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ORIGINAL RESEARCH

A COMPARATIVE STUDY OF INTERMITTENT BOLUS VERSUS CONTINUOUS INFUSION OF CISATRACURIUM IN NEURO SURGICAL PROCEDURES

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ABSTRACT

Background: The aim of the study is, to compare intermittent bolus versus continuous infusion of cisatracurium in neurosurgical procedures.

Materials and Methods: A prospective, randomized, single blind control study was conducted on 32 adult patients undergoing craniotomy under general anesthesia at King George Hospital, Visakhapatnam during the period from August 2019-August 2021, after obtaining the approval from Institutional Ethical Committee (Andhra Medical College) and written informed consent from the patients who participated in this study. In this study 32 adult patients aged between 18 – 65 years, belonging to ASA grade I and II, undergoing craniotomy under general anesthesia were randomly assigned into two equal Intermittent Bolus and Continuous Infusion groups, to assess the intraoperative hemodynamics, cost effectiveness, muscle relaxation and postoperative recovery characteristics of the two technique of administering muscle relaxants during intraoperative period.

Results: The mean age, mean duration of surgery, and gender distribution was statistically similar in both groups. The mean pulse rate , SBP,DBP in group IN was significantly lower 10 min after starting infusion, 2 minutes after stopping infusion and 10 minutes after stopping infusion of cisatracurium ($p<0.05$] compared with intermittent bolus group. There was no statistical significant difference in weight of the patients between the two groups. Initial bolus dose requirements in group IN are 8.51±1.08mg and group IB is 8.58±1.06mg, which is statistically insignificant. There was statistical difference in maintenance dose requirement between two groups. Mean dose required for intermittent bolus is statistically lower than the infusion (P=0.0001). TIME in min to achieve ideal intubating conditions after initial bolus dose that is TOF 0 among two groups was statistically similar. Time in min for return of TOF 1 after initial bolus dose is statistically similar in both groups. Time to reach steady plasma state that is TOF 0 among two groups was statistically significant that is infusion group achieves steady state faster than intermittent bolus group with p value of 0.0001. There was no

statistical significance in recovery between two groups after stopping infusion and last dose of intermittent bolus.
Conclusion: Cisatracurium infusion had greater hemodynamic stability than intermittent bolus administration. However totals drug consumption was significantly lower in intermittent bolus method of administration than infusion.
Keywords: Cisatracurium infusion, SBP, DBP, neurosurgical procedures.

INTRODUCTION

Muscle relaxation forms a part of balanced anesthesia along with analgesia, suppression of reflexes and hypnosis. Griffith and Johnson utilised pure curare to achieve appropriate muscular relaxation in 1942, and since then, curare has been used as a muscle relaxant.[1,2] However, the usage of d-tubocurarine has resulted in a number of disasters in the past Muscle relaxants are two groups, the depolarizers and the non-depolarizers.

At neuromuscular junction, depolarizers mimics acetylcholine, triggering muscle contractions (fasciculations) and subsequently paralysis. Succinylcholine, the depolarizer in use, has the advantage of rapid onset of 60-second.

Malignant hyperpyrexia, elevated intraocular pressure, and hyperkalemia are all possible side effects. Usage of succinylcholine in children with undetected muscular dystrophies has resulted in some deaths due to hyperkalemic cardiac arrest. Nondepolarizers have a longer onset time (2-3 minutes), making them inappropriate for fast airway control. They function by blocking the neuromuscular junction in a competitive manner. Muscle fasciculation does not occur at first.[3]

Cisatracuriumbesylate – the intermediate-acting, non-depolarizing neuromuscular blocking drug (NMBD)[4]. Cisatracurium is the 1R cis-1'R cis isomer of atracurium,[4] with a benzylisoquinolinium structure. has been used as a supplement to general anaesthesia, allowing for easier tracheal intubation and skeletal muscle relaxation during surgery potency of cisatracurium is roughly three times that of atracurium.[4]

Cisatracuriumundergoes Hofmann elimination—a chemical process dependent on pH and temperature— forms the acrylate metabolite and laudanosine.[4] Hofmann elimination, an organ-independent elimination process, occurs in plasma and tissue and accounts for roughly 77% of total cisatracuriumbesilate elimination.[5]

The liver and kidney both play a limited role in cisatracurium removal, although they are the predominant pathways for metabolite elimination.. When compared to an equipotent dose of atracurium, cisatracurium delivered as an intravenous bolus in ventilated adult neurosurgery patients has been demonstrated to cause fewer cerebral and cardiovascular side effects.[6]

Stronger action, rapid recovery, no accumulation, no histamine release, metabolism independent of the liver and kidney, and minimal effects on the cardiovascular system are all advantages of cisatracurium.[7] Currently, most of the non-depolarizing muscle relaxants are administrated by a single intravenous injection in anesthesia practice.[7]

Due to the lack of neuromuscular monitoring, administration is often based on clinical experience, such as increased airway pressure, spontaneously breathing, bucking, or body movement.[7] As a result, the degree of neuromuscular blockage changes, making it difficult to maintain a consistent level of neuromuscular blockade. The time and dose of delivery are more difficult to control, especially at the end of the procedure. Inappropriate administration

of muscle relaxants results for prolonged surgeries like neurosurgical procedures resulting in prolonged recovery from neuromuscular blockade.[7]

Residual neuromuscular blockade can cause respiratory depression, reduce hypoxic ventilatory response and forced inspiratory flow, and raise the risk of upper respiratory tract obstruction, dysphagia, regurgitation, and pulmonary complications.[7]

In comparison to intermittent bolus delivery, continuous intravenous drug infusion allows for greater control of anesthetic depth, resulting in improved hemodynamic control, reduced total drug consumption, and a faster recovery from anesthesia.[7]

Hence this study is to observe whether dose consumption is high in intermittent bolus or in continuous infusion group in neurosurgical procedures as neurosurgical procedures require prolonged muscle relaxation so that decreasing the dose helps in reducing the cost of muscle relaxants.

Neuromuscular monitoring helps to prevent residual block and should be included in routine monitoring equipment. The train-of-four (TOF) count is the most suitable method. The majority of research used tactile or visual detection of neuromuscular block by peripheral nerve stimulator; however, the current investigation used objective TOF monitoring with an acceleromyograph.

Previous studies compared cisatracurium infusion versus large bolus in cardiac surgeries but there were no studies comparing cisatracurium infusions versus intermittent bolus in craniotomies. Craniotomies are the surgeries where sudden movement must be eliminated, and there is a need for deep neuromuscular block for prolonged duration of surgery. Hence the present studies is to asses and compare total dose consumed, hemodynamics and postoperative recovery by administering continuous IV infusions of cisatracurium and intermittent bolus after initial bolus dose for craniotomies and monitoring degree of muscle relaxation by TOF.

Aims and objectives

Aim: The aim of the study is, to compare intermittent bolus versus continuous infusion of cisatracurium in neurosurgical procedures.

Objectives of the study are:

Primary objective:

- To assess and compare the hemodynamic performance in perioperative period.

Secondary objectives:

- To compare the recovery time between intermittent bolus group and infusion group at the end of surgery.
- Cost effective analysis by comparing the dosage requirement of intermittent bolus and continuous infusion of cisatracurium.

MATERIALS & METHODS

A prospective, randomized, single blind control study was conducted on 32 adult patients undergoing craniotomy under general anesthesia at King George Hospital, Visakhapatnam during the period from August 2019-August 2021, after obtaining the approval from

Institutional Ethical Committee (Andhra Medical College) and written informed consent from the patients who participated in this study.

Patients aged between 18 – 65 years, belonging to ASA grade I and grade II, undergoing craniotomies under general anesthesia that are willing to give informed written consent were included in this study.

Inclusion Criteria:

1) Adults aged 18-65 years
2) American society of anaesthesiologists (ASA] physical status 1&2 3) undergoing elective surgeries under general anaesthesia.

Exclusion Criteria:

1) Patient refusal
2) Pregnant and breast feeding
3) History of malignant hyperthermia
4) Hypersensitivity to neuromuscular blocking agents
5) ALCOHOLISM and durg addiction
6) Patients who are suffering from neuromuscular disorder
7) Patients with major heart diseases
8) Those undergoing treatment with drugs likely to interfere with neuromuscular blocking agents eg:aminoglycosides, anti arrythmias or ganglion blocking drugs

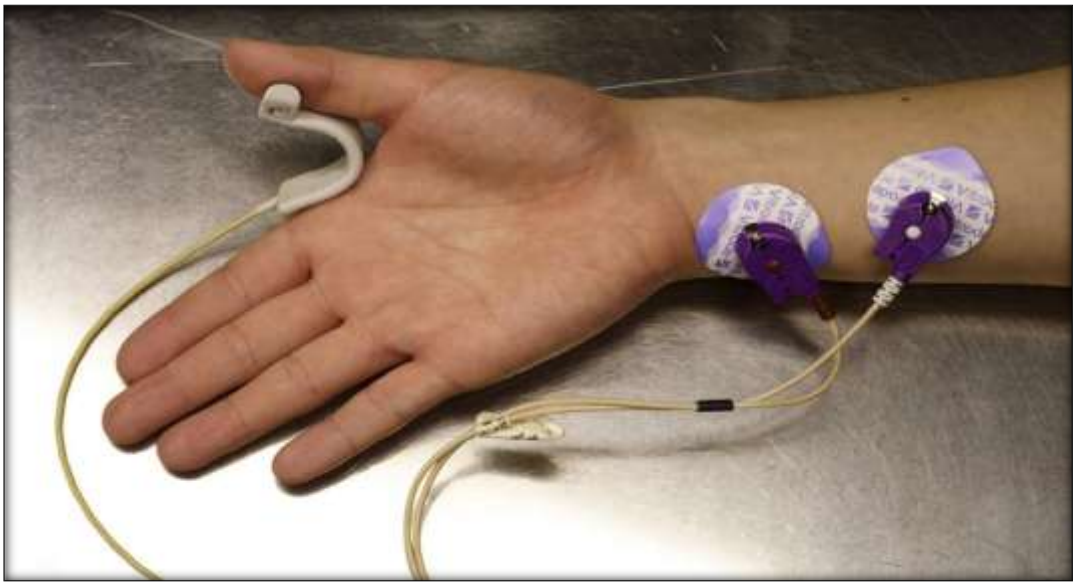
Methodology: Preanesthetic examination was done one day before the surgery. A detailed history about present illness, past medical illness, history of drug allergy and the medication history in the preoperative period are recorded. General physical examination, systemic examination and a thorough airway examination were conducted. Preoperative investigations including complete blood count (CBC), urine examination, blood sugar, serum electrolytes, coagulation profile, liver and renal function tests, electrocardiography and echocardiography, chest x-ray are obtained as indicated. All the patients were advised overnight fasting for 8 hours before surgery. Adequate blood reserve was kept ready. Premedication with oral ranitidine hydrochloride 3 mg/kg and alprazolam 0.01mg / kg were given the night before surgery. 32 patients belonging to the American Society of Anaesthesiologists (ASA) classes I and II scheduled for craniotomy were studied. The patients are randomly allocated into two groups of 16 each, using computer generated randomization.

Group IN: cisatracurium infusion group (n=16)

Group IB: cisatracurium intermittent bolus group (n=16)

After shifting the patient to operating room, IV access is obtained with 18G IV cannula and CVP line through right subclavian. Electrocardiogram, pulse oximetry, noninvasive blood pressure, Etco2 and mind ray NMT [nerve muscle testing] monitor i.eacceleromyograph were connected.

Baseline vitals – heart rate, systolic BP, diastolic BP, MAP, SpO2 and Etco2 are recorded. For neuromuscular monitoring, the distal electrode is placed 1 cm proximal to the point where proximal wrist crease crosses the flexor carpi ulnaris tendon.



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All patients in the both groups were premedicated with inj. Glycopyrrolate 0.05mg/kg IV, inj. Midazolam 0.02mg/kg IV and inj. fentanyl 2mcg/kg IV and a loading dose of inj. phenytoin IV [15mg/kg] and inj. dexamethasone 8mg were given 20min before induction, then after preoxygenation with 100% oxygen for 3 minutes, patients are induced with inj. thiopentone 5mg/kg IV, after then calibration of NMT Monitor is done in single twitch mode, then the mode changed to TOF at an 20 sec interval. Both group patients were given cisatracurium (0.15mg / kg) bolus dose achieve muscle relaxation for endotracheal intubation. Intubation was done with cuffed flexo metallic endotracheal tube of appropriate size when there is no response to train-of-four stimuli. [TOF 0] and the time taken for TOF count to become 0 after initial bolus dose was noted. Intraoperative monitoring of electrocardiography (ECG), oxygen saturation (SpO2), non-invasive blood pressure (NIBP), end tidal carbon dioxide (EtCO2), and train of four (TOF) monitoring were continued. Anesthesia was maintained with isoflurane 0 – 1 % w/v, 66% nitrous oxide in oxygen and fentanyl and propofol as and when required based on hemodynamic parameters. Mechanically ventilated with a tidal volume of 6-8 ml/kg and respiratory rate of 14-16 breaths/ min, to maintain the end tidal CO2 between 25 – 30 mmHg.

Muscle relaxation was maintained with, continuous intravenous infusion of cisatracurium (2µg/kg/min) in group IN and with intermittent boluses of cisatracurium (0.03mg/kg) in group IB, started as soon as the first response to train of four stimuli appears. Dose of infusion and intermittent bolus of relaxants is adjusted in such a way that there is no response to train of four stimulation. Time taken to achieve steady state of block from the time of starting the infusion is noted. The infusion is titrated by resistance to ventilation, surgical relaxation (by surgeon's satisfaction) and hemodynamic changes.

Infusion was stopped at the time closure of dura [near the ending of surgery] Time of appearance of TOF Count 3 after stopping infusion is noted. In intermittent bolus group last dose was stopped near the end of surgery. When the TOF Count 3 or TOF Ratio 25%, residual neuromuscular blockade is reversed with injection neostigmine (0.05 mg/kg) and injection glycopyrrolate (0.01 mg/kg) intravenously. Patient is assessed by clinical criteria.

Adequate reversal of neuromuscular blockade is confirmed with the help of double burst stimulation (DBS) mode. When patients are fully awake, moving all four limbs to vocal commands with recovery of good muscle tone and power, extubation was done. Subsequently patients were shifted to the postoperative ward. To assess the percentage of neuromuscular blockade throughout the procedure, train of four is used – No twitch response indicates 100% block and presence of 1, 2 or 3 response indicates 90%, 80% or 75% block respectively.

At different time points pulse rate, SBP and DBP are measured. They include baseline preoperative values, 2 minutes and 10 minutes after bolus dose administration, 2 minutes and 10 minutes after starting infusion and postoperatively. Measurements 2 minutes after bolus dose (that is before laryngoscopy and intubation) indicating bolus dose effect on hemodynamics. Measured again after 10 minutes because the effect of laryngoscopy and intubation are considered to wear off at that time point. Parameters measured 2 minutes and 10 minutes after starting infusion indicates hemodynamic performance during the infusion. Total drug consumed in both techniques was measured.

Statistical Analysis: Data is entered in Microsoft excel spread sheet , analysis is done by statistical package for social sciences (spss version 21).categorical data is expressed as proportions and quantitative data as means and standard deviation. Appropriate tests are applied whereever necessary

RESULTS

A Comparative prospective randomized study of 32 patients randomly divided in to two groups 16 patients in Group IN (continuous infusion) and 16 patients in Group IB (intermittent bolus) scheduled for craniotomy under general anesthesia was undertaken to assess the intraoperative hemodynamics, cost effectiveness, muscle relaxation and postoperative recovery characteristics of the two technique of administering muscle relaxants during intraoperative period.

The results were tabulated and data was evaluated using mean and standard deviation. Students'' test standard error of difference between means was used to calculate the 'p' value statistical significance.

On the analysis of the demographic data i.e., age, sex, weight, height and duration of surgery, there was no statistically significant difference between the two groups.

Table 1: Age Distribution of Patients among Group IN (Infusion) and Group IB (Intermittent Bolus)

Age	Group IN		Group IB		Total	
	N	%	N	%	N	%
18-25	4	25	3	18.75	7	21.87
26-30	1	6.25	1	6.25	2	6.25
31-40	1	6.25	2	12.5	3	9.375
41-50	5	32	4	25	9	28.125
>50 years	5	32	6	37.5	11	34.375
Total	16	100	16	100	32	100
Mean±Sd	42.31±14.47		42.875±13.80			
p-value	0.9108					

The mean age was 42±14.47 years in Group IN and 42.8±13.8 years in Group IB which was comparable. There was no statistically significant difference between the groups with regard to age with a p value = 0.9.

Table 2: Gender Distribution of Patients among Group IN (Infusion) and Group IB (Intermittent Bolus)

	Group In		**Group Ib**	
	NO.	%	NO.	%
Male	7	43.75	9	56.75
Female	9	56.75	7	43.75
Total	16	100	16	100

32 patients of either sex had participated in the study. Number of the male patients in Group IN and Group IB was 7 and 9 respectively. The number of female patients who received Group In and Group IB was 9 and 7 respectively. The percentage of male patients in Group In and Group IB was 43.75% and 56.75% respectively. The percentage of female patients. In Group IN and Group IB was 56.75% and 43.75% respectively. The gender distribution was comparable in both the groups.

Table 3: Weight (Kg) Distribution of Patients among Group IN (Infusion) and Group IB (Intermittent Bolus)

Weight	**Group IN**		**Group IB**		**Total**	
	N	**%**	**N**	**%**	**N**	**%**
<45	4	6.25	1	6.25	2	
46-50	2	12.5	3	18.75	5	
51-55	4	25	3	18.75	7	
56-60	3	18.75	4	25	7	
61-65	5	31.25	5	31.25	10	
66-70	1	6.25	0	0	1	
Total	16	100	16	100	32	100
Mean±Sd	56.75±7.21		57.18±7.03			
p-value	0.8655					

The mean weight of the patients in Group IN and Group IB was 56.75±7.21 kgs and 57.18±7.03 kgs respectively. Mean weight was statistically similar in both the groups and were comparable with a p value = 0.8655.

Table 4: Comparison of Duration of Surgery between Group IN and Group IB

	Group IN	**Group IB**	**P value**
Duration of Surgery (Mean±Sd)	181.25±14.24	177.625±13.46	0.4651

Mean duration of surgery in both groups was 181.25±14.24 and 177.62±13.46 min respectively. Mean duration of surgery was statistically similar in both groups and were comparable with a p value=0.46.

Table 5- Comparison of Pulse Rate between Group IN and Group IB

	Group IN Mean ±Sd	**Group IB Mean±Sd**	**P Value**
Pre-Operative	79.81±11.86	77.06±9.21	0.4695
2 Minutes After Bolus Dose	78.06±8.54	80.375±7.83	0.4304
10 Minutes After Bolus Dose	74.56±8.95	75.75±7.14	0.6805
2 Minutes After Starting Infusion/Intermittent Bolus	74.375±8.03	76.812±7.23	0.3745
10 Minutes After Starting Infusion/Intermittent Bolus	69.5625±5.45	74.43±6.34	0.0268*
2 Minutes After Stopping Infusion/Intermittent Bolus	71.25±7.25	78.31±7.795	0.0126*
10 Minutes After Stopping Infusion/Intermittent Bolus	72.6875±7.65	80.625±9.59	0.0147*

There was no significant in two groups preoperatively, and after initial bolus. The mean pulse rate in Group IN was significantly lower 10 min after starting infusion, 2 minutes after stopping infusion and 10 minutes after stopping infusion of cisatracurium ($p<0.05$).

Table 6: Comparision of Systolic Blood Pressure (Sbp) Between Group IN and Group IN

	Group IN Mean ±Sd	**Group IB Mean±Sd**	**P Value**
Pre-Operative	131.31±13.98	135.12±13.01	0.4311
2 Minutes After Bolus Dose	126.25±16.46	132.06±9.79	0.2344
10 Minutes After Bolus Dose	123.75±13.16	131.75±10.73	0.0692
2 Minutes After Starting Infusion/Intermittent Bolus	120.93±10.76	131.5±10.57	0.0088*
10 Minutes After Starting Infusion / Intermittent Bolus	113.875±11.848	128.625±10.55	0.0008*
2 Minutes After Stopping Infusion / Intermittent Bolus	126.25±10.99	133.5±8.55	0.0459*
10 Minutes After Stopping Infusion / Intermittent Bolus	127.875±12.98	136.06±8.66	0.0444*

There was no significant in two groups preoperatively, and after initial bolus. The mean SBP in Group IN was significantly lower 2 min and, 10 min after starting infusion, 2 minutes after stopping infusion and 10 minutes after stopping infusion of cisatracurium ($p<0.05$.

Table 7: Comparison of Diastolic Blood Pressure in Infusion and Intermittent Bolus Groups

	Group IN Mean ±Sd	Group IB Mean±Sd	P Value
Pre-Operative	87.81±7.70	83.81±10.01	0.2505
2 Minutes After Bolus Dose	85.375±6.53	84.94±7.26	0.8598
10 Minutes After Bolus Dose	83.06±6.88	81.19±7.4	0.4649
2 Minutes After Starting Infusion/Intermittent Bolus	77.4375±9.15	82.125±8.15	0.1364*
10 Minutes After Starting Infusion/Intermittent Bolus	74.4375±7.44	81.375±7.33	0.0125*
2 Minutes After Stopping Infusion/Intermittent Bolus	75.25±10.15	83.94±6.28	0.0067*
10 Minutes After Stopping Infusion/Intermittent Bolus	80.4375±9.45	86.5±5.73	0.0361*

There was no significant in two groups preoperatively, and after initial bolus. The mean DBP in Group IN was significantly lower 2 min and, 10 min after starting infusion, 2 minutes after stopping infusion and 10 minutes after stopping infusion of cisatracurium ($p<0.05$).

Table 8:- Comparison of Dose Requirements between the Infusion (IN) Group and Intermittent Bolus (IB) Group

	Group IN Mean ±Sd	Group IB Mean ±Sd	P Value
Weight In Kgs	56.75±7.21	57.18±7.03	0.8655
Initial Bolus Dose	8.51±1.08	8.58±1.06	0.8545
Infusion/Intermittent Dose	13.31±3.37	7.15±1.98	0.0001***
Total Dose	21.95±4.48	15.73±2.66	0.0001***

There was no significant difference in weight of the patients between the two groups. Initial bolus dose requirements in Group IN are 8.51±1.08mg and Group IB is 8.58±1.06mg, which is statistically insignificant. There was statistical difference in maintenance dose requirement between two groups. Mean dose required for intermittent bolus is statistically lower than the infusion (P=0.0001).

Table 9: Comparison of Time in Min to Achieve Required TOF after Equipotent Doses Among Group IN (Infusion) and Group IB (Intermittent Bolus)

Time (min)	Group IN Mean ±Sd	Group IB Mean ±Sd	P Value
After bolus dose to TOF '0'	3.325±0.45	3.3±0.45	0.8762
After bolus dose to TOF '1'	38.625±5.96	41.06±4.07	0.1872
After starting infusion / intermittent bolus to TOF '0'	15.81±3.39	27.18±5.02	0.0001***

After stopping infusion / intermittent bolus to TOF '3'	26.25±6.10	23.93±5.70	0.8792

TIME in min to achieve ideal intubating conditions after initial bolus dose that is TOF 0 among two groups was statistically similar. Time in min for return of TOF 1 after initial bolus dose is statistically similar in both groups. Time to reach steady plasma state that is TOF 0 among two groups was statistically significant that is infusion group achieves steady state faster than intermittent bolus group with p value of 0.0001.There was no statistical significance in recovery between two groups after stopping infusion and last dose of intermittent bolus.

DISCUSSION

The primary objective of muscle relaxants is to provide ideal surgical conditions which also facilitate the intubation of trachea and controlled mechanical ventilation. Muscle relaxants also help in the patients with ventilator asynchrony and patients fighting with the ventilator in the intensive care unit. Muscle relaxants also aid in the facilitation of surgical field without increasing the depth of anesthesia so that major hemodynamic changes associated with increasing depth of anesthesia can be prevented.

In this study 32 adult patients of age 18 – 65 years, belonging to ASA physical status I & II, undergoing craniotomy via general anesthesia were randomly allocated into two equal Groups, one group IB received intravenous cisatracurium bolus dose with intermittent bolus doses and group IN received cisatracurium bolus followed by infusion. Degree of muscle relaxation was monitored using TOF count to assess the intraoperative muscle relaxation and postoperative recovery from neuromuscular blockade. Throughout the surgery TOF Count 0 was maintained, by adjusting the infusion rate of muscle relaxants.

The infusion dosage needs to sustain deep block with muscle relaxants were investigated in this study employing a TOF monitor to keep TOF COUNT 0 at all times. After a bolus dosage of 0.15 mg/kg, the total infusion dose needs of cisatracurium (Group IN) were 2.1 µg/kg/min, while the dose requirement of cisatracurium in the intermittent bolus dose group was 1.54 µg kg/min. This conclusion is consistent with the findings of the Moosa Mirinejad,[14] et al research, which indicated that cisatracurium intermittent bolus dosage needs were 32.8±20.6 µg kg/hour and continuous infusion dose requirements were 89.7± 39.4 µg kg/hour. Patients with no neuromuscular illness who were scheduled for elective surgery under general anaesthesia were studied by Dong et al.[15] For appropriate muscular relaxation, the mean infusion dosage in the continuous infusion rate group was 0.78± 0.15 µg /kg/min, and in the intermittent bolus group was 1.09±0.33 µg /kg/min, which is similar to the dose found in our study.

The potencies of atracurium, vecuronium and pancuronium were compared by l. Gramstad and p. Lilleaasen,[16] using bolus injections and continuous infusion, the maintenance doses (µg/kg/hr) for 90 % blockade were: atracurium 382.8, vecuronium 101.9, and pancuronium 36.9.

K Kirov et al studied the potency and onset of atracurium and cisatracurium directly at the larynx adductors in 54 patients. They found the onset at the larynx in cisatracurium was 196± 28 seconds after 100 microgram/kg when compared with 140 ±14 seconds after 500

microgram/kg and ED95 was 87 microgram/kg for cisatracurium compared with 400 microgram/kg for atracurium. The slow onset of action explains the higher potency of cisatracurium when compared with atracurium. WangNingShangGuan et al compared three doses of cisatracurium in children aged 15 to 60 months of age. They found that cisatracurium had no effect on hemodynamics at any dose. They concluded that four times the effective dose of cisatracurium did not significantly shorten the onset time when compared with the three times the effective doses in young children.

George H Meakin et al found that cisatracurium at a dose of 0.15mg/kg produces acceptable intubating conditions at 120 seconds in majority of infants and in children.Cis-atracurium is a 'cleaner' isomer of atracurium that is more potent than atracurium and does not produce as much histamine.

Wastila concluded that Cisatracurium has neuromuscular blocking effects identical to those of atracurium, is more potent, and does not produce cardiovascular effects or increase plasma histamine concentrations.

In ICU patients, Dieye et al discovered a delay in the onset of neuromuscular inhibition. The cumulative dosages of cisatracurium in the ICU group were substantially greater, with 38 ±14 mg (10± 4.7 ED95) vs 11± 2 mg (3± 0.3 ED95) in the elective surgery group (P< 0.0001). They found that dosing cisatracrurium for ICU patients, who is based on the amount, indicated for elective anaesthetic, is ineffective due to the late onset, and urged that neuromuscular monitoring be employed in the ICU as well.

rocuronium 0.6 mg/kg (Group R0), vecuronium 0.1 mg/kg (Group V), and cisatracurium 0.1 mg/kg (Group C) were given by Sagir O et al. During and after the procedure, train-of-four (TOF) ratios were obtained at 10-minute intervals. They discovered that intubation time in Group R was much shorter than in Groups V and C (P <0.001). Group C had shorter times to positive visual disturbances and grip strength tests than Group V (P = 0.016 and P = 0.011, respectively). Except for grip strength (P 0.05), time to TOF 0.9 in Group R and C was substantially longer than all positive clinical test timings. They came to the conclusion that cisatracurium is safer for older individuals than other drugs.

Naguib M et al,[8] found the calculated ED_{50} values and their 95% confidence intervals were 111 (107-115) and 26.2 (25.8-26.5) mcg/kg [corrected] for rocuronium and cisatracurium, respectively. When compared with equipotent doses of cisatracurium, rocuronium had a faster onset, and a faster spontaneous T1 and trainof-four recovery times that were significant except at maximum recovery with the $2xED_{95}$ dose. They concluded that Cisatracurium is four to five times more effective than rocuronium. But Rocuronium had a rapid onset of action, a shorter clinical duration, and a faster spontaneous recovery rate when compared with equipotent doses of cisatracurium.

El-Kasaby,[9] et al concluded that atracurium is a more effective neuromuscular blocking agent than cisatracurium at the same dose ($2\times ED_{95}$ dose), whereas higher doses of cisatracurium ($4\times ED_{95}$ and $6\times ED_{95}$ doses) provide more effective, more rapid neuromuscular blocking with longer duration of action, stable hemodynamic status, and no clinical signs of histamine release..

Thus in our study, we used the dose of 0.1mg/kg of cisatracurium which is 2 times of ED_{95} as a single bolus in both the groups Doenicke,[10] et al concluded that cisatracurium and

vecuronium do not cause systemic or cutaneous histamine release. Tryptase levels show that there was no evidence of mast cell degranulation.

A Movafegh,[11] et al concluded that atracurium and cisatracurium had similar safety profile and atracurium had a cost benefit relative to cisatracurium in initial loading doses. But In patients with instability in hemodynamic parameters, the cisatracurium was the appropriate choice.

P Madhavi,[12] et al concluded that intravenous continuous infusion is suitable alternative method of administration of atracurium in renal failure patients. It also provides continuous adequate steady state of anaesthesia, stable hemodynamics and lesser intraoperative dosage requirement.

Diefenbach,[13] et al found the differences of up to 20 min were noted during the recovery indices in the following order: atracurium repeated injection = atracurium infusion <vecuronium repeated injection <vecuronium infusion. A single dose of neostigmine (70mcg /kg) significantly reduced the recovery indices, thereby eliminating their differences.

G. Cammu et al compared high bolus dose (0.4 mg/kg) of cisatracurium ($8*ED_{95}$) given at induction and cisatracurium with 0.1mg/kg followed by continuous infusion. The escape medication given in case of any movement from the patient was a bolus dose of cisatracurium 0.03mg/kg. They found that the clinical duration of effect was 110 minutes. Out of 10 patients, 6 patients needed additional boluses of cisatracurium intraoperatively in the high bolus dose group. In continuous infusion group, none of the patients moved and no one received additional bolus doses. The total amount of cisatracurium used in the bolus group was 34.5± 7.8 and in the infusion group was 21.3 ±5.7 respectively with p-value 0.0004 which is comparable to our study. In our study, the total cisatracurium used in the bolus group was 15.73±2.66 and in infusion group was 21.95± 4.48mg which is also statistically significant. In our study, we found that intermittent bolus group has decreased dose consumption compared to that of infusion group due to the fact that high dose of cisatracurium was used by G. Cammu et al in induction period.

They also concluded that high bolus dose of cisatracurium appeared to be safe but not an alternative to continuous infusion. Also high dose of cisatracurium does not cover the whole postoperative period and high incidence of movements can occur. Moreover, high incidence of post-operative recurarization can also occur in the high dose cisatracurium group.

In this study changes in pulse rate with time were statistically not significant compared to preoperative pulse rate in both groups. There was no statistical significance in between two groups after initial bolus dose and after starting infusion.

Group In had a mean pulse rate of 79.81 minutes, whereas Group IB had a mean pulse rate of 77.06 minutes, with no statistically significant difference between the two groups. There was no statistically significant difference in mean pulse rate 2 minutes after bolus dosage and 10 minutes after bolus dose between the two groups. The mean pulse rate was 69.56 in Group IN and 74.43 in Group IB after initiating the infusion, which was statistically significant (p0.05).

After stoppage of infusion for 2 minutes, the mean pulse rate in Group IN was 71.25 and in group IB was 78.31 which were also statistically significant. After stopping the infusion/intermittent doses for 10 minutes, the mean pulse rate in Group IN was 72.68 and in Group IB were 80.625 which were also statistically significant. This study concludes that using cisatracurium, the pulse rate was lower

When compared with the intermittent bolus group.

There was no statistically significant difference between the two groups in the pre-operative, 2 minutes and 10 minutes after the bolus dose in the SBP measurements. However, 2 minutes after starting the bolus/ infusion doses, the mean SBP in Group IN was 120.93 and in Group IB was 131.75 which was

Statistically significant (p=0.0088). The SBP measured 10 minutes after the starting the bolus/ infusion doses in Group IN was 113.875 and in Group IB was 128.625 and it was statistically significant with p value of 0.0008.

The mean systolic blood pressure in Group IN was 126.25 and in Group IB were 133.5 after the infusion and bolus dosages were stopped for 2 minutes, which was statistically significant with a p-value of 0.0459. The mean systolic blood pressure in Group IN was 127.85 after the infusion was stopped for 10 minutes, and in Group IB it was 136.06, which was statistically significant with p value of 0.0444.

Our present study found that the mean SBP was lower in the patients in Group IN where the patient receives cisatracurium in infusion.In our study, there is no statistically significant difference in the diastolic blood pressure [DBP] in the pre-operative, 2 minutes and 10 minutes after the bolus doses and 2 minutes after starting the infusion/intermittent doses in both the groups.

However, 10 minutes after starting the infusion/intermittent boluses, the mean DBP in Group IN was 74.43 and in Group IB were 81.73 which has statistical significance with p value of 0.0125. The mean DBP in Group IN during 2 minutes after stopping the infusion/intermittent bolus doses was 75.25 and in Group IB were 83.94 which have statistical significance with p-value of 0.0067.

After 10 minutes of stopping the infusion/intermittent bolus doses, the mean DBP in Group IN was 80.43 and in Group IB were 86.5 which were statistically significant with p value of 0.0361.

In our study, it was found that the mean DBP was lower in the infusion group when compared with the intermittent bolus group.

LS Chaudhari et al,[17] in their study concluded that Vecuronium infusions are more hemodynamically stable than atracurium infusions. Vecuronium produced lesse change in SBP (mean change of 3. 46 +/- 3.33%) from baseline values when compared to atracurium (mean change of 5.81 +/- 3.73%) from baseline values ($p < 0.01$) which have statistical significance. The difference in mean pulse rate change from baseline value in the atracurium group (4.78 +/- 2.745%) was less than that in the vecuronium group (5.99 +/- 2.67%), which was not statistically significant.

In a study by Ratulbasu et al,[18] found that in Group vecuronium significant change in pulse rate was seen only between pre-operative value with 2 minutes after bolus and 2 minutes after starting infusion and also between postoperative value with 2 minutes after starting of infusion. But in Group atracurium significant pulse rate changes were seen within different time periods. Median pulse rate 2 minutes after bolus dose (78±11) was significantly higher in Group A than preoperative rate (70.5 ± 9). With systolic blood pressure no statistical significant difference between the groups as well as within each group. With DBP, No significant differences were found within Group V. But a difference was seen between

preoperative and 2minutes after bolus dose, 2 minutes after starting infusion and 10 minutes after stopping infusion values in group A.

During surgical procedure there are many causes of pulse rate changes. But the difference between the two groups during the infusion period was due to the stable cisatracurium concentrations in the blood in the infusion group when compared with the intermittent bolus group.

B. M. EAGAR et al,[19] in their study showed that After injection of bolus dose of atracurium 0.6 mg/kg changes in mean arterial pressure or heart rate, for the whole patient group did not showed statistical significance, in one patient there was an increase in mean arterial pressure of 16 mm Hg with an increase in heart rate of 18 beats / min on intubation of the trachea. In another patient there was a mild decrease in mean arterial pressure of 14 mm Hg and an urticarial rash was seen on the arm into which atracurium, and a supplement of thiopentone (50 mg), had been injected. This rash extended as far as the arterial pressure cuff.

Another patient showed slight transient flushing over the chest and neck after the injection of atracurium. No changes in mean arterial pressure or heart rate occurred during the infusion which was attributable to the use of atracurium.

However with cisatracurium, the histamine release was very neglible when compared with that to atracurium and there is no incidence of any rash or any features suggestive of histamine release during cisatracurium use.

The amount of laundanosine metabolite released during cisatracurium use was also very low (almost one third) when compared with atracurium.In our study there was no evidence of histamine release.

As there is no exact estimate of laudanosine production in cisatracurium, it was found that it produces only one third of laundanosine when compared with of atracurium.

The equilibrium plasma concentration of laudanosine following infusion of atracurium at 0.6 mg kg/hr in healthy men is 1.0 ±0.6 ug/ml, and 1.6 ±0.755 ug /ml in individuals with renal failure, as determined using atracurium bolus dosage data (Ward et al.71 1985). laudanosine values in the range of 1.9-5.1 ug/ml were observed in plasma from a group of six patients in critical care with a variety of severe diseases needing atracurium blocking (Yate et al73., 1985). Pharmacokinetic predictions and clinical observations of laudanosineeffects after long infusions both suggest that a reasonable window exists in which severely ill patients can be infused with atracurium without an unacceptable risk of drug-induced convulsions, at least if they have remaining liver function. The clearance of laudanosine through metabolism or excretion is expected to be reduced in individuals with hepatic insufficiency (Neill and Chappie57, 1982; Miller59, 1986), hence the risks/benefit equation for these patients may need to be re-evaluated. But in the present study, preoperatively all the patients were given 8mg dexamethasone and injection phenytoin loading dose prophylactically to minimize chances of cerebral edema and to decrease seizure threshold, as the patients in the study group were posted for craniotomy and the patients with renal and hepatic diseases were excluded from the study.so that in this study there were no reports of histamine release and seizure episodes. The mean total dose requirements in Group IN were 21.95 mg and in Group IB were 15.73 which have statistical significance with p value of 0.0001. Our results were consistent with M Mirinjedad et al.

Our study found that the dose requirements were more in the infusion group when compared with intermittent bolus group and hence intermittent boluses of cisatracurium was more cost-effective when compared with the infusion group. However, the total dose requirements may also vary due to patient's characteristics, varying anesthetic depths used among various patients. Use of BIS monitoring may be warranted in such cases. The time required to achieve the TOF of 0 after the bolus dose was comparable and there was no statistical significant difference among the two groups. Time required achieving TOF 1 after the bolus dose also comparable and there is no significant difference between the two groups. time required after stopping the infusion to TOF '1' in Group IN was 15.81 minutes and in Group IB was 27.18 minutes which was comparable and this was statistically significant with p value of 0.0001 and after stopping the infusion to TOF was also comparable and there was no statistical significant difference among the two groups. This shows that patients with infusion groups recovered faster when compared to the intermittent bolus group. However, in intermittent bolus group, the timing to give top-up doses vary because there are some patients who may recovered from the neuromuscular blockade or even resumed spontaneous ventilation with adequate depth of anesthesia. With adequate depth of anesthesia, the patient may not move during surgery which does not warrant the need for neuromuscular blocking agents.

CONCLUSION

Cisatracurium infusion had greater hemodynamic stability than intermittent bolus administration. However totals drug consumption was significantly lower in intermittent bolus method of administration than infusion. Recovery rate was similar in both methods of administration.

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