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A Study of Haemodynamic and Pharmacodynamic Effects of Cis-Atracurium and Vecuronium in Patients Undergoing Laparoscopic Appendicectomy

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Abstract

Aim: To study the haemodynamic and pharmacodynamic effects of cis-atracurium and vecuronium. *Settings and Design:* Prospective, Randomized, Parallel group, Double blind study *Plan of Study:* After institutional review board approval and informed written consent from patients, eighty patients undergoing laparoscopic appendicectomy were randomized into two groups. Group-C n=40 received loading dose of inj. Cis-atracurium 0.15mg/kg and maintenance doses of 0.03mg/kg while Group-V, n=40 received loading dose of inj. Vecuronium 0.10mg/kg and maintenance doses of 0.02mg/kg. As premedication Inj. Ondansetron, Glycopyrolate, Midazolam were administered followed by Inj. Propofol + Inj. Fentanyl + loading dose of assigned drug for induction & intubation of the patient. Maintenance of general anaesthesia was done with O_2+N_2O (50:50), Sevoflurane inhalation, and intermittent doses of assigned muscle relaxant drug according to PNS. The observations as time of onset of action, intubation time, time interval between loading and first maintenance dose, time interval between maintenance doses, extubation time, total number of drug dosage requiredand haemodynamic parameters were noted. *Statistical analysis:* Data were analysed by using repeated measure ANOVA and by Manwitney U test. *Results:* Time of onset of action and intubation time in Group- V were significantly lower as compared to Group-C.Time interval between loading & first maintenance dose was comparatively higher in Group- C than Group- V. Time intervals between maintenance doses were comparable among both the groups. When compared with Group-V, extubation time was shorter in Group-C. *Conclusion:* Cis-atracurium had a longer time of onset of action, longer duration of action, hence less doses were required for maintenance of anaesthesia, faster recovery as compared to Vecuronium. Both drugs were haemodynamically stable.

Keywords: Cis-atracurium, Vecuronium, Train of Four, Onset of action, Duration of action & recovery

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Introduction

The introduction of neuromuscular blocking drugs revolutionized the practice of anaesthesia. Before the advent of muscle relaxants, anaesthesia was induced and maintained by intravenous or inhalation agents. After the introduction of muscle relaxant, the anaesthesia underwent a conceptual change. Anaesthesia was redefined as a triad of narcosis, analgesia, and muscle relaxation. (1)

In 1975 Savarese and Kitz outlined the characteristics of an ideal anaesthetic agent; which are enumerated as follows:

- Non-depolarizing type of action ; Rapid onset of action ;Short duration of action

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- Rapid recovery; No cumulative pharmacokinetics; No histamine release
- Minimal cardiovascular effects; Pharmacological inactive metabolites
- Reversible by cholinesterase inhibitors

Depolarizing and nondepolarizing drugs are routinely used to facilitate tracheal intubation during the induction of anaesthesia and to maintain the muscle relaxation during surgery. Atracurium meets many characteristics for an ideal intermediate-acting drug. It also shows weak histamine-releasing properties, which limits the administration of large and rapid boluses.[2]

As a result of this, new molecule was developed named as Cis-atracurium. Cis-atracurium, a cis-cis isomer of Atracurium, constitutes 15% of the racemic mixture of the parent compound and it is three times more potent than Atracurium.[3] It does not causes histamine release,[4] possesses greater haemodynamic stability,[3] the favourable characteristics of Hoffman metabolism[5] so that the elimination of the drug is independent of hepatic and renal function.[6] Dosages may not need to be changed in the geriatric or younger population.

Atracurium has been demonstrated to exhibit shorter duration of action in elderly patients when compared with Vecuronium.[7] It appears reasonable to apply the same considerations to Cis-atracurium; but Cis-atracurium onset of action is slower[8] and its clinical duration of action slightly longer than that of Atracurium.[9] Cis-atracurium has been compared favourably as an alternative to Vecuronium in cardiac patients due to its inherent cardiovascular stability[10] and hence a better choice than Atracurium in this point of view.[11] The present study was planned to study the haemodynamic and pharmacodynamic effects of Cis-atracurium and its clinical comparison with widely used agent Vecuronium.

Materials and Methods

This prospective, randomized, parallel, double blind study was carried out in one of the tertiary care centre. Institutional Review Board permission was obtained from the institutional. The informed written consent was obtained from all the patients under study.

Eighty patients of either sex posted for laparoscopic appendicectomy under general anaesthesia were enrolled in this study according to following criteria. ***Age:*** 18–50yr and ***ASA class:*** I & II who were posted for elective laparoscopic appendicectomy under general anaesthesia.

Exclusion Criteria: Anticipated difficult airway, pre-existing liver or renal failure, ANC cases & lactating females, patient with neuromuscular disease& neurological disease.

Investigations: Preoperative investigations (Hb, TLC, platelet count, RBS, RFT,S.electrolytes, chest X-ray, ECG) were done. On the day of surgery, after shifting the patient to the preanaesthetic care room, standard monitoring for heart rate (ECG), systolic and diastolic blood pressure (NIBP), SpO_2 cables were connected to the patient & baseline vital parameters were recorded. IV access was secured using 20G intracath in right hand andinfusion 5% dextrose was started at the rate of 4ml/Kg/ hr.The patient was shifted to operation theatre. Inj. Ondansetron 0.08mg/kg, Inj. Glycopyrolate 0.004mg/kg, Inj. Midazolam 0.02mg/kg were administered intravenously.

The patients were randomized using computer generated random number sequence method into two groups with 40 patients in each group.

Group- C: Each patient received loading dose of inj. Cis-atracurium 0.15 mg/kg and maintenance doses of 0.03mg/kg.

Group- V: Each patient received loading dose of inj. Vecuronium 0.10 mg/kg and maintenance doses of 0.02mg/kg.

During the surgical procedure patient was monitored for ECG, SpO_2. Neuromuscular function was monitored, by assessing the contraction of adductor pollicis muscle by stimulating ulnar nerve at wrist using peripheral nerve stimulator (PNS). After cleansing the skin, ECG surface electrodes were placed over ulnar nerve at the wrist. Baseline TOF count was done before induction of anaesthesia. Ulnar nerve was stimulated with TOF supra-maximal stimulation (4 pulses, 0.2msec in duration at a frequency of 2Hz, 2 seconds in duration).

Induction of Anaesthesia: Preoxygenation with 100% oxygen for 3minutes; Induction of general anaesthesia was done with Inj. Fentanyl 1µg/kg followed by inj. Propofol 2mg/kg. Following check ventilation, muscle paralysis was achieved by loading dose of muscle relaxant drug according to the assigned group. When there is no response to Train of Four on peripheral nerve stimulation, trachea was intubated with sterile, polyvinylchloride, cuffed, appropriate sized endotracheal tube. Time of administration of study drug & time of onset of drug under study& intubation time were noted.

Maintenance of Anaesthesia: General anaesthesia was maintained with oxygen and nitrous oxide (50:50), Sevoflurane & intermittent doses of assigned neuromuscular blocking agent according to PNS. When the TOF count increases by more than two, the top-up dose of respective study drug was given. Time intervals between maintenance doses were noted. Tidal volume and ventilatory frequency will be adjusted so as to maintain normocapnia ($EtCO_2$: 40 ± 4 mm/Hg). Sevoflurane was titrated to maintain adequate depth of anaesthesia and to maintain haemodynamic parameters within 20% of their preoperative baseline values. Number of doses of the drug under study, total duration of surgery and intra-operative haemodynamic parameters were noted.

Reversal and Extubation: At the end of surgery, residual neuromuscular blockade was reversed with inj. Neostigmine 50µg/kg and inj. Glycopyrolate 10µg/kg intravenously after TOF count will be more than two.Extubation was done only after TOF count four was achieved and on recovering satisfactory consciousness and as per extubation criteria.

Monitoring: Haemodynamic parameters were monitored at baseline values; 5 minutes after inj Fentanyl; during laryngoscopy and intubation; every 10 minutes thereafter upto 30 minutes; and every 30 minutes upto the end of operation; at the end of operation; at extubation & at 2 minutes after extubation. PNS monitoring was done every 10sec till the onset of action and every minute till duration of action of drugs.

Statistical Analysis: All data were expressed as Mean ± SEM and compared by appropriate statistical tests. Hemodynamic data were compared by using Repeated measure ANOVA and other data by Manwitney U test. p value < 0.05 is consider as significant value.

Results

Patient characteristics in terms of age, gender, weight and height were comparable among both the groups (p > 0.05) (Table 1). Onset of action was [143.88 ± 15.62 secs] and intubation time was [191.6 ± 20.26 secs] in Group- V were significantly lower as compared to onset of action [187.13 ± 15.68 secs] and intubation time [244.50 ± 16.00 secs] in Group- C. The p-value < 0.0001 was found to be significant. Time interval between loading &first maintenance dose was comparatively higher in Group- C [49.50 ± 06.48 min] as compared to Group- V [29.85 ± 05.80 min] (p-value was <0.05). Time intervals between maintenance doses of Group- C & Group- V were21.25 ± 04.07 min & 23.07 ± 04.42 min respectively. Thetime intervals between maintenance doses of both groups were comparable & the p-value was >0.05.

Extubation time was comparatively shorter in Group- C (08.85 ± 02.62 min) than in Group– V. (14.47 ± 03.41 min) (p value < 0.05). Total number of doses were comparatively higher in Group- V (03.40 ± 00.63) compared to Group- C (01.47 ± 00.50) (p -value< 0.0001). Heart rate (HR) and mean arterial pressure (MAP) were comparable between both the groups. After intubation, it was decreased significantly after intubation in both the groups.

Discussion

While selecting neuromuscular agent for tracheal intubation or skeletal muscle relaxation, main aim of an anaesthesiologist is to select an agent with rapid onset, longer clinical duration of action, better haemodynamic stability and good spontaneous reversal.[12] Cis-atracurium, a nondepolarizing, intermediate acting, neuromuscular agent, decomposes into laudanosine and a tetravalent alcohol metabolite by Hoffman elimination. So, recovery of muscle relaxation is little affected by liver or kidney diseases.

In present study, patient's characteristics in terms of age, gender, weight and height were comparable among both the groups (Table 1) (p-value > 0.05). In present study while comparing the variables

Table 1. Demography data

Data	Group- C (n-40) Mean ± SD	Group- V (n -40) Mean ± SD	p- Value
Age(years)	28.80 ± 09.35	27.92 ± 09.57	0.6805
Gender(M/F)	21 /19	19 /21	0.8233
Height(cm)	157.90 ± 04.36	159.50 ± 02.99	0.0597
Weight(kg)	57.57 ± 05.54	55.40 ± 05.89	0.0931

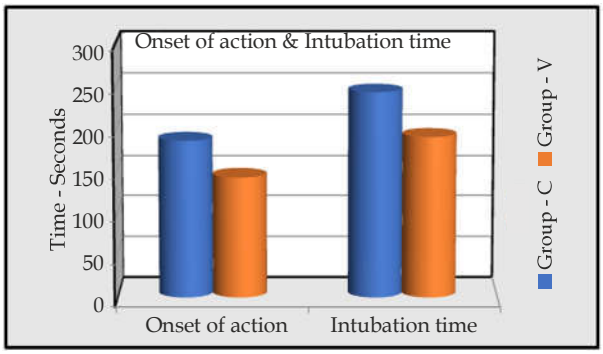

Fig. 1: Onset of action & Intubation time

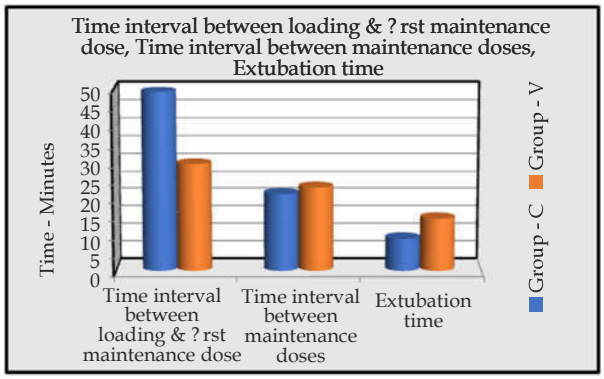

Fig. 2: Time interval between loading & first maintenance dose, Time interval between maintenance doses, Extubation time

Fig. 3: Total no. of doses required

like, onset of action (143.88 ± 15.62 seconds) and intubationtime (191.6 ± 20.26 seconds) in Group- V those were significantly loweras compared to onset of action (187.13 ±15.68 seconds) and Intubationtime (244.50 ± 16.00 seconds) in Group- C. (p-value <0.05) (Fig. 1).

Keles et al.[13] suggested that, the onset time was significantly shorter with Vecuronium than that with Cis-atracurium. Eppich L et al.[3] suggested that Cis-atracurium demonstrated a slightly longer onset and duration of action compared with Vecuronium and also the onset of maximum block was dose related in the Cis-atracurium group. Increasing the Cis-atracurium dose from 0.1 - 0.2 mg/kg shortened by 2minutes the onset of maximum dose block. However this delay did not influence the overall quality of intubating conditions.

The present study shows that,

- Time interval between loading &first maintenance dose was comparatively higher in Group- C (49.50 ± 06.48 minutes) than Group- V. (29.85 ± 05.80 minutes) (p-value < 0.05) (Fig. 2).
- Time intervals between maintenance doses were comparable among both the groups. Group- C (21.25 ± 04.07 minutes) & Group- V (23.07 ± 04.42 minutes) (p-value <0.05) (Fig. 2)

C Melloni et al.[14] suggested that Cis-atracurium duration of action was slightly longer than that of Vecuronium which was similar to our study. Vecuronium owes its relatively short duration of action to rapid distribution kinetics such that recovery occurs largely during the distribution phase. In contrast, Atracurium and Cis-atracurium are rapidly degraded by a pathway which is independent of hepatic and renal function, so that the pharmacological recovery occurs during the elimination phase. Amini Shahram et al.[15] studied effects of different doses of Cisatracurium on appropriate time for endotracheal intubation and haemodynamic changes during anaesthesia and found that the clinical duration of action with 0.15 mg/kg was 44.93 ± 05.40 minutes; comparable to our study, while with 0.20 mg/kg it was 57.03 ± 04.21 minutes.

In present study, extubation time was comparatively shorter in Group- C (08.85 ± 02.62 minutes) than in Group- V. (14.47 ± 03.41 minutes) (p-value <0.05) (Fig. 2). C Melloni et al.[14] found that spontaneous complete recovery time (SCRT) were similarly short with a trend toward a faster recovery with Cis-atracurium. Sarooshian SS et al.[16] found that young patients have more rapid onset of block than elderly patients because of slow bio-phase equilibration in elderly patients but clinical duration of action and recovery profile was found to be similar between two groups. Similar finding were observed by Ornstein et al.[17]

In present study, total number of doses were comparatively higher in Group- V (03.40 ± 00.63) as compared to Group- C (01.47 ± 00.50) (p value <0.05) (Fig. 3). There were no differences in baseline

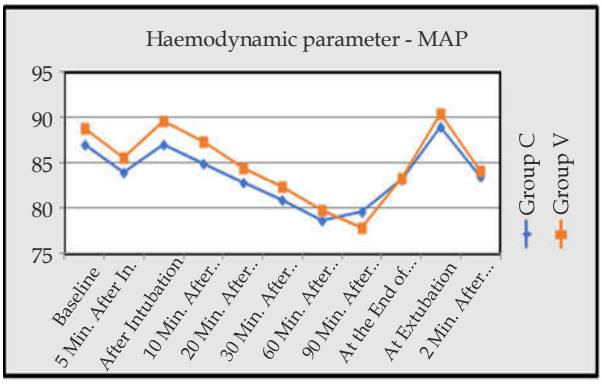

Fig. 4: Haemodynamic parameter - MAP

haemodynamic values among both the groups. After the induction of anaesthesia, both the groups showed significant but similar decrease in mean arterial pressure (MAP) and heart rate (HR) (Fig. 4). Hear rate (HR) was comparable between both the groups. It Was decreases significantly after intubation, but in the both groups (Fig. 5).

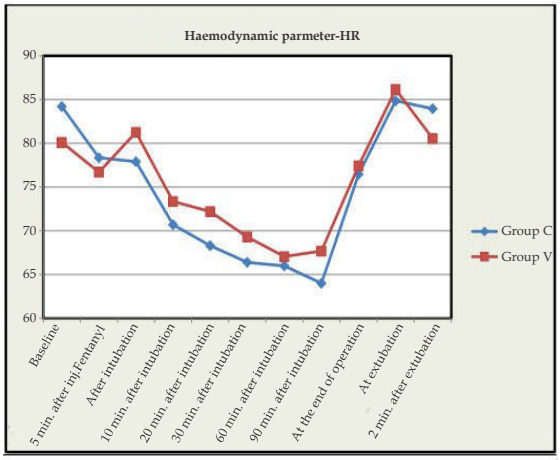

Fig. 5: Haemodynamic parmeter-HR.

EL Kasaby A M et al.[18] observed that small changes occurred in MAP and HR post induction and post intubation but these changes were not significant statistically and clinically at higher doses of Cis-atracurium. So, haemodynamic stability was evident among higher doses of Cis-atracurium.

In our study, no complications were observed in any of the patients. Complications like cumulative effect (defined as a progressive increase in the duration of action of repeat doses) did not appear; however elderly patients demonstrated a prolongation of NMB action with Vecuronium in comparison with Cis-atracurium, supporting differences in cumulation between muscle relaxants especially during recovery.[19,20] From this point of view Cis-atracurium seems a superior drug because it does not exhibit even the slightest minimal cumulation as evident with Atracurium.[19]

Limitations of the study: We used TOF count for assessment of intubation time, time required for maintenance doses, recovery times. However there are more sensitive test in neuromuscular monitoring such as single twitch and double burst stimulations for neuromuscular monitoring and also clinical tests for extubation.

Conclusion

- Though the Cis-atracurium and Vecuronium are intermediate acting agents, Cis-atracurium has a longer onset of action as compared to Vecuronium.
- Cis-atracurium has a longer duration of action, so minimal no. of doses required for maintenance of anaesthesia.
- Cis-atracurium has a faster recovery as compared to Vecuronium.
- No much changes in haemodynamic parameters in both the groups.

Conflict of Interest: Nil

Funding/ Sponsorship: Nil

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