ORIGINAL ARTICLE

COMPARISON OF INTERMITTENT BOLUS AND CONTINUOUS INFUSION TECHNIQUES FOR ADMINISTRATION OF ATRACURIUM IN RENAL FAILURE

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ABSTRACT

Introduction: Atracurium besylate is bisquaternary isoquinolinium compound, a potent non depolarizing muscle relaxant of intermediate duration. Its duration of action appears not to be prolonged in absence of normal renal function. Atracurium lacks cumulative effects and its shorter duration of action and rapid recovery from block suggest that Atracurium may be suitable for continuous intravenous infusion.

Objectives: the present study was planned to compare effect of intermittent and intravenous infusion of atracurium in kidney diseases.

Methods: Eighty patients scheduled for elective surgery were randomized into two groups: A and B. Their blood urea was > 80mg/dl, S.Creatinine >2mg%.Patients were assigned randomly to atracurium either as intermittent bolus(group A, n=40) or continuous infusion(group B, n=40). During induction phase each patient was given Inj. Propofol 1.5mg/kg I.V. and was paralysed with Inj.Atracurium 0.5mg/kg I.V. Various clinical parameters are monitored and compared.

Results: In group A, the average pulse rate was 87.59±8.57mins with 9.78 percentage of intraoperative changes in pulse. While in group B the average pulse rate was 92.45±5.71mins with 6.18 percentage of intraoperative changes in pulse P = 0.002. No significant change was seen in blood pressure fluctuation. There is no significant difference in recovery time in either groups (A : 11.1±2.2 and B : 11.4±2.6 min). The average total intraoperative dosage of atracurium in group A was 22.46±7.9 mg and the average total intraoperative dosage of atracurium in group B was 15.44±5.69 mg. (P = 0.0001).

Conclusion: Intravenous continuous infusion is suitable alternative method of administration of atracurium in renal failure patients as it provides continuous adequate steady state of anaesthesia, stable haemodynamics and lesser intraoperative dosage requirement.

Keywords: Atracurium, Renal Failure, Bolus, Infusion, Blood Pressure, Pulse Rate

INTRODUCTION

Medical science is one of the accomplishments of tireless efforts and it is greatly helpful to the whole mankind. Similarly, discovery of anaesthesia itself is the great achievement for mankind to get relief from pain and anxiety of surgery.

The term Balanced Anaesthesia was introduced by Lundy in 1926. The introduction of neuromuscular blocking drugs revolutionized the practice of anaesthesia. After the introduction of muscle relaxants, anaesthesia underwent a conceptual change. Anaesthesia was redefined as a triad of narcosis, analgesia and muscle relaxation, specific drugs being used to produce each of these effects[1].

The non depolarizing muscle relaxant in common clinical use are all eliminated to some degree by kidney and its use in patients with renal failure is associated with the risk of persistent curarisation or even recurarisation. The persistent curarisation or even recurarisation are reported when gallamine, tubocurarine, pancuronium are used in renal failure.

Atracurium besylate[2] is bisquaternary isoquinolinium compound, a potent non depolarizing muscle relaxant of intermediate duration. It was developed and synthesized by J.B.Stenleke in 1979. Atracurium lacks any cumulative effects. It undergoes spontaneous non enzymatic degradation under normal body pH and body temperature by "Hofmann elimination" reaction in addition to a non specific esterase which is another major pathway for metabolism. Renal or hepatic excretion is not an important route of elimination for atracurium. Atracurium besylate is a non depolarizing muscle relaxant, where duration of action appears not to be prolonged in absence of normal renal function. Unfortunately the measurement of Atracurium in plasma is very difficult because molecules of Atracurium break down spontaneously [3].

The rapid rate of recovery, which is characteristic of atracurium, may lead to undesirable fluctuation in level of neuromuscular blockade, unless increments are given promptly at regular intervals with careful monitoring of the patients. Atracurium lacks cumulative effects and its shorter duration of action and rapid recovery from block suggest that Atracurium may be suitable for continuous intravenous infusion. With this back ground the present study was planned to compare effect of intermittent and intravenous infusion of atracurium in kidney diseases.

MATERIALS AND METHODS

Following institutional approval by the ethical committee at Muljibhai Patel Urological Hospital, Nadiad (Gujarat, India), written informed consent to participate in this study was obtained. The study was conducted from sep. 2009 to oct. 2010 in the population consisted of 80 renal failure patients of either sex. The selected patients had ages ranged 20-55years, weight 40-80kgs, ASA II and III, blood urea > 80mg/dl, S.Creatinine > 2mg%, duration of surgery up to 90 minutes.

Patients with major heart disease, suffering from neuromuscular disorder, patients with poor general state of health or those undergoing treatment with drugs likely to interfere with neuromuscular blockage e.g. aminoglycosides, anti-arrhythmia or ganglion blocking drugs were excluded from this study.

Patients were assigned randomly to atracurium either as ntermittent bolus(group A, n=40) or continuous infusion(group B, n=40). The study was standard randomized. Each patient was randomly assigned to single blinded study by closed envelope method. All of the patients were blinded for the method of the drug administration (single blinded trial).

Premedication

Patient was premedicated with Inj.Glycopyrolate 4μgm/kg I.V. to provide antisialagogue effect, Inj.Midazolam 0.01mg/kg I.V. to provide anxiolysis, Inj.Fentanyl 2μgm/kg I.V. to provide analgesia, and Inj.Ondansatron 100μgm/kg I.V. for anti-emetic effect. Vitals were recorded.

Induction of Anaesthesia

After preoxygenation for 3 min, patients were induced with Inj. Propofol 1.5mg/kg I.V. and was paralysed with Inj.Atracurium 0.5mg/kg I.V. and patient was ventilated with 100% O_2 and the level of neuromuscular blockade was assessed every 20 seconds using train of four stimulation till the train of four count (TOFC) was achieved 0 by using supramaximal stimuli. Intubation was done with proper size portex cuffed endotracheal tube. Onset of action was considered as time interval between TOFC-4 to TOFC-0. Time of intubation was noted. HR, BP, temperature were recorded. Warmer was started to prevent hypothermia.

Maintainance

Maintainance of anaesthesia was established with oxygen: nitrous oxide(50:50), continuous propofol infusion and fentanyl. Propofol infusion was initiated as 10mg/kg/hr dosage for first 10mins. It was than reduced to 8mg/kg/hr for next 10mins and thereafter was maintained at 6mg/kg/hr throughout the surgery. HR, BP, Temp, SPO_2, $Etco_2$ were noted every 5 mins. At the recovery of TOFC-1, atracurium was started according to following groups:

Patients in group A received 0.125mg/kg atracurium as intermittent bolus dosage and the intensity of neuromuscular blockade was monitored every 5 mins for maintaining one TOF twitch response and time for every dosage was recorded.

Patients in group B received continuous atracurium infusion at the rate of 8μg/kg/min and adjusted according to maintain one TOF twitch response (ED_{95} - which maintained the block of 95% twitch depression) and level of neuromuscular blockade was monitored every 5 mins for maintaining one TOF twitch response throughout the surgery.

Atracurium infusion drip was prepared in 0.9% normal saline solution having 2mg/ml concentration in 50 ml of syringe pump. Time of starting and stopping atracurium drip was noted. Total duration of infusion and any change in rate of infusion were also noted throughout the surgery.

Inj.Fentanyl 0.5 μg/kg was repeated after 45mins of starting of surgery. Intraoperatively in both the groups, HR,BP, Temp, SPO_2 ,$Etco_2$ and level of neuromuscular blockade were noted every 5 mins. As atracurium is known to produce hypersensitive reaction, observation was done to note any such manifestation.

Atracurium was stopped 15mins before the completion of surgery in both the group. Total amount of Atracurium dosage given by either group was calculated. Inj.Propofol infusion was stopped 5-10 mins before the completion of surgery. In all cases, intravenous fluid and blood was adequately replaced during anaesthesia and surgery according to blood loss, fasting hours and urine output by clinical observation.

REVERSAL:

100% oxygen was given at the end of surgery. All patients were reversed with Inj.Glycopyrolate 8μgm/kg I.V. and Inj.Neostigmine 50 μgm/kg I.V. Patient's trachea was extubated after full awakening and meeting the standard criteria of extubation, e.g. responded to verbal command like opening the eyes, protruding the tongue and raising the limbs and adequate muscle tone.100% oxygen was given even after giving reversal and completing extubation. Patients were observed for half an hour for observation for any residual neuromuscular blockade and post operative itching. Recovery is judged by recovery criteria. Postoperative vital parameter was noted and patient shifted to ward.

Data were processed by SPSS statistical package. Continuous variation were expressed as mean±SD. Comparisions between patient of two groups was performed by student 't' test. Statistical significance was inferred at P=<0.05.

OBSERVATION

There is no significant difference in either groups with regard to age, sex, weight and ASA grading.

Table 1 Demographic Profile of Patient in Both Groups

	Group A (n:40)	Group B (n:40)	P Value
Age(Yrs)	44.2±10.2	43.9± 8.4	0.44
Sex(M:F)	31:9	32:8	0.59
ASA Grading(II/III)	3:37	4:36	0.43
Weight(Kgs)	56.1± 8.6	55.8± 8.5	0.44
Surgical Procedure: PCNL	28	30	-
Ureterorenoscopy	6	5	-
Lap. Chole.	6	5	-

There is no significant difference in bolus atracurium dosage in either of groups. There is no significant difference in onset of action of atracurium in either of groups.

In group A, the average pulse rate was 87.59±8.57mins with 9.78 percentages of intraoperative changes in pulse. While in group B the average pulse rate was 92.45±5.71mins with 6.18 percentages of intraoperative changes in pulse. This difference was statistically significant.

Table 2: Average Bolus Dosage of Atracurium and Onset of Action

	Group A (n:40)	Group B (n:40)	P Value
Average Bolus Dosage	27.9±4.3	27.8±4.3	0.46
TOFC 4-TOFC 0 (Mins)	2.56±0.21	2.58± 0.24	0.35

In group A, the average systolic and diastolic blood pressure was 135.02±13.19 and 82.99±7.66mmHg respectively. While, in group B the average systolic and diastolic blood pressure were 131.75±15.81mmHg and 82.34±7.72mmHg respectively with no significant change of intraoperative blood pressure compare to group A. This difference in average systolic and diastolic blood pressure was statistically not significant.

Table 3: Comparison of various clinical parameters in both group

	Group A (N:40)	Group B (N:40)	P Value
Pulse Rate Intraoperatively (Mean±Sd)	87.59±8.57	92.45±5.71	**0.002**
Blood Pressure Intraoperatively			
Systolic BP (Mean±SD)	135.02±13.19	131.75±15.81	0.26
Diastolic BP (Mean±SD)	82.99±7.6	82.34± 7.72	0.92
Recovery Time (Mins)	11.1±2.2	11.4±2.6	0.29
Total Intraoperative Dosage(Mg)	22.46±7.9	15.44±5.69	0.0001*
Duration of Surgery(Mins)	43.50±9.21	45.75±10.65	0.16
Duration of Anaesthesia(Mins)	64.50±9.97	67.10±11.93	0.14

There is no significant difference in recovery time in either group. The average total intraoperative dosage of atracurium in group A was 22.46±7.9 mg and in group B was 15.44±5.69 mg. **U**sage of atracurium dosage intraoperatively in group A was significantly higher than group B.

There is no significant difference in duration of surgery and anaesthesia in both the groups.

DISCUSSION

According to pharmacology of Atracurium, it is metabolised through Hofmann elimination and Ester hydrolysis, which does not require normal renal function. This study was carried out to understand pharmacodynamics and efficacy of atracurium infusion versus intermittent doses in renal failure cases.

One of the most important parameter for evaluating the action of any muscle relaxant is its onset of action. Sufficient muscle relaxation to permit surgery can be achieved by an amount of ED_{95} which is that dose which produces 95% twitch depression.

J.M.Hunter[4] had given 0.6mg/kg bolus dose in normal patient and its onset of action was 1.83±0.46mins while in anephric patients, its time of onset of action was 3.1±0.88mins which is quiet higher than both the groups of our study.

Different workers used different doses to study cardiovascular changes. Though atracurium is considered to be a cardiovascularly stable drug, minor non-significant changes were observed in various studies. S.J.Basta, H.H. Ali, J.J.Savarese et al[5] (1982) concluded that with 0.4 mg/kg there were no significant changes in heart rate. While , with the dosage of 0.5 and 0.6mg/kg there were increase in heart rate of 5% and 8% respectively.

In present study, we found 9.78% pulse rate changes in Group A and 6.18% pulse rate changes in Group B patients. Pulse rate changes intraoperatively were lesser in Group B (Infusion Group) as compared to Group A (Intermittent Group) due to continuous spontaneous degradation property of atracurium. Continuous I.V. infusion can provide steady state plasma concentration of atracurium maintaining adequate depth of anaesthesia and give less pulse rate changes even in renal failure patients. Due to continuous spontaneous recovery of neuromuscular blockade, pulse rate changes was significantly more in Group A (Intermittent Group) as compared to Group B(Infusion Group).

S.J.Basta, H.H.Ali, J.J.Savarese et al[5] (1982) concluded that with 0.4mg/kg dosage of atracurium, there were no significant cardiovascular changes. Whereas with high dosage of 0.5 and 0.6mg/kg, there were decrease in blood pressure by 13% and 20% respectively.

In our study, average mean blood pressure in group A was 100.66± 8.35mmHg and in group B was 98.34±9.33mmHg with more fluctuation in intraoperative blood pressure in group A as compared to group B, though nonsignificant. Thus continuous infusion provides more steady state of plasma level and cardiovascular stability as compared to intermittent dose in renal failure cases.

M.A. Gargarian et al[6] studied the efficacy of continuous atracurium infusion and found that it is an effective method of providing excellent muscle relaxation for surgical patients.

R.Hughes, P.J.Flynn and B.Eagar[7] assessed the stability of infusion of atracurium for long surgical procedures in 1984. A continuous infusion of atracurium at an average rate of 0.0061±0.0003mg/kg/min for 128 to 223 minutes provided a readily controllable neuromuscular block and adequate surgical relaxation. When the infusion was discontinued, there was full spontaneous recovery from 90-100% block in a mean time of 42.2±3.1 minute and it was as prompt that reported after bolus administration of the drug. There was no evidence of recurarisation and reversal with atropine and neostigmine shortened recovery time to a mean 16.4±2.2 minute. Appreciably they have concluded that an infusion of atracurium was eminently suitable for long surgical procedures.

R.Russo, R.Ravagnan, V. Buzzeti and P.Favini[8] studied the atracurium in patients with chronic renal failure in form of infusion drip after 15 minutes of bolus dose i.e. 0.6 mg/kg. He found that none of the patient showed adverse cardiovascular changes and total neuromuscular blockade was always achieved, as confirmed by clinical and instrumental evaluation. Ten minutes after the end of surgery 75.5% of the patients were fully recovered from neuromuscular blockade and remaining 24.5% had a complete response after administration of prostigmine and atropine. [7]

In our study, we had studied atracurium infusion in renal failure patients. We had intubated all the patients with 0.5mg/kg bolus dose with good intubating condition and started infusion after recovery of train of four count 1 with average rate of 7.19±0.8µg/kg/min with average time duration of 38±11 mins. We had got readily controllable neuromuscular block and adequate surgical relaxation. There was complete recovery from neuromuscular block with Inj.glycopyrolate and Inj. Neostigmine with mean time 11.35 ±2.60 mins .

Infusion rate and recovery time of our study are comparable with the results of other investigators. Good muscle relaxation was found during steady state anaesthesia with the continuous infusion. Recovery time after stoppage of drip was similar to other studies and it was independent of the time and concentration of infusion fluids even in renal failure patients. It had provided constant and controllable neuromuscular block with ideal operating conditions up to the end of surgery in this study. The recovery was predictable and prompt after discontinuation of infusion and reversal agents had decreased the recovery time.

C. Diefenbach, Hermann Mellinghoff, Stefan Grond et al[9] studied Atracurium and Vecuronium with intravenous infusion versus repeated injection in normal renal function patients. They found that the requirement of atracurium for maintenance did not significantly differ from their mode of administration. Recovery index did not differ with either infusion or repeated injection of atracurium.

In our study too, there was no significant difference in recovery irrespective of mode of atracurium intraoperatively.

J. M. Hunter et al[10] studied atracurium in patients with no renal function and neuromuscular block was monitored using the train-of-four stimuli. Unlike other non-depolarizing muscle relaxants, it was possible to continue giving incremental doses of atracurium (0.2mg/kg) to the anephric patients without evidence of cumulation. Even when the total dose used (over a period of up to 2.5 h) was in the order of seven to eight times than that required for endotracheal intubation. There was no evidence of residual curarisation.

In our study we used intermittent dose 0.125mg/kg and mean time for repeating the dose is 10.53±0.66 mins, which is lower than Hunter's study because he had used larger dose for increment. Thus our results are comparable with his results.

When we compare our results of atracurium infusion and intermittent dose, there was more haemodynamic stability with infusion than intermittent dose. That may be attributed to steady state and depth of anaesthesia with continuous infusion. It may be absent in repeated doses group due to continuous spontaneous degradation of drug and faster recovery from neuromuscular block as compared to other non-depolarising muscle relaxants.

CONCLUSION

Intravenous continuous infusion is suitable alternative method of administration of atracurium in renal failure patients as it provides continuous adequate steady state of anaesthesia, stable haemodynamics, lesser intraoperative dosage requirement and easy reversibility.

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