, 8 patients of group B and 14 patients of group A, but there was slight diaphragmatic movement visible in 7 patients of group C, 22 patients of group B and 16 patients of group A.In our study, the intubating condition was found more excellent with 4×ED95 dose of cisatracurium in group C, when compared with the 2×ED95 dose of atracurium in group A and 2×ED95 dose of cisatracurium in group B. No one of the studied patients in the three groups been reported as not possible intubation.

Results found by Bluestein *et al* were consistent with our results. They reported that intubation conditions were good or excellent in over 90% of patients in all treatment groups

Mandal *et al*[19]. (2002) conducted a study in 60 adult patients of either sex, to find out the minimum possible dose of cisatracurium for achieving excellent to good intubating conditions with in 90sec of its administration under general anesthesia. the minimum dose required to achieve excellent to good intubating conditions with cisatracurium is 0.20 mg/kg at 90 sec after its administration. Results found by Mandal *et al* were consistent with our results.

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