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Comparison of intra operative muscle relaxation and neuro muscular recovery from continuous infusion of vecuronium and atracurium in ASA grade I @ II patients undergoing midline and paramedian laparotomies

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Abstract: *Background:* Vecuronium and Atracurium are two muscle relaxants that come close to fulfill most of the criteria for using them as continuous infusion. In this study in sixty adult patients of either sex, 25-45 years of age, belonging to ASA physical status I&II, were chosen, who were scheduled for midline and paramedian laparotomies under GA. *Objective:* (1) To assess the recovery time from neuromuscular blockade on stopping the infusion of vecuronium and atracurium. (2) To assess the haemodynamic performance in peri operative period. *Materials & Methods:* Patients were randomly allocated into two equal groups and received either vecuronium 0.8-1 μg/kg/min following a bolus dose of 0.1mg/kg or Atracurium 4-12 μg/kg/min following a bolus dose of 0.5 mg/kg. Intravenous infusion of muscle relaxants were adjusted to maintain 90% of neuromuscular blockade monitored by stimulating ulnar nerve at the wrist by a peripheral nerve stimulator throughout surgery. *Results:* The median time & interquartile range which were taken from intravenous bolus dose to 10% recovery was less in Vecuronium group (23±2 min) than atracurium group (25.± 2 min). Vecuronium (median 15.5 ± 3 min) took less time to achieve steady state of block after starting infusion than atracurium (median 18 ± 3 min). *Conclusions:* Patients who received vecuronium recovered early from relaxant effect with more stable hemodynamics.

Keyword: Infusion, Muscle relaxant, Vecuronium, Atracurium, Peripheral nerve stimulator.

Abbreviations: ASA - American Society of Anesthesiologists, CDL -Choledocholithotomy, DBS - Double burst stimulation, ECG – Electrocardiography, TOF - Train of four.

Introduction

Anaesthesia involves administration of drugs to produce analgesia, amnesia, hypnosis and muscle relaxation. The use of neuromuscular blockers has been important in the evolution of anaesthesia and surgery and is a common practice in present day operating rooms. The use of muscle relaxants in clinical practice can be traced back to the finding of Benjamin Brodie in 1811-12, that animals poisoned by the drug curare could be kept alive by artificial ventilation. In the landmark experiment of Grifith and Johnson in the year 1942, in Montreal, purified curare was used to obtain adequate muscle relaxation. This was one of the milestones in the history of specialty [1]. Muscle relaxants, by providing immobility and thus ease for a surgeon's operation, not only revolutionized the practice of anaesthesia in the modern era but have also led to explosive developments in cardiothoracic, neurologic and organ transplantation surgery. But several catastrophes have occurred with the use of d-tubocurarine in the past due to the lack of adequate knowledge about its pharmacology and lack of antagonists [1-2].

However, bolus administration of long acting drugs like Pancuronium, leads to variations in the degree of relaxation and also hemodynamics, making it difficult to maintain uniformly relaxed state and stable hemodynamics to facilitate uneventful anaesthesia and surgery. So, the concept of continuous infusion of muscle relaxants came into existence. However, longer acting agents cannot be used as continuous infusions for maintenance of anaesthesia because they have a tendency to accumulate, leading to prolonged residual effect. An ideal muscle

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relaxant that can be used as a continuous infusion should have low potency, rapid onset, and a short duration of action, without any cumulative effect and their action should be easily reversible with proper antagonists. Vecuronium, an aminosteroid and atracurium, a benzylisoquinolinium compound, are two muscle relaxants that come close to fulfilling most of the above criteria.

Mirakhur RK and Ferres CJ, 1984, studied 10 adult patients of ASA grade I scheduled to undergo elective surgeries In their study they found that the average dose requirement of vecuronium was 0.083mg/kg/hr. the time taken to 10 % recovery of twitch height averaged 26 minutes. The average time taken for stabilization of block at 90% following recovery from the intubating dose, that is the time taken to achieve steady state block, was 15.4±6.8 minutes. The time required for the twitch height to recover from 10 to 25 % of control on stopping of vecuronium infusion averaged 7.4±2.65 minutes [3]. Chaudhari LS, Shetty AN, Buddhi M et al, 1999, found in their study comparing continuous infusion of atracurium with continuous infusion of vecuronium, in 62 patients, scheduled for laparotomies that vecuronium produced greater haemodynamic stability than atracurium and that spontaneous recovery was faster with vecuronium (540.94±76.46 seconds) than in atracurium (596.33±72.48 seconds). 84.4% of patients who received vecuronium fell within good to very good category of muscle relaxation compared to 63.3 % in atracurium group [4]. This study aims to assess the perioperative performance and post operative recovery from relaxant effects when vecuronium and atracurium are both used as a continuous infusion.

Material and Methods

This study was carried out in the Department of Anaesthesiology and Critical Care at Patna Medical College & Hospital, Patna. Sixty adult patients of American Society of Anesthesiology (ASA) physical status I and II, scheduled for median and paramedian laparotomies under general anaesthesia, were included in the study. Informed consent was obtained from each patient prior to including him/her for the study.

Patients were randomly allocated to two equal groups (n = 30 in each group) using computer generated random number list. Group I comprised patients who received vecuronium bromide and group II comprised those who received atracurium besylate. The study was prospective, parallel group, single blind and controlled. Patients having asthma, diabetes, known neuromuscular disorder, hepatic failure & receiving medications which have known interaction with neuromuscular blocker were excluded.

Monitoring devices like BP cuff, ECG leads, pulse oxymeter and surface electrode were made ready. In all patients, after 3 minutes of pre-oxygenation, injection fentanyl 2 μg/kg was given and general anaesthesia was induced with injection thiopental sodium (4-6 mg/kg body weight) intravenously till loss of eyelash reflex was observed. Injection vecuronium (0.1 mg/kg) and atracurium (0.5 mg/kg) were used in group I and group II respectively to achieve muscle relaxation for endotracheal intubation. Intubation was done with cuffed endotracheal tube of appropriate size when there was no response to train of four stimuli.

Anaesthesia was maintained with infusion propofol, 66% nitrous oxide in oxygen and fentanyl as and when required. After intubation train of four responses were studied at regular intervals. As soon as the first response to train of four stimuli appeared, intravenous infusion of vecuronium (0.8-1 μg/kg/min) or atracurium (4-12 μg/kg/min) was started at a rate that was appropriate for that patient. Dose of infusion of relaxants was adjusted in such a way that first response of train of four was spared but second response remained suppressed. Time taken to achieve this steady state of block from the time of starting the infusion was noted.

The infusion was also titrated by resistance to ventilation, surgical relaxation (assessed by surgeon's satisfaction) and haemodynamic changes. While doing surgery, immediately after muscle layers were approximated, infusion was stopped and spontaneous recovery monitored using peripheral nerve stimulator and clinical criteria. Time of appearance of three responses to train of four stimuli was noted; residual neuromuscular blockade was reversed with injection

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neostigmine (0.05 mg/kg) and injection glycopyrrolate (0.01 mg/kg) intravenously. Adequate reversal of neuromuscular blockade was confirmed with the help of double burst stimulation (DBS) mode of peripheral nerve stimulator. When patients were fully awake, moving all four limbs to vocal commands with recovery of good muscle tone and power, extubation was done. Subsequently all patients were shifted to the postoperative ward.

Throughout the procedure, train of four was used to assess the degree of neuromuscular blockade – absence of any twitch response indicating 100% block and appearance of 1, 2 or 3 response indicating 90%, 80% or 75% block respectively. The INNERVATOR 272 model manufactured by M/s Fisher and Paykel Healthcare International (NewZealand) was the instrument used. Hemodynamic parameters like pulse rate, systolic BP and diastolic BP were measured at different time points. These included 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) indicated bolus dose effect on haemodymnamics. This was repeated at 10 minutes because the effect of laryngoscopy and intubation was considered to wear off at that time point. Parameters measured 2 minutes and 10 minutes after starting infusion indicated hemodynamic performance during the infusion. Postoperative values were used to compare with other values measured pre- and intra-operatively and to assess the adequacy of analgesia.

Results

This prospective, parallel group, single blind and controlled study was conducted at Patna Medical College & Hospital, Patna, involving 60 patients divided into two groups. In Group I (n = 30), patients received vecuronium while those in Group II (n = 30) received atracurium for maintenance of muscle relaxation.

Tables 1 and 2 depict the study of drug requirements in individual subjects in the two groups.

Table-1: Mean Drug requirements (of Vecuronium) and SD in Group I subjects

Sl. No	Weight (kg)	Initial IV bolus (mg)	Subsequent dose in infusion (mg)	Total dose (mg)	Duration of surgery (minutes)	Dose requirement of vecuronium (mg/kg/min)
Mean	57.23	5.73	3.84	9.57	85.8	0.0010
SD	8.81	0.91	1.13	1.94	10.911	0.0002

Table-2: Mean Drug requirements (of Atracurium) and SD in Group II subjects

Sl. No	Weight (kg)	Initial IV bolus (mg)	Subsequent dose in infusion (mg)	Total dose (mg)	Duration of surgery (minutes)	Dose requirement of vecuronium (mg/kg/min)
Mean	58.6	28.8	37.73	66.86	84.93	0.009
SD	7.77	4.27	6.61	9.33	11.90	0.002

Table 3 shows comparison of time (in seconds) required after stopping infusion and 25% recovery from neuromuscular blockade (appearance of third twitch of train of four).

Table 4 summarizes the descriptive statistics for the pulse rate (beats per minute) in patients belonging to Group I and Group II at various time points. In both groups, changes in pulse rate with time were statistically significant. The median pulse rate in group II patients was significantly higher two minutes after injection of bolus dose of muscle relaxant ($p < 0.001$).

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Table-3: Comparison of time (in seconds) required after stopping infusion and 25% recovery from neuromuscular blockade (appearance of third twitch of train of four)						
Group	**Mean**	**Median**	**Minimum**	**Maximum**	**Quartile Range**	**Standard Deviation**
I	539.23	**538.5**	530	550	7.5	5.444
II	592.20	**593.5#**	580	605	17	8.536
p < 0.001 in comparison to group I (Mann Whitney U test).						

Table-4: Comparison of perioperative pulse (beats per minute) between group I & II at various time points							
	n	**Mean**	**Median**	**Minimum**	**Maximum**	**Quartile Range**	**Standard Deviation**
Preoperative							
Group I	30	73.43	73	62	85	11	6.611
Group II	30	70.47	70.5	62	86	9	5.582
2 minutes after giving bolus dose							
Group I	30	71.7	**72**	50	84	6	1.344
Group II	30	78.2	**78**[#]	63	89	11	1.241
10 minutes after bolus dose							
Group I	30	71.3	71	59	82	12	1.112
Group II	30	72.7	74	65	79	10	0.847
2 minutes after starting of infusion							
Group I	30	70.3	70	60	80	7	1.035
Group II	30	72.23	73	60	86	6	1.060
10 minutes after starting infusion							
Group I	30	70.6	69	58	83	13	1.004
Group II	30	69.23	68.5	56	80	12	1.261
10 minutes after stopping infusion							
Group I	30	73.63	74	64	82	10	0.969
Group II	30	74.67	74	68	84	7	0.781
Change in pulse rates was significant within both groups (Friedman's analysis of variance; p < 0.001). # *p* <0.01 in comparison to group I (Mann Whitney U test)							

Table 5 shows the descriptive statistics of the systolic blood pressures (SBP) of patients in Group I and II at various time points. No significant changes was seen in systolic blood pressure between the groups (Mann Whitney U test) and also within each group (Friedman's Analysis of variance).

Table 6 shows the descriptive statistics of the diastolic blood pressures (DBP) of patients in Group I and II at various time points. The median diastolic blood pressure in group II patients was significantly lower two minutes after injection of bolus dose of muscle relaxant ($p < 0.001$).No significant change was seen between the groups (Mann Whitney U test).

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Table-5: Comparison of perioperative systolic BP (in mmHg) between Group I and Group II at different time points							
	n	**Mean**	**Median**	**Minimum**	**Maximum**	**Quartile Range**	**Standard Deviation**
Pre operative							
Group I	30	121.87	120	61	150	18	12.134
Group II	30	119.53	117.5	100	152	25.5	11.458
2 minutes after giving bolus dose							
Group I	30	119.80	117.5	100	145	16.5	12.21
Group II	30	119.27	113	100	132	16	16.043
10 minutes after bolus dose							
Group I	30	121.33	118	102	142	17.5	11.789
Group II	30	116.20	115	100	146	17.5	8.950
2 minutes after starting of infusion							
Group I	30	117.80	115.5	101	142	20.5	11.684
Group II	30	117.63	115	99	142	10.5	12.620
10 minutes after starting infusion							
Group I	30	121.17	112	106	146	12.8	10.79
Group II	30	119.33	119	108	140	17	11.731
10 minutes after stopping infusion							
Group I	30	121.30	120	73	174	12.9	7.875
Group II	30	122.07	121	110	140	16.5	9.028
Changes in systolic blood pressure over time was not significant between the groups (Mann Whitney U test) as well as within the group (Freidman's Analysis of variance)							

Table-6: Comparison of diastolic BP (mmHg) between Group I and Group II at different time points							
	n	**Mean**	**Median**	**Minimum**	**Maximum**	**Quartile Range**	**Standard Deviation**
Pre operative							
Group I	30	71.20	69	60	85	17	8.845
Group II	30	72.57	72*	60	86	19	9.107
2 minutes after giving bolus dose							
Group I	30	71.20	**68.5**	60	87	17.5	8.894
Group II	30	65.53	**64***	56	77	11	6.044
10 minutes after bolus dose							
Group I	30	71.80	72	61	85	17	8.409
Group II	30	69.67	68	60	82	14.5	7.425
2 minutes after starting of infusion							
Group I	30	69.17	66	60	83	16	7.848
Group II	30	69.70	66	60	87	17	8.595
10 minutes after starting infusion							
Group I	30	68.03	65	58	88	20	8.094
Group II	30	71.27	69	60	84	17	8.267
10 minutes after stopping infusion							
Group I	30	77.064	78	64	88	7	5.414
Group II	30	75.777	76	62	102	9	7.432
Changes in diastolic blood pressure over time was significant only in Group II by Freidman's Analysis of variance ($p < 0.001$). No significant change was seen between the groups (Mann Whitney U test).							

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Discussion

The primary objective of providing muscle relaxation is to provide adequate conditions for good surgical access. It is also necessary for endotracheal intubation and controlled ventilation required during some surgeries. The main advantage of using muscle relaxants is provision of a state that would facilitate a surgeon's function without increasing the depth of anaesthesia and thus preventing major haemodynamic changes associated with increased depth of anaesthesia.

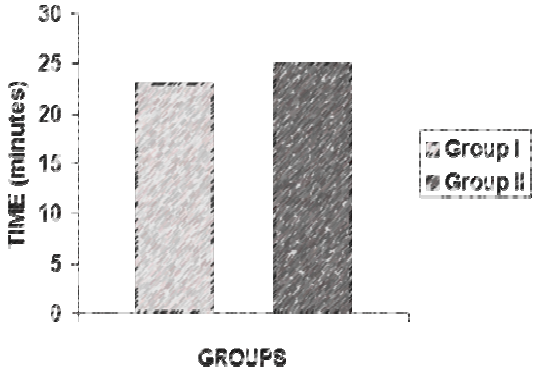
In this study 60 adult patient, of ASA physical status I & II, were randomly allocated into two groups to receive either intravenous infusion of vecuronium (group I) or atracurium (group II) for maintenance of muscle relaxation.

It was observed that the dose requirements of vecuronium averaged 0.06 mg/kg/hr (SD 0.0012). This finding corroborates the findings of Angoston et al (1980), who during a study on the neuromuscular blocking actions of ORG NC45 in anaesthetized patients, found that vecuronium in a dose of 0.08mg/kg/hr provided smoother control of neuromuscular blockade than pancuronium [5]. The dose requirement of atracurium averaged 0.54 mg/kg/hr (SD 0.012). This supports the finding of Gordon KL and Reilly CS (1989) who during their study found that dose requirement of atracurium was 0.45mg/kg/hr [6].

d'Hollander et al (1982), while studying the effect of an infusion of vecuronium, started 10 minutes after the IV bolus loading dose, found that the average dose to maintain a 90% twitch depression, was 0.07mg/kg/hr. This result too corroborates our average dose requirement [7].

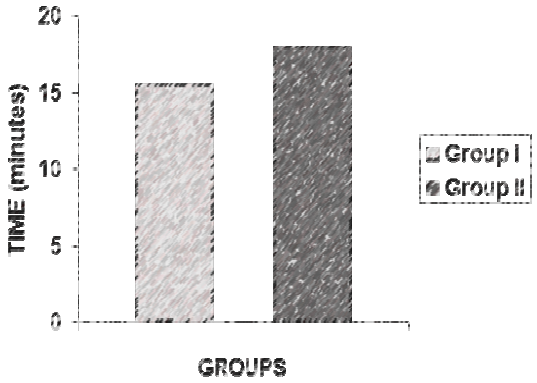
The average infusion rate or dose requirement of vecuronium (0.063 ± 0.7 mg/kg/hr) and that of atracurium (0.476 ± 0.4411 mg/kg/hr) for stable muscle relaxation as observed by Chaudhari et al in 1999 was nearly the same as in this study but it is lower than the value determined by Swen et al (fentanyl based anaesthesia) and higher than that determined by Eager et al(using inhalational anesthetics) [4,8-9].

Graph-1: Median time interval between the initial bolus and start of continuous infusion



Graph 1 shows the time interval between IV bolus dose and start of infusion. The interval between these two time points was significantly less for vecuronium than for atracurium.

Graph-2: Time taken to achieve steady state of block in the two groups



Graph 2 shows the time taken for achieving a steady state of block after starting the infusion. After the initial bolus dose of relaxants there was no response to train of four stimuli for some time. The infusion was started whenever the first twitch response in train of four was observed. These correspond to 10% recovery from control. However, there was further recovery from neuromuscular blockade in every case even after the infusion was started and it took some time to achieve the steady state of block which is defined as a condition where there is a single twitch (T1) response to TOF.

In this study the median and inter quartile range of time taken for achieving a steady

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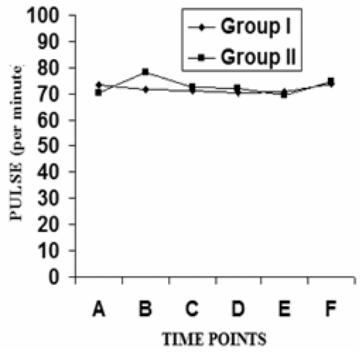
state of block for vecuronium group (15.5 ± 3 minutes) was significantly less than for atracurium group (18 ± 3). This finding is comparable with the findings of Mirakhur and Ferres, 1984, [3] who had achieved steady state in 15.4 minutes(mean) for vecuronium. Our results were significantly different from the result of Holland et al, 1982, [7] who had achieved this state in 30 minutes. This difference could be due to the differences in the rate of infusion.

Table 3 shows the time taken for appearance of the first sign of recovery from neuromuscular blockade following the stoppage of infusion that is twitch height recovery 10% to 25%. In our study it is 538.5 ± 7.5 seconds (median and inter quartile range) in vecuronium group and 593.5 ± 17 seconds (median and inter quartile range) in atracurium group. For vecuronium group it is consistent with the study of Hollander et al (mean8.84 ± SD1.16 min) and that by Mirrakhur and Ferres (mean7.4 ± SD 2.65 min). But the result is in contrast to the result of Noeldge et al who found the time interval as mean 20 ± SD 10 min [3, 10]. In our study time taken for appearance of the first sign of recovery from neuromuscular blockade is significantly less in vecuronium group than atracurium group which is consistent with the study of Chaudhary et al. In their study the recovery was faster with vecuronium (mean 540.94 ± SD 76.46 s) as compared to atracurium (mean 596.33 ± SD 72.48 s). But the study done by Gordon and Reilly showed that it was mean 11.3 ± SD 20 min for vecuronium group and mean 10.8 ± SD 2.2 for atracurium group [6]. The hemodynamic profile of the patients were also monitored in order to identify any effects related to the study drugs and to assess which drug is more efficient in maintenance of smooth anaesthesia.

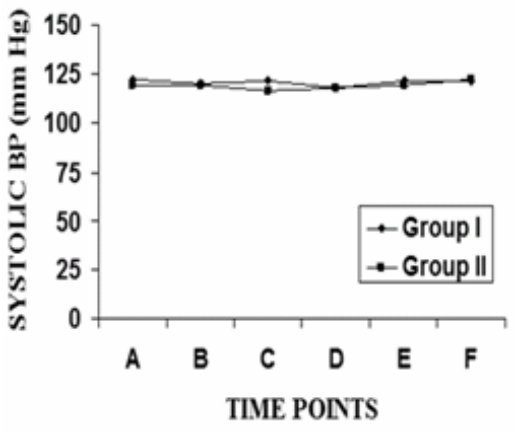
Graph-3: The changes in pulse rate in the two groups has been depicted



A - Pre operative
B - 2 minutes after giving bolus dose
C - 10 minutes after giving bolus dose
D - 2 minutes after starting infusion
E - 10 minutes after starting infusion
F - 2 minutes after stopping infusion

Table 4 & graph 3 summarizes the distribution of pulse rate and their comparison using various statistical tests. In Group I 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 II significant pulse rate changes were seen within different time periods. Median pulse rate and inter quartile range 2 minutes after bolus dose (78 ±11) was significantly higher in Group II than preoperative rate (70.5 ± 9). During surgical procedure there are many causes of pulse rate changes. But the difference between median preoperative and 2 minutes after bolus dose value may be due to atracurium as same ASA grade patients and same drugs in equivalent doses were used.

Graph-4: The variation in SBP is depicted



A - Pre operative
B - 2 minutes after giving bolus dose
C - 10 minutes after giving bolus dose
D - 2 minutes after starting infusion
E - 10 minutes after starting infusion
F - 2 minutes after stopping infusion

Table 5 and graph 4 show the descriptive statistics of systolic blood pressure in different time periods. There is no statistically significant difference between the groups as well as within each group.

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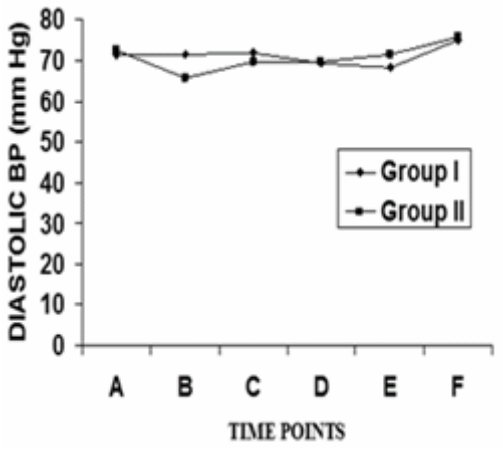
Graph-5: The variation in DBP has been depicted



A - Pre operative
B - 2 minutes after giving bolus dose
C - 10 minutes after giving bolus dose
D - 2 minutes after starting infusion
E - 10 minutes after starting infusion
F - 2 minutes after stopping infusion

Table 6 and graph 5 depicts the descriptive statistics of diastolic blood pressures of the patients belonging to Group I and Group II and summary of their statistical comparison at different predetermined time points. No significant differences were found within Group I. But a difference was seen between preoperative (median and inter quartile range 72 ± 19) and 2 minutes after bolus dose (64 ± 11), 2 minutes after starting infusion (68 ± 14.5) and 10 minutes after stopping infusion values (76 ± 9) in group II As all other conditions were same in two groups these difference may be due to effects of atracurium.

In this study we did not use accelaromyograph or mechanomyograph and neuromuscular stimulation was monitored visually. So result of this study may differ from those who used these in their study. In assessing neuromuscular function we used a relatively sensitive muscle the adductor pollicis of hand. Drawback of using it is that even total elimination of the response to single twitch and TOF stimulation does not exclude the possibility of movement of the diaphragm and inadequate relaxation of abdominal muscles. The quality of muscle relaxation was satisfactory in most of the cases which were assessed by surgeons. There was no incidence of postoperative recurarisation in our study.

Conclusion

Sixty adult patients of either sex, 25 – 45 years of age, belonging to ASA physical status I or II, who were scheduled for midline and paramedian laparotomies under general anaesthesia lasting for up to two hours were recruited for a prospective randomized controlled study intended to compare vecuronium and atracurium when the drugs were used as a continuous infusion.

Patients were randomly allocated into two equal groups and received either vecuronium (Group I) or atracurium (Group II) in intravenous infusion for maintenance of muscle relaxation. Intravenous infusion of muscle relaxants were adjusted to maintain 90% of neuromuscular blockade monitored by stimulating ulnar nerve at the wrist by a peripheral nerve stimulator throughout surgery. At the end of the procedure, at 25% recovery of twitch height, neuromuscular blockade was reversed with neostigmine and glycopyrrolate.

Patients who received vecuronium recovered early from relaxant effect with more stable hemodynamics.

To summarize:

1. Time which is taken from intravenous bolus dose to 10% recovery is less in vecuronium group.
2. Vecuronium took less time to achieve steady state of block after starting infusion
3. Twenty five percent recovery after stopping infusion was earlier in vecuronium group.
4. Vecuronium maintained more stable hemodynamics than atracurium when used in continuous infusion

Thus vecuronium can be considered as a safe and effective alternative to atracurium as a muscle relaxant when using in continuous infusion in ASA grade I and II patients posted for median and paramedian elective laparotomies.

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