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Comparison of hemodynamic effects and intubating conditions with two different doses of Cisatracurium in patients undergoing elective surgery under general anaesthesia

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***Abstract*---**Introduction: Cisatracurium, a Benzyl-iso-quinolinium compound is a non-depolarizing muscle relaxant with intermediate duration of action. The ED95 dose of Cisatracurium is 0.04mg/kg (0.032-0.05mg/kg).The intubating dose of a non-depolarizing muscle relaxant drug (NDMD) is 2 times ED95, but for Cisatracurium the recommended intubating dose is 0.15mg/kg which is 3 times ED 95. We did this study to compare the hemodynamic stability and ease of intubation with two different doses of Cisatracurium (0.1mg/kg and 0.15mg/kg) in patients undergoing elective surgery under general anaesthesia with regards to hemodynamic stability, intubating conditions at 3minutes of administration of the drug, requirement of additional dose to provide adequate muscle relaxation, need for drugs to suppress response to laryngoscopy and to check for signs of histamine release. Materials and Methods: 200 patients of the American Society of Anesthesiologists Grade 1 and undergoing elective surgeries under general anesthesia were taken up and divided into two groups of 100 each by computer-generated randomization. Group 1 received Inj. Cisatracurium besylate 0.15 mg/kg IV, Group 2 received Inj. cisatracurium besylate 0.1 mg/kg IV. Results: Both the groups had good to excellent intubating condition after 3 minutes of administration of the study drug. The pattern of changes in the

hemodynamic variables were similar in both groups. None of the patients required any additional dose of Cisatracurium nor the drugs to suppress the stress response. None of the patients had signs of histamine release. Airway related complication were more seen in 0.1mg/kg group, with higher incidence of bucking and coughing. Conclusion: 0.1mg/kg of Cisatracurium had similar intubating conditions and hemodynamic stability with 0.15mg/kg of Cisatracurium. But, more patients in 0.1mg/kg group had coughing and bucking compared to 0.15mg/kg of Cisatracurium. Hence from our study we conclude that 0.1mg/kg dose of Cisatracurium is as effective as 0.15mg/kg dose of Cisatracurium in terms of hemodynamic stability and intubating conditions but with risk for airway related complications.

***Keywords*---**Cisatracurium, Intubating conditions, General anesthesia, Hemodynamic stability.

Introduction

Neuromuscular blocking drugs (NMBD) are used to provide skeletal muscle relaxation to facilitate tracheal intubation and to improve surgical working conditions during general anaesthesia. Cisatracurium, a Benzyl-iso-quinolinium compound is a non-depolarizing NMBD with intermediate duration of action. It is a stereoisomer of Atracurium, with a potency of approximately 3 to 4 times greater than that of Atracurium.[1,2] Despite the higher potency, Cisatracurium is associated with more stable hemodynamics than Atracurium and does not cause histamine release even at dose of 0.4mg/kg (8×Effective Dose 95).[3]

The ED95 dose of Cisatracurium is 0.04mg/kg (0.032-0.05mg/kg).[4,5] However, studies had shown that increasing the dose of Cisatracurium to 4×ED 95 (0.2mg/kg) and 6×ED 95 (0.3mg/kg) provided more effective neuromuscular blockade and excellent cardiovascular stability but with prolongation of duration of action of NMBD.[6,7] The duration of action of 0.1mg/kg, 0.2mg/kg and 0.4mg/kg of Cisatracurium is 46 minutes, 68 minutes and 91 minutes respectively.[4,5] As the dose of drug increase, more the amount of drug administered, more the side effects and the duration of neuromuscular blockade. Common side effects seen with Cisatracurium are light headedness, mild itching, and flushing.

The intubating dose of a non-depolarizing muscle relaxant drug (NDMD) is 2 times ED95. Several clinical studies compared equipotent doses of Atracurium and Cisatracurium and concluded that Atracurium is more effective than Cisatracurium (0.1mg/kg) at the same dose (2×ED 95). Bluestein found that more than 90% of patients in his study had good or excellent intubating conditions, at 2 minutes following administration of 0.1mg/kg of Cisatracurium.[8]

The recommended intubating dose of Cisatracurium is 0.15mg/kg but in our hospital, we use both doses of Cisatracurium i.e. 0.1mg/kg and 0.15mg/kg, which provides good muscle relaxation with less hemodynamic side effects.[1] There

are limited studies available for the comparison of the efficacy of 0.15mg/kg with 0.1mg/kg of Cisatracurium.[7]

In my study, I would like to compare the intubating condition and hemodynamic stability of two different doses of Cisatracurium i.e. 0.1mg/kg and 0.15mg/kg, and to find out whether 0.1mg/kg is as effective as 0.15mg/kg for endotracheal intubation, so that we can decrease the intubating(0.15mg/kg) dose of Cisatracurium.

Materials and Methods

This randomized control trail was done between November 2018 and May 2020. 200 patients who underwent elective surgery under GA with endotracheal tube after meeting the inclusion criteria were selected for the study.

Inclusion Criteria:

- ASA 1 and ASA 2 patients.
- Age between 18-65yrs.
- BMI less than 30kg/m^2
- Duration of surgery more than and equal to one hour.

Exclusion Criteria:

- Emergency surgeries
- Full stomach patients
- Pregnancy
- Difficult airway
- Patients with neuromuscular disease
- Patients with head and neck trauma
- Burns
- Surgery in prone position
- Patients on Beta blockers
- Patients with thyroid disease
- Patients with liver and kidney disease
- Patient with history of allergy to any drugs

They were then randomized into 2 groups by block randomization technique.
Group 1: patients received 0.15mg/kg of Inj. Cisatracurium
Group 2: patients received 0.1mg/kg of Inj. Cisatracurium

After pre-oxygenating the patient for 3-5 minutes with 100% oxygen. Inj.Midazolam 1mg iv and Inj. Fentanyl 2mcg/kg iv were given followed by induction with Inj. Propofol 1-1.5mg/kg IV and then, checked for the adequacy of ventilation with face mask. After making sure that we can mask ventilate the patient, one of the two doses of Cisatracurium was given to the patient according to the randomization. After mask ventilating the patients with oxygen, and Isoflurane, direct laryngoscopy was done at 3 minutes of administration of the study drug and intubation was done with an appropriately sized cuffed endotracheal tube and its position was confirmed. The consultant or anaesthetist with more than 3 years of experience, who intubated the patient had also checked

for the ease of intubation based on scoring by Goldberg et al. The patient was then monitored for 20 minutes (Baseline, after induction, at the time of administration of muscle relaxant, 2minutes after giving muscle relaxant, at the time of intubation, at 1min, 2min, 3min, 5min, 10min, 15min and 20min of intubation), post intubation for hemodynamic variables such as heart rate (HR), SBP, DBP, MAP. Signs of histamine release was monitored clinically through skin changes graded as flushes, erythema, wheal or presence of hemodynamic changes and bronchospasm, additional dose of muscle relaxant given (if any), treatment of Stress response given (if any), any complications were recorded.

Hypertension and tachycardia at the time of intubation and immediately after intubation was treated with Inj.Lignocaine 1.5mg/kg IV as first line of treatment and Inj. Esmolol 0.3-0.5 mg/kg IV as second line of treatment. Increase in BP and HR more than 20% from baseline between 5 to 20 min after intubation was treated with Inj. Fentanyl 0.5mcg/kg. Significant bradycardia was managed with inj. Atropine 0.6mg IV. Significant Hypotension with bradycardia was treated with inj. Ephedrine 6mg IV, titrated to the response. Hypotension with tachycardia was managed with Inj. Phenylephrine 50mcg IV, titrated to response.

If intubating condition was poor or not possible, after waiting for another 1 minute it was reassessed. If still poor, an additional dose of same muscle relaxant (0.05mg/kg of Cisatracurium) was administered. If intubating condition was good with persistent coughing/bucking, it was managed with Inj. Lignocaine 1.5mg/kg IV.

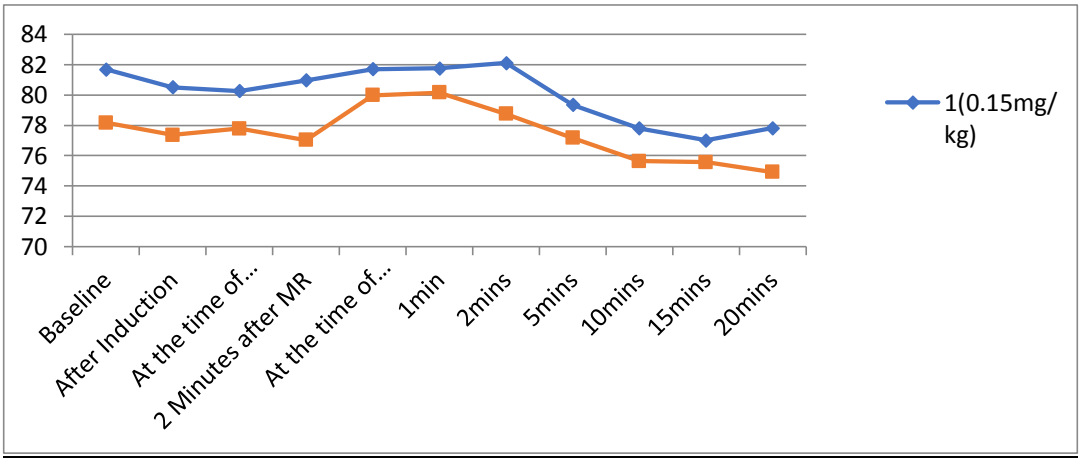
Any additional dose of Cisatracurium if required, requirement of drugs to suppress response during laryngoscopy and intubation, signs of histamine release and complications such as hypertension, hypotension, tachycardia, bradycardia, coughing, bucking were also checked.

Results

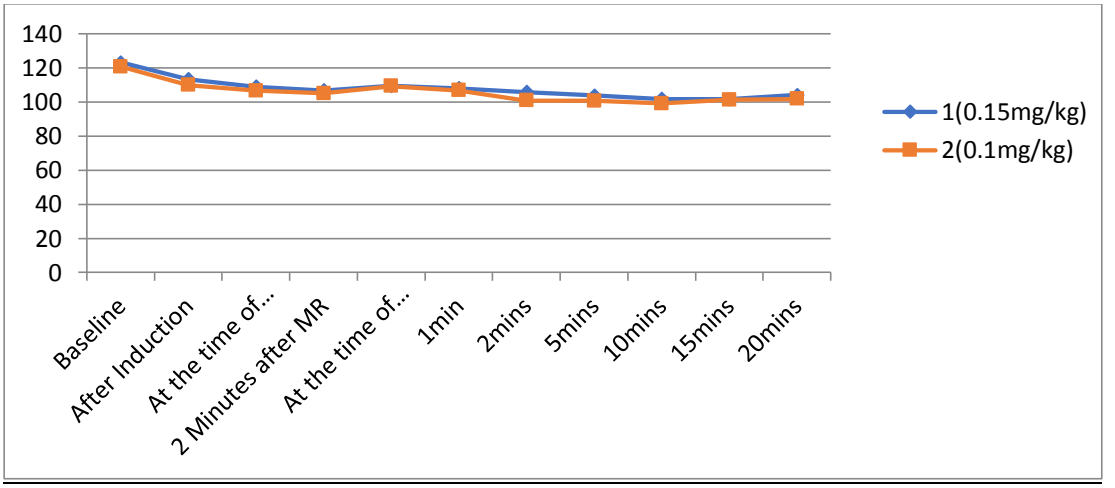
The mean age in group 1 (with 0.15mg/kg of Cisatracurium) was 39.3 years (±*11.94*) and in group 2 (with 0.1mg/kg Cisatracurium) was 38.3years (±12.47) which was statistically not significant (p value 0.55). The numbers of female and male patients in Group 1 were 68 and 32 respectively and in Group 2 were 74 and 26 respectively. There were a greater number of female patients in both the groups. The number of ASA1 and ASA 2 patients in group 1 were 57 and 43 respectively, and in group 2 were 50each, which was statistically not significant (p value 0.3646). The mean height in group 1 was 158.24cms (±9.70) and in group 2 was 155.61cms (±8.21) which was statistically not significant (p = 0.0752). The mean weight in group 1 was 64.47kg (±10.751) and in group 2 was 58.68kg (±10.476) which was statistically significant. (p value 0.005). The mean BMI in group 1 was 25.58kg/m^2 (±3.29) and in group 2 was 24.49kg/m^2 (±4.33) which was statistically not significant (p value 0.087).

In both the study groups, the heart rate variation at the time of intubation and for 20 minutes post intubation was minimal. The mean heart rate was mostly equal to baseline till 2minutes post intubation and then it started decreasing slowly

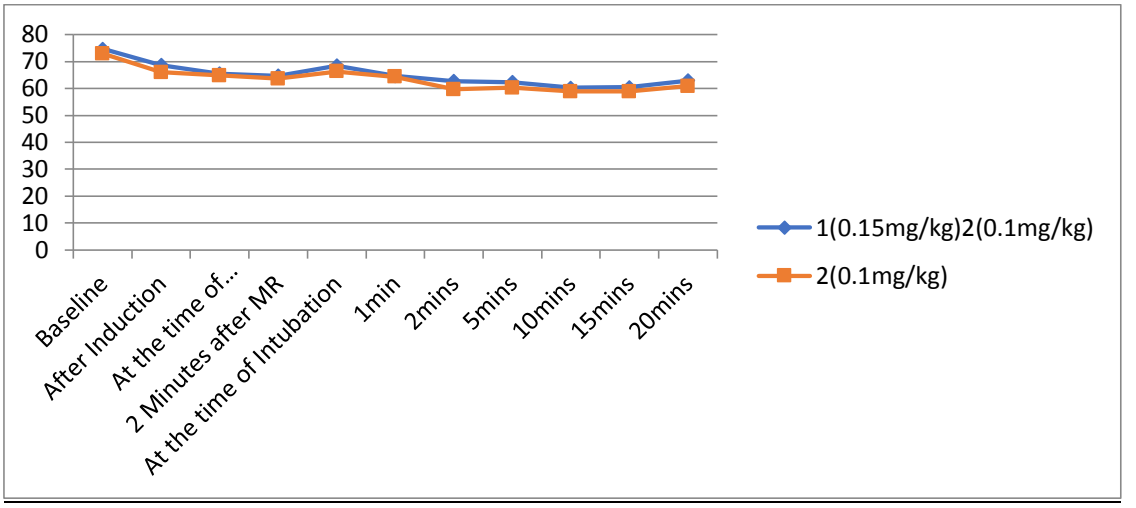
until 20minutes post intubation. Therefore, the pattern of heart rate was similar in both the groups.



Graph 1 : pattern of heart rate

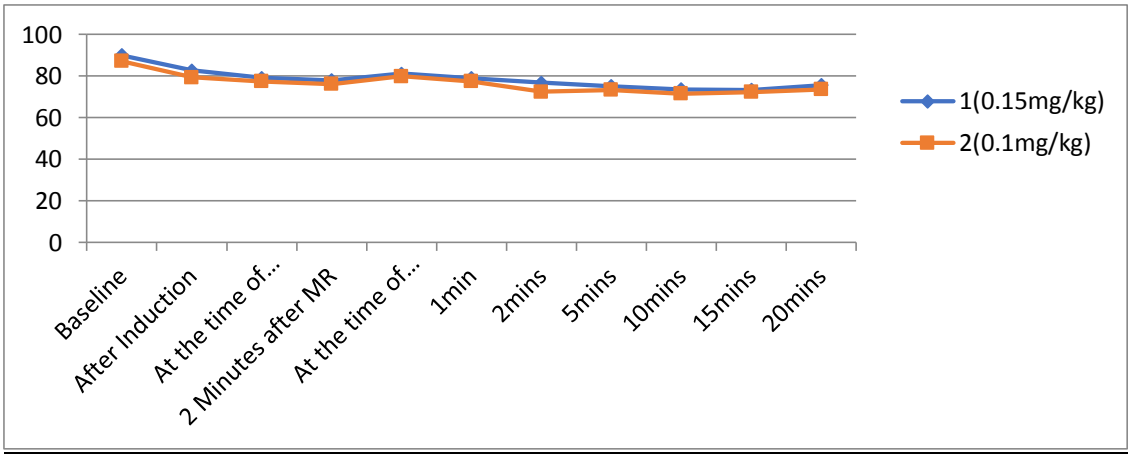


Graph: 2 The pattern of change in systolic blood pressure was similar in both the groups



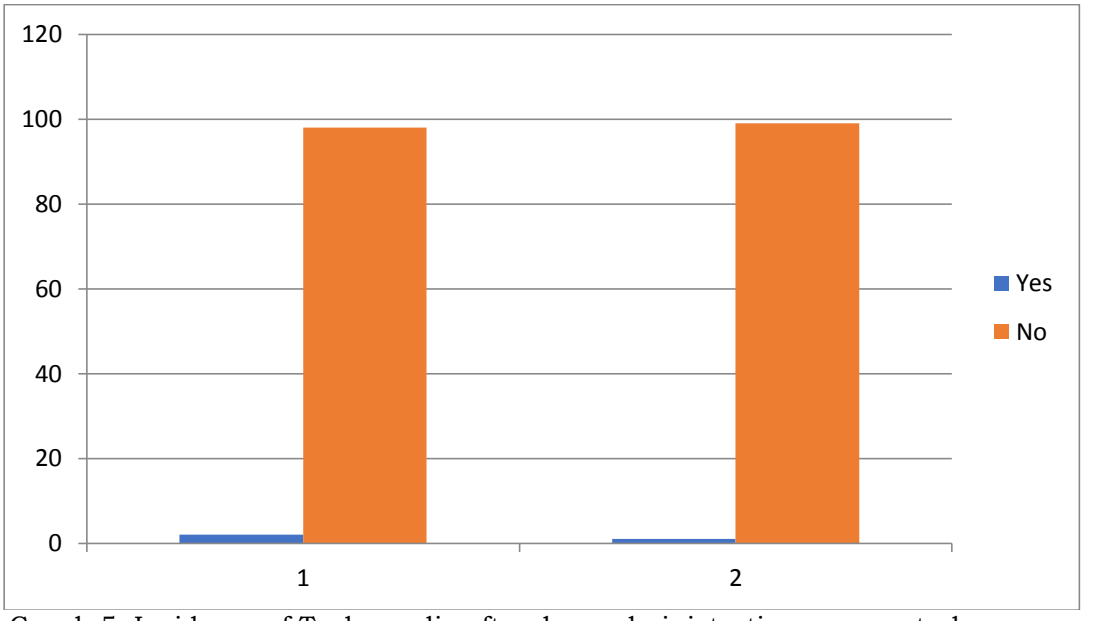
Graph 3: Pattern of diastolic blood pressure among two study groups

The pattern of change in diastolic blood pressure was similar in both the groups.



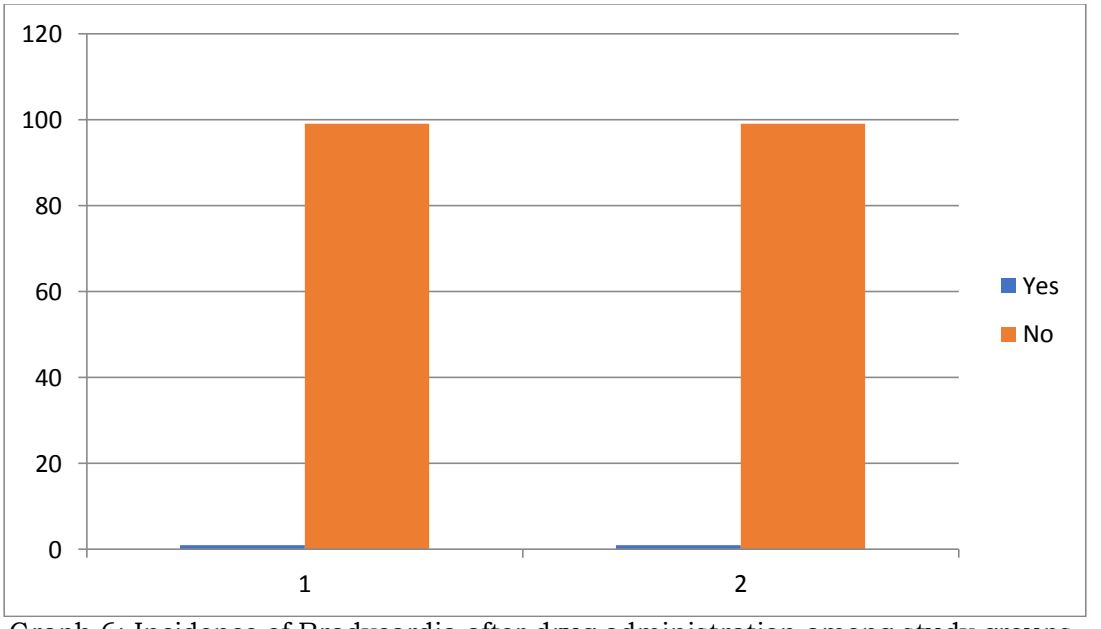
Graph 4: Pattern of Mean blood pressure among two study groups

The pattern of change in mean arterial pressure was similar in both the groups.



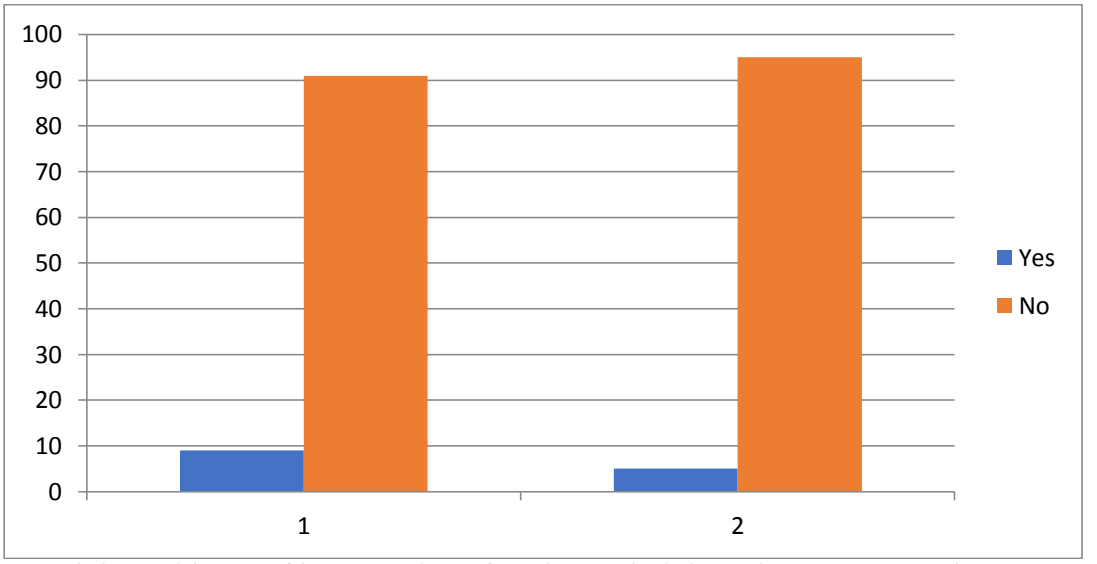
Graph 5: Incidence of Tachycardia after drug administration among study groups

Among 200 patients, only 3 patients had tachycardia of which two patients were in group 1 and one patient in group 2, which was statistically not significant (p >0.5617).



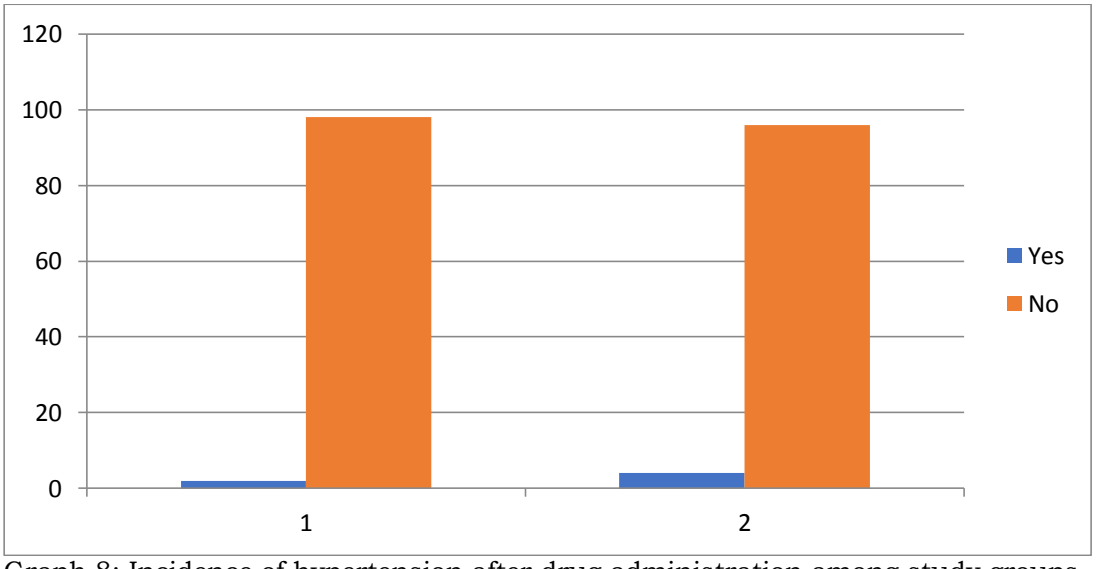
Graph 6: Incidence of Bradycardia after drug administration among study groups

The incidence of Bradycardia after drug administration was seen in one patient in each group, which was statistically not significant (p >1.0).



Graph 7: Incidence of hypotension after drug administration among study groups

The incidence of hypotension after drug administration was seen in nine patients in group 1 as compared to five patients in group 2, which was statistically not significant (p >0.4081).



Graph 8: Incidence of hypertension after drug administration among study groups

The incidence of hypertension after drug administration was seen in two patients in group 1 as compared to four patients in group 2, which was statistically not significant (p >0.4083).

Table 1
Incidence of Coughing/Bucking/Inadequate Vocal cords (VC) relaxation among study groups during intubation

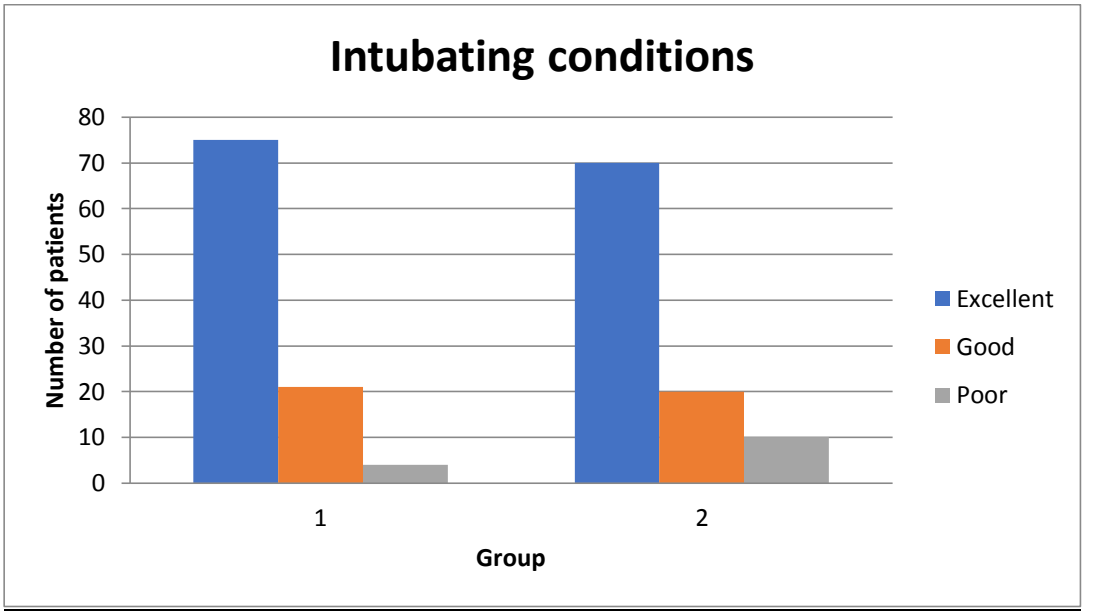
	1(0.15mg/kg)	*2(0.1mg/kg)*
Bucking	4	10
Coughing	0	2
Inadequate VC relaxation	1	2
Bucking + Coughing	1	6
Bucking + Inadequate VC relaxation	0	3
Coughing+ Inadequate VC relaxation	1	0
Nil	93	77
Total	100	100

The overall incidence of Coughing/Bucking/Inadequate vocal cord relaxation during intubation was seen in seven patients of group 1 as compared to twenty-three patients of group 2, which is statistically significant. (p=0.0018). 4 patients who received 0.15mg/kg had bucking whereas 10 patients had bucking who received 0.1mg/kg. 2 patients who received 0.1mg/kg had coughing, but none had coughing in Group 1. 2 patient who received 0.1mg/kg had inadequate vocal cord relaxation but only one patient had the same in 0.15mg/kg group.

Table 2
Signs of histamine release after drug administration among study groups

	Signs of histamine release	
	Absent	*Present*
1(0.15mg/kg)	*100*	*0*
2(0.1mg/kg)	*100*	*0*
Total	*200*	*0*

There were no signs of histamine release in any of the patients in either of the groups.



Graph 9: Intubating conditions in general among the study groups

In group 1, 75 patients had excellent intubating conditions compared to 70 patients in group 2, and 21 patients had good intubating conditions in group 1 compared to 20 patients in group 2, which was statistically not significant (p value 0.3244). There were 14 patients who had poor intubating conditions out of which 10 were from group 2 (0.1mg/kg of Cisatracurium) but not statistically significant.

Discussion

Cisatracurium is a stereo isomer of Atracurium, which is three to four times more potent than Atracurium, with stable hemodynamics and no evidence of histamine release even in higher doses (8×ED95).[3]

The main goal of neuromuscular blockade includes paralysis of vocal cords and muscles of jaw to facilitate endotracheal intubation. The intensity of maximum blockade is directly affected by the dose. When doses lower than those required to produce 100% neuromuscular block are administrated, the time taken to reach maximum effect is a fraction of neuromuscular blocking drug and blood flow to the muscles. It is independent of the dose administrated.

The intubating dose of Cisatracurium is 0.15mg/kg. Even with 0.1mg/kg of Cisatracurium, we found good muscle relaxation in our hospital. Since there are limited studies available comparing these two doses, we decided to compare two different intubating doses, 0.1mg/kg versus 0.15mg/kg of Cisatracurium in terms of hemodynamic stability and intubating conditions and to find out whether 0.1mg/kg is as effective as 0.15mg/kg for endotracheal intubation so that we can replace the recommended intubating dose of Cisatracurium 0.15mg/kg, with 0.1mg/kg. In our study, 200 patients were randomly divided into following two groups using block randomisation technique.

Group 1: patients who received 0.15mg/kg of Cisatracurium
Group 2: patients who received 0.1mg/kg of Cisatracurium.

Similar anaesthetic techniques were employed in both groups to avoid any discrepancy. Both groups were compared for the following parameters such as hemodynamic stability, intubating conditions, requirement of additional dose of Cisatracurium, requirement of drugs that can suppress the stress response to laryngoscopy and intubation and any evidence of release of histamine. The results obtained were noted and data for different parameters were analysed subsequently.

Demographic Data

Patients enrolled in group 1 had a mean age (years) of 39.3 and it was 38.3 in group 2 but there were greater number of female patients in both the groups. In group 1, there were 57 patients of ASA I class and 43 patients of ASA class II, whereas in group 2, 50 patients each were in ASA I and II class. The mean BMI in group 1 and group 2 was 25.58 kg/m^2(±3.29) and 24.49 kg/m^2 (±4.33) respectively. Hence, both groups had similar demographic profile.

Intubating Conditions

Intubating conditions of the study population was assessed after 3 minutes of administration of Cisatracurium by the anaesthetist intubating the patient by a scoring scale, described by Goldeberg et al.[6] In our study we found that, 75% patients in group 1 had excellent intubating conditions as compared to 70% patients in group 2, and 21% patients had good intubating conditions in group 1 compared to 20% patients in group 2, even though 10 % patients in group 2 had poor intubating conditions compared to 4% patients in group 1, and it was statistically not significant (p value 0.3244).

The results of our study was similar to the study done by H Little John et al, where they found 67% of the patients in 0.1mg/kg group and 90% of the patients in 0.15mg/kg group had acceptable intubating conditions after 2minutes of administration of Cisatracurium.[18] Whereas Bluestein LS observed that 90% of patients had good or excellent intubating conditions by 2 minutes following 0.1mg/kg of Cisatracurium whereas 100% of the patients achieved excellent or good intubating conditions following 0.15mg/kg of Cisatracurium.[8]

There were several studies using 0.15mg/kg of Cisatracurium. Agavelian EG and Arkharova TB conducted a study where they used Cisatracurium (0.15mg/kg and 0.12mg/kg) with intravenous anaesthesia technique and created good or excellent intubation conditions with easy laryngoscopy with both the doses.[25] Schmautz E, Deriaz H used 0.15 mg/ kg (3×ED95) along with a propofol /nitrous oxide/oxygen induction intubation technique and concluded that it provided good or excellent intubating conditions with no vocal cord movements similar to our study.[26] Rimaniol JM et al reported that 80% of the patients achieved good to excellent intubating conditions 2minutes after the administration of 0.15mg/kg of Cisatracurium.[19]

M.T. Carroll compared 0.1mg/kg and 0.15mg/kg of Cisatracurium and did not find any significant difference between in terms of clinically acceptable intubating conditions at 2 minutes of administration.[20]

Hemodynamic Stability

In our study, mean heart rate remained similar to baseline between 78-80 beats per minutes and the range of mean systolic blood pressure was between 98-120 mmHg which was similar to baseline. Even the mean diastolic blood pressure and mean arterial pressure also remained similar to baseline with a range between 58-70mmHg and 70-86 mmHg respectively. Therefore, the pattern of change in the heart rate, systolic blood pressure, diastolic blood pressure and mean arterial pressure was similar in both groups during induction, intubation and 20minutes post intubation. Hemodynamic stability in our study was very much similar to other quoted studies.

El-kasaby AM, in his study found that HR, MABP increased post-intubation which was statistically significant with administration of 2 times ED95 (0.1mg/kg) dose of Cisatracurium, which was not found in our study, but 5-20 min later it was not statistically significant.[6] Schramm WM, in his study demonstrated that an intravenous bolus dose of 0.15mg/kg of Cisatracurium resulted in less cerebral and cardiovascular hemodynamic side effects.[22]

Vishnu Vardhan Athaluri reported that hemodynamic variables were not significantly altered with 0.1mg/kg and 0.15mg/kg dose of Cisatracurium.[27] Dr Arun Kumar Mohanty's in his analysis found that there was an increase in MAP compared to baseline after intubation and at 5 mins which gradually returned to baseline at 15 but there was no statistically significant difference with 0.1 and 0.15mg/kg of Cisatracurium.[28]

Complications

Among 200 patients, only 3 patients had tachycardia of which two patients were in group 1 and one patient in group 2, which was statistically not significant (p >0.5617). Only 1 patient from each group had bradycardia. The incidence of hypotension after drug administration was seen in nine patients in group 1 as compared to five patients in group 2. The incidence of hypertension after drug administration was seen in two patients in group 1 as compared to four patients in group 2.

The overall incidence of Coughing/Bucking/Inadequate vocal cord relaxation during intubation was seen in seven patients of group 1 as compared to twenty-three patients of group 2, which was statistically significant. In group 1 only 4 out of 7 patients had bucking where as in group 2 that was 10 out of 23. 6 patients in group 2 had both coughing and bucking but in group 1 that was seen only in 1 patient. Inadequate vocal cord relaxation was seen in only 1 patient in group 1 and 2 in group 2. There were no studies where they studied about the complications during laryngoscopy and intubation.

In our study, none of the patients in either group had signs of histamine release. El-Kasaby AM et al, Bluestein LS et al (1996), H Little John et al and Magdy Omera reported that there was no intraoperative skin reaction, bronchospasm or flushing in patients treated with Cisatracurium (0.1mg/kg and 0.15mg/kg), which correlates with our study.[6,8,18,24,]

Conclusion

We compared two doses of Cisatracurium 0.15mg/kg and 0.1mg/kg for endotracheal intubation and the findings are as follows:

1. Both the groups had good to excellent intubating condition after 3 minutes of administration of the study drug.
2. The pattern of changes in the hemodynamic variables (heart rate, MAP, SBP, DBP, MAP) were similar in both groups. It remained almost equal to or slightly less than the baseline.
3. None of the patients required any additional dose of Cisatracurium nor the drugs to suppress the stress response.
4. None of the patients had any evidence of histamine release
5. Airway related complication were more seen in 0.1mg/kg group, with higher incidence of bucking and coughing.

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