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A Comparative Study of Effects of Vecuronium and Cisatracurium on Neuromuscular Blockade in Patients Undergoing Laparoscopic Cholecystectomy

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Abstract: Background and Aims: Vecuronium and Cisatracurium are two intermediate acting neuromuscular blocking agents currently in clinical use. Studies comparing their various effects, to determine which agent offers greater advantage are limited. We aim to compare the time of onset, intubating conditions, duration of action and time taken for recovery from neuromuscular blockade produced by each drug in patients undergoing laparoscopic cholecystectomy. This was a randomised controlled double blinded study. After institutional ethical clearance, 60 patients of ASA physical status I and II were enrolled in the study. And divided into two groups. Group V received vecuronium at 0.1mg/kg loading dose and 0.02 mg/kg as maintenance. Group C received 0.15mg/kg of Cisatracurium as loading dose and 0.03 mg/kg as maintenance. The technique of general anesthesia was standardized for both groups. The primary outcome measured was the time taken for onset of action of neuromuscular blocker defined as the loss of all four twitch responses to a supramaximal Train of Four stimulus. The secondary outcomes measured were the intubating conditions, duration of action and time taken for recovery. The statistical package used was RStudio. Both groups were well matched for demographic data. Time of onset of action was significantly less in Group V compared to Group C. Intubating conditions in both groups showed no difference statistically. Duration of action was significantly greater in Group C. But time taken for recovery was significantly greater in Group V. Although vecuronium offers quicker onset and lesser duration of action after a loading dose compared to Cisatracurium, recovery from multiple doses is significantly faster following Cisatracurium. This offers definite advantage in cases of hepatic and renal compromise and in the elderly.
Keywords: Anesthesia, Vecuronium, Cisatracurim, Intubation, Recovery.

INTRODUCTION

Vecuronium is a non-depolarizing muscle relaxant that has gained clinical utility over the past few years. It possesses minimal side effects in clinically useful doses and its relatively rapid onset time combined with its intermediate duration of action has been a major influence in its current popularity. It is a mono-quaternary analogue of steroid relaxant pancuronium.

Cisatracurium is a recently introduced benzylisoquinolium non-depolarizing muscle relaxant, which is a stereo-isomer of atracurium and constitutes about 15% of commercially produced atracurium, and with potency approximately 3-4 times that of atracurium [1, 2].

Like atracurium, cisatracurium is also an intermediate acting non-depolarizing muscle relaxant. It is metabolized by Hoffman elimination and ester hydrolysis. Hence it is safe for use in liver and kidney dysfunction [3], whereas, Vecuronium is cleared mainly by the liver and kidney [4]. Vecuronium is metabolised in liver by deacetylation into three metabolites. The 3-OH metabolite has 80% potency of vecuronium. Therefore, during prolonged administration of Vecuronium, the metabolite may contribute to a prolunged neuromuscular blockade [5], leading to a cumulative effect.

Histamine release by atracurium can cause skin flushing, decrease in blood pressure and systemic vascular resistance and increase in pulse rate [6]. Unlike

atracurium, cisatracurium in the clinical dose range does not cause histamine release [7, 8]

In a study conducted by Lipnitski *et al*., [9], comparing atracurium and cisatracurium for laparoscopic surgeries, it was found that cisatracurium caused a faster onset and creates better conditions for endotracheal intubation as compared to atracurium. Cisatracurium also had a longer duration of action.

In another study by Pasko-Majewska *et al*., [10], vecuronium was found to provide fastest onset of action, and most suitable intubating conditions as compared to atracurium and cisatracurium.

In another study by Melloni *et al*., [11], comparing cisatracurium with vecuronium in adult patients under propofol, fentanyl and nitrous oxide anesthesia, it was reported that although the onset and duration of action of both drugs were comparable, recovery time following vecuronium administration was prolonged.

Cisatracurium being a newer agent, sufficient studies comparing its neuromuscular blocking profile with those of established agents like vecuroniumare lacking. We aimed to compare the time of onset and intubating conditions, duration of action and time taken for recovery from blockade of vecuronium and cisatracurium in patients undergoing laparoscopic cholecystectomy.

MATERIALS AND METHODS

This double blinded randomized controlled prospective parallel designed clinical trial was planned with Patients undergoing laparoscopic cholecystectomy under general anesthesia in VIMSAR, Burla; following CONSORT guidelines for clinical trials. Based on previous studies, [11] it was calculated that a sample size of 18 patients would be required per group to demonstrate a clinically significant difference among the groups with regards to time of onset of action, at α=0.05 with a power (1-β) =80%. In order to improve the weight of results of the study, 30 patients were enrolled into each group. Sample size was calculated using RStudio v1.0.1 software package (RStudio, Inc. 250 Northern Avenue Suite 410 Boston, Massachusetts 02210).

Ethical clearance for the study was obtained from the Institutional Ethical Committee and instruments were standardized prior to commencement of the study. Simple random sampling was done for recruitment of subjects (30 in each group) into the study following Inclusion Criteria: Age 18-50 years of both sexes with ASA grade I and II and Mallampatti Grade I and II.

Patients with associated comorbidities like cardiovascular, hepatic and renal disease, patients with neuromuscular disorders, identified from history or clinical examination, pregnant patients, patients with history of medications known to interact with neuromuscular blockers Eg- Aminoglycosides, Tetracyclines, Anticonvulsants etc., patients with psychiatric disorders, patients with history of drug allergy were excluded from the study.

After proper pre-anesthetic check, all patients weregiven Alprazolam 0.5mg and Ranitidine 150mg orally on the day before surgery and will be kept nil per orally for a minimum duration of 8 hours. In the operation theatre, monitor showing heart rate, non-invasive blood pressure, ECG, oxygen saturation, and End tidal carbon dioxide were attached to the patient. Glycopyrrolate 4mcg/kg iv, midazolam 0.05mg/kg iv and fentanyl2mcg/kg iv were administered before induction. Patient were then preoxygenated with 100% oxygen. Induction was achieved with Propofol 2mg/kg.

Neuromuscular blocker was administered in their intubating doses [12] according to the following schedule:

Group V: Vecuronium 0.1mg/kg iv (n=30)
Group C: Cisatracurium 0.15mg/kg iv (n=30)

Neuromuscular monitoring was done by a peripheral nerve stimulator using Train of Four. Time taken from injection to loss of all four twitch responses was taken as intubating time. Patient was intubated with appropriate sized endotracheal tube by an expert anesthesiologist.Intubating conditions were assessed by the Cooper Scoring System [13].

Score	Jaw Relaxation to Laryngoscopy	Vocal Cords	Response to Intubation
0	Poor (impossible)	Closed	Severe coughing or bucking
1	Minimal (difficult)	Closed	Mild coughing
2	Moderate (fair)	Moving	Slight diaphragmatic movement
3	Good (easy)	Open	None

Total score: 8-9=excellent, 6-7= good, 3-5=fair, 0-2=poor.

Anesthesia was maintained with 2:1 ratio of Nitrous Oxide to oxygen mixture along with isoflurane 1-1.5%. For maintenance of muscle relaxation, vecuronium 0.02mg/kg and cisatracurium 0.03mg/kg respectively were given on the appearance of first twitch response. The time taken from injection of

intubating dose of neuromuscular blocker to appearance of first twitch response was taken as duration of action. At the end of surgery, blockade reversal was done with Neostigmine and Glycopyrrolate after appearance of all four twitch responses. Time taken for recovery was defined as the time taken for appearance of all four twitch responses after last dose of neuromuscular blocker.

Statistical analysis was done using RStudio v1.0.1 software package (RStudio, Inc. 250 Northern Avenue Suite 410 Boston, Massachusetts 02210). Time taken for intubation and duration of action were compared using Independent t-test. Intubating conditions were compared using Fisher Exact test. P value <0.05 was considered statistically significant.

RESULTS

Our study followed the CONSORT recommendation (Fig-2). The groups were well matched for their demographic data and duration of surgery (Table 1). The basal readings of HR, SBP, DBP and MAP were similar in both the groups.

The time taken for onset of action for Group V and C respectively is shown in Table-2 (Fig-2). The mean time taken for onset was 2.24 min in group V and 2.48 min in group C. (p value < 0.05)

The duration of action defined by appearance of 1st twitch response in both groups is shown in Table-3 (Fig-3). It was 22.25 min in group V and 26.31 min in group C. (p value < 0.05).

The intubating conditions for both groups are compared in Table-4. Data was comparable in both groups and not statistically significant (Fig-4).

The time taken for recovery following last dose of neuromuscular blocker is compared in Table-5 (Fig-5). It was 27.1 mins for Group V and 18.8 mins in Group C. (p value < 0.05).

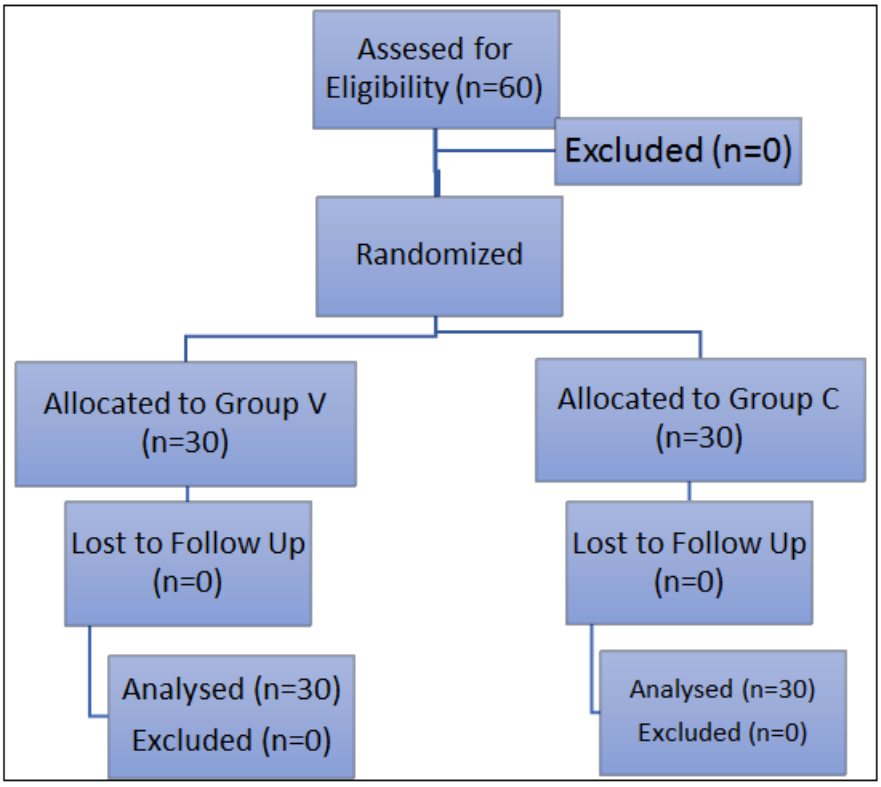

Fig-1: Consort Diagram

Table-1: Demographic Details and Duration of Surgery

Groups	Mean Age (years) +/- SD	Male (%)	Female (%)	Mean Weight (kg) +/- SD	Mean Duration of Surgery (mins)+/- SD
V	41.25±7.38	11(36.6%)	19(63.3%)	55.25±8.48	99.05±9.34
C	42.05±7.72	13(43.3%)	17(56.6%)	53.65±6.31	93.55±12.96
Intergroup P	0.262			0.403	0.073

Table-2: Time of Onset

Time in seconds	Group V	Group C
	No. of Cases (%)	No. of Cases (%)
80-100	-	-
101-120	3 (10%)	1 (3.3%)
121-140	18 (60%)	11 (36.6%)
141-160	9 (30%)	18 (60%)
161-180	-	-
Mean(SD)	134.3 (11.37)	148.8 (12.26)
Mins	2.24	2.48
P Value	0.014	

Table-3: Duration of Action

Time in Minutes	Group V	Group C
	No. of Cases (%)	No. of Cases (%)
10-20	5 (16.6%)	2 (6.6%)
21-30	21 (70%)	20 (66.6%)
31-40	4 (13.3%)	8 (26.6%)
41-50	-	
Mean (SD)	22.24 (4.25)	26.31 (6.07)
P Value	0.009	

Table-4: Intubating Conditions (Cooper Scale)

Group	Excellent (8-9)	Good (6-7)	Fair (3-5)	Poor (0-2)
	No. of Cases (%)	No. of Cases (%)	No. of Cases (%)	No. of Cases (%)
Group V	23 (76.6%)	7 (23.3%)	-	-
Group C	21 (70%)	9 (30%)	-	-
P Value	0.072			

Table-5: Time taken for Recovery

Time in Mins	Group V	Group C
	No. of Cases (%)	No. of Cases (%)
0-10	-	4
11-20	5 (16.6%)	15
21-30	22 (73.3%)	11
31-40	3 (10%)	-
Mean (SD)	27.1 (7.33)	18.8 (5.62)
P Value	0.0019	

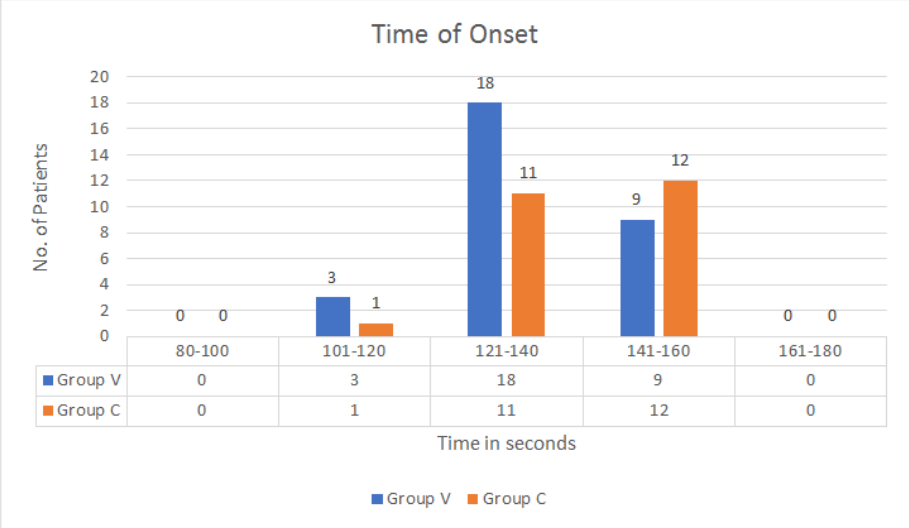

Fig-2: Time of Onset of Action in seconds

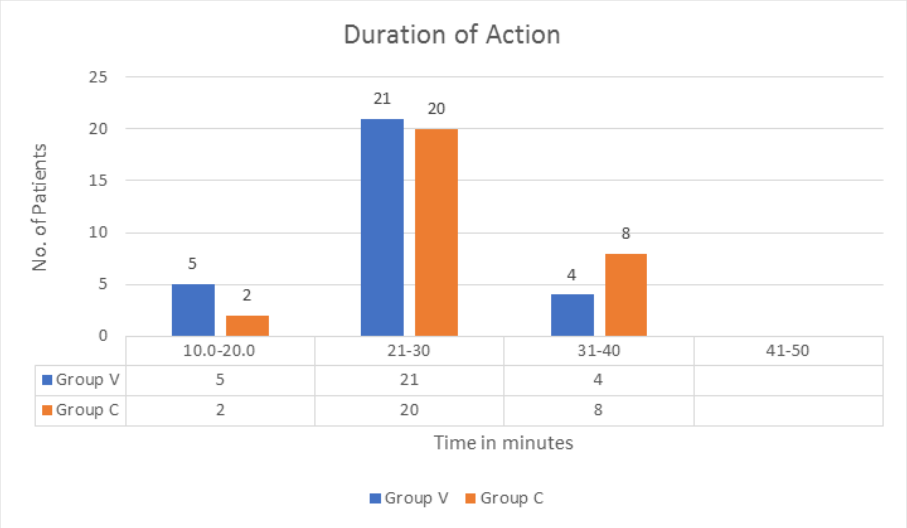

Fig-3: Duration of Action in Minutes

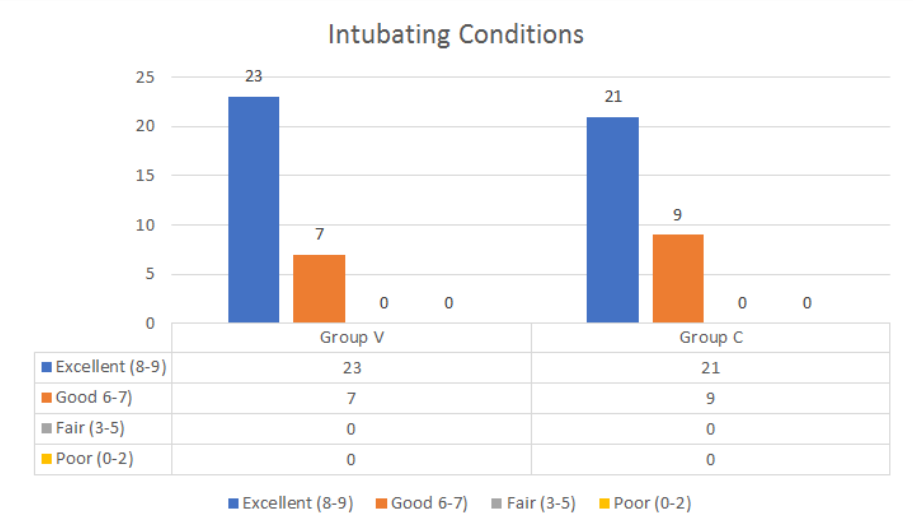

Fig-4: Intubating Conditions

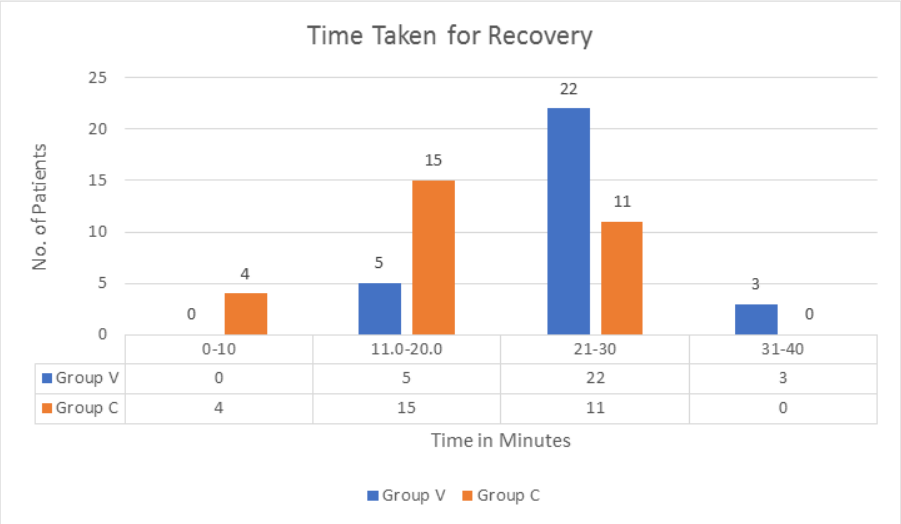

Fig-5: Time taken for Recovery in Minutes

DISCUSSION

Both Vecuronium and Cisatracurium appeared safe and efficacious under the conditions of our study. At the recommended intubating doses of vecuronium and cisatracurium, onset and duration of action were found to be slightly longer with cisatracurium. This corresponds with the results of the study conducted by Belmont *et al*., [2] and Pasko-Majewska *et al*., [10]

Intubating conditions were satisfactory in both groups with excellent or good conditions in all cases in our study.

The recovery time after administration of last dose of cisatracurium was significantly shorter than that of vecuronium in our study. This correlates with the findings of Melloni *et al*., [11], although in their study, the difference was not significant.

Vecuronium has a relatively shorter duration of action due to its rapid distribution kinetics. Hence, recovery usually occurs during the distribution phase. In contrast, atracurium and cisatracurium are rapidly degraded independent of hepatic and renal function, and pharmacological recovery occurs during the elimination phase. A decrease in glomerular function along with ageing, explains the decrease in plasma clearance of vecuronium. Renal failure prolongs the recovery from vecuronium especially after use of multiple doses in prolonged surgery. Cisatracurium, in contrast is unaffected by renal function and is safer in cases of renal compromise.

The prolonged effect of vecuronium may also be explained in part by the cumulation of its metabolites 3-desacetylvecuronium, 17-desacetylvecuronium, and 3, 17-desacetylvecuronium which themselves possess neuromuscular blocking properties, albeit less potent than vecuronium [14]. The delay in recovery following use of vecuronium in our study may be attributed to this, and correlates with the findings of Wright *et al*., [5].

CONCLUSION

The onset of action and duration of recommended intubating doses of both vecuronium and cisatracurium appear to be clinically similar with neither having any distinctive advantage. Both provide satisfactory conditions for intubation. However, cisatracurium, owing to its renal and hepatic independent metabolism shows quicker and more predictable recovery as compared to vecuronium. It offers a definite advantage especially in hepatic and renal compromise and in the elderly.

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