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Research Article

Clinical Evaluation of Pipecuronium Bromide and its Comparison with Pancuronium Bromide

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Abstract: The study was carried out to compare the intubating conditions, cardiovascular responses, neuro-muscular blocking properties and reversal characteristics of pipecuronium bromide and pancuronium bromide. This is a prospective hospital based study. 100 patients belonging to ASA grade I or II physical status aged 18 to 70 years were divided into two groups of 50 patients each. Group 1 received pipecuronium bromide in the dose of .08 mg / kg and group 2 patients received pancuronium bromide in dose of 0.1 mg/kg. Each patient was pre medicated uniformly. Time for onset of apnoea for pipecuronium and pancuronium were 91.64± 3.59 sec. and 118.84 ± 12.53 sec. respectively. The mean time for intubation was 126.60 ±12.55 sec. and 144.60 ± 22.87 sec. with pipecuronium and pancuronium respectively. Mean duration of block for pipecuronium was 78.64 ± 8.97 min. the block for pancuronium lasted from ±36-40 min with a mean duration of block 41.60± 5.57 min. The mean duration of maintenance dose in pipecuronium cases was 45.08 ± 7.19 min., while it was 27.06 ± 5.01 min in pancuronium cases. Pipecuronium patients did not show significant hemodynamic changes while hemodynamic changes were seen with pancuronium patients due to mild atropine like and sympathomimetic action of pancuronium. There was no spontaneous recovery in both groups of patients. All patients required titrated dosage of atropine / neostigmine. In pipecuronium patients, after reversal, 90% of patients had adequate recovery and scored a high score between 11-15. In pancuronium patients, after reversal, 88% had adequate recovery and scored a high score between11-15. It is evident that pipecuronium bromide provided excellent intubating conditions, negligible cardiovascular disturbances, longer duration of action, lack of cumulative action, easy reversibility of neuromuscular block with high postoperative recovery score. Thus it proves to be the ideal muscle relaxant of choice in the long surgical procedure.
Keywords: pipecuronium, pancuronium, neuromuscular block

INTRODUCTION

The introduction of curare into clinical practice did not achieve immediate success. In USA and U.K., it was looked suspiciously in early fifties, use of neuromuscular blocking drug was associated with high mortality and its use in general was avoided. Initially, the high mortality was attributed to "high toxicity" or impurities of the drug but it was soon realized to be the improper use of curare. e.g. with ether and spontaneous ventilation without adequate control of breathing- could and did result in disaster. Later, when importance of controlled breathing and carbon dioxide elimination was established, the use of this drug became safe and the concept of triad of anesthesia or balanced anesthesia emerged. Subsequently purified curare like, tube curare, pipe curare, and intercostin etc were used.

An Ideal Muscle Relaxant should have the following requirements: Non-depolarising mechanism of action, Rapid onset of action, Intermediate duration of action, Rapid recovery, Non – Cumulative, Highly selective at the neuromuscular junction, No histamine release, High potency, Easily Reversible and Pharmacologically inactive metabolites [1].

As Curare became popular in anesthetic practice, search for other non depolarizing muscle relaxants without side effects of curare started. This lead to the development of series of non-depolarizing muscle relaxants. King synthesized metocurine in 1935 [2]. Alcuronium, pancuronium, Vecuronium, pipecuronium , Atracurium, Mivacurium and Rocuronium etc. were introduced later on in clinical anaesthesia [3].

Aims and Objects

- To compare and evaluate intubating conditions and responses to endotracheal intubation with pipecuronium bromide and pancuronium bromide.
- To assess and compare the neuromuscular blocking characters of pipecuronium bromide and pancuronium bromide by employing – Evoked potential i.e. T.D.F. by peripheral nerve stimultior.
- To compare cardiovascular effects of pipecuronium bromide and pancuronium bromide.

MATERIALS AND METHODS

Present study entitled "Clinical evaluation of pipecuronium bromide and its comparison with Pancuronium bromide was carried in the "Department of Anaesthesiology MGM Medical College" Indore with an object to find out the neuromuscular blocking properties of pipercuronium bromoide recently introduced and to compare it with Pancuronium bromide.

Present study included 100 patients from wide range of age group (18 Yrs to 70 Yrs) were divided in two groups of 50 patients each. Group 1 patients received pipecuronium bromide in dose of .08 mg/kg and group 2 patients received pancuronium bromide in dose of 0.1 mg/kg.

All the patients included in the study were subjected to thorough preoperative clinical examination and investigations to rule out systemic disease thus, the patients included in the study belonged to ASA grade I or II Physical status.

Each patient was was premedicated uniformly as under :

Inj. Artopine 0.01 mg/kg maximum of 0.6 mg/1/m.

Inj. Pentazocine .5 mg/kg maxiumum of 30 mg/1/m.

These drugs were administered intramuscularly about 45 minutes before induction of anesthesia. After arrival of patient in OT, besides intravenous lines, and other monitoring devices, peripheral nerve stimulators were placed in position to stimulate the ulnar nerve.

The height of twitch response before relaxant was noted and all the four contractions were of almost same height. Patients were preoxygenated with 100% 0_2 for 3 min and induced with Pentothal sodium in appropriate dose intravenously. Prior intravenous injection of predetermined dose of muscle relaxant was given. The period of hypoventilation/ apnoea was covered with assisted ventilation. The time for appearance of apnoea was noted and recorded the twitch height. After 60 to 90 sec. of inj. of relaxant drug, assessment of conditions for laryngoscopy and Endotracheal intubation was made. In case of favorable conditions, endotracheal intubation was performed and in otherwise situations, further assisted ventilation was carried for another 30 seconds and then upon availability of favorable conditions, intubation was performed.

Ventilation of patient was continued with Oxygen and Nitrous oxide on circle absorber/Bain's circuit. Every 10 min. the ulnar nerve was stimulated by TDF method and responses were noted. A degree of neuromuscular blockade upto extent of 90% resulted in disappearance of 4^{th} response of TDF. Appearance of 4^{th} response suggested waning of block to 50% which indicated the administration of supplementary dose to suppress 4 responses i.e. to achieve 90% blockade suitable for surgery. Thus, duration of action of supplementary dose was calculated as the time required for appearance of 4^{th} response.

Hemodynamic measurements (Pulse, B.P.) were taken just before administration of relaxant and just after muscle relaxant, after intubation, and then 10 mts. and 30 mts. Later.

At the conclusion of surgery patient was reversed as usual with atropine and neostigmine. The later drug was given by titrating dose against TDF response till height of all the four contractions were same and patient clinically met criteria's of reversal.

Post operative recovery scoring was done periodically. Five parameters were taken into account and a score of 0, 1, 2, 3, was given for each parameter and points were graded as 7,8,9.

High score (11-15) was safe for discharge but medium Score (6-10) needs further observation. Low Score (1-5) required intensive care and observation.

RESULTS

All patients included in the study belonged to ASA grade 1 or 2 as per American society of anaesthetists classification. The patients were divided in two groups of 50 each. Groups 1 were given pancuronium bromide and group -2 were given pipecuronium bromide as muscle relaxants in narcotic analgesic sequence.

The clinical observations made on these 100 patients have been tabulated from 1 to 16

Table 1: Age distribution among the patients (male/female)

Age	Number of patient		Total
	Male	Female	
< 20	15	4	19
21-30	11	14	25
31-40	12	13	25
41-50	06	13	19
51-60	03	06	09
61-70	00	03	03
Total	47	53	100

Majority of patients are between 21 to 30 years. Mean age observed was 35.53 Years.

Table 2: Types of Surgical Procedure

Types of PS operation	Number of Patients	
	Pipecuronium	Pancuronium
General Surgery	24	16
Neurosurgery	17	03
Obst Surgery	00	03
Gynaecology	03	07
Orthopaedics	06	21
Total	50	50

Table 3: Shows time for onset of apnoea

Time for Onset of Apnoea	Pipecuronium	Panucuronium
< 60 sec	00	00
61 and 90 sec	38 (76%)	00
91 and 120	12 (24%)	33(66%)
121 and 150	00	17(34%)
151 and 180	00	00
Mean Apnoes time onset ±S.D.	91.64 ±3.59 sec	118.84 ±12.53 sec

Pipecuronium was administered in group -I. In 76% patient's apnoea occurred in 60-90 sec and in 24% occurred in 90-120 sec. The mean time for onset of apnoea was 91.64 ±3.59 Sec.

In Group II, in 66% patient's apnoea occurred in 90-120 sec. and in 34% occurred in 120-150 sec. The mean time for onset of apnoea was 118-84 ±12.53 sec.

Table 4: Intubating Time

Time (Sec.)	Number of Cases	
	Pipecuronium	Pancuronium
60 – 90	0	0
91 – 120	39 (70%)	15 (30%)
121 – 150	11 (22%)	29 (58%)
151 – 180	00	06 (12%)
Mean apnoea time Onset ± S.D.	126.60±12.55sec.	144.60 ±22.87 sec.

78% patients of group 1 easily intubated within 120 sec. after injection of pipecuronium. Rest 22% required slightly longer to facilitate easy intubation. The mean time for favorable intubation in Group 1 was 126.60 ± 12.55 second. 30% patients of group-ll intubated after 15-180 sec. of pancuronium administration. The mean time for favorable intubation in Group II was e 144.60 ± 22.87 second.

Table 5: Incidence of Intubating Difficulty

Grade	Score	Number of Patients	
		Pipecuronium	Pancuronium
Excellent	03	49 (98%)	42 (84%)
Satisfactory	02	01 (2%)	08 (16%)
Fair	01	00	00
Impossible	00	00	00

Table No. 5 shows incidence of intubation difficulty. The grading system followed in the present study was as suggested by Lund and Stovner (1962). Pipecuronium provided excellent intubating conditions in 98% patients and in 2% patients, satisfactory conditions. Pancuronium provided excellent intubating conditions in 84% and in 16% satisfactory conditions. In none of the case from either group we failed to intubate the patient.

Table 6: Mean Pulse Rate

Mean Pulse Rate	Pipecuronium	Pancuronium
Pre Operative	94.56 (± 13.87)	91.92 (±6.75)
Just after muscle Relaxant	94.80 (±11.27)	101.36 (±8.88)
After Intubation	97.94 (±12.33)	105.16 (±7.35)
10 Mts. After	94.88 (±11.27)	101.64 (±7.39)
20 Mts. After	94.92 (±11.48)	98.96 (±7.40)
30 Mts. After	94.88 (±11.27)	97.00 (±6.27)

Table 7: Blood Pressure

	Mean Systolic in Blood Pressure in mm-Hg	
	Pipecuronium	**Pancuronium**
Pre Operative	119.20 (± 13.42)	113.40 (±12.17)
Just after muscle Relaxant	119.60 (±13.22)	126.10 (±13.08)
After Intubation	121.60 (±12.99)	132.90 (±12.10)
10 Mts. After	119.20 (±12.06)	125.92 (±11.11)
20 Mts. After	121.40 (±12.23)	124.98 (±10.28)
30 Mts. After	119.60 (±12.01)	121.20 (±10.92)

Table No. 6 and 7 shows the study of cardiovascular parameters made preoperatively, just after injection of muscle relaxant, after intubation and at every 10 Mins. till the end of surgery.

Table 8(a): Duration of Initial Dose of Pipecuronium

Duration in mts.	**Number of Patients Pipecuronium**
Upto 60 Mts.	02
61 – 70 mts.	12
71 – 80 mts.	14
81 – 90 mts.	20
91- 100 mts.	02
Mean apnoea time Blocks ± S.D.	78.64±8.97

Table 8(b): Duration of Action Initial Dose

Duration in Mts.	**Number of Patients Pancuronium**
Less than 20	0
20 – 25	01
26 – 30	01
31 – 35	08
36 – 40	19
41 – 45	13
46 – 50	08
Mean apnoea time Initial ± S.D.	41.60±5.57 sec.

Table No. 8 (a & b) shows the duration of action of the initial dose of pipecuronium and Pancuronium.

Table 9: Duration of Maintenance Dose Pipecuronium

Duration in Mts.	**Pipecuronium**
Upto 30 Mts.	00
31 – 40 mts.	16
41 – 50 mts.	23
51 – 60 mts.	11
61- 70 mts.	00
Total number of patients	50
Mean apnoea time ± S.D.	45.08±7.19

Table 10: Duration of Maintenance Dose Pancuronium

Duration In Mts.	**Pancuronium**
Upto 15 Mts.	00
16 – 20 mts.	09
21 – 25 mts.	20
26 - 30 mts.	12
31- 35 mts.	09
Total number of patients	50
Mean apnoea time ± S.D.	27.06±5.01

Table 11: Reversal Character

Dose of Neostigmine Required	Number of Patients	
	Pipecuronium	Pancuronium
Spont Recovery		
05 mg	0	0
1 mg	0	0
1.5 mg	0	0
2 mg	0	0
2.5 mg	50	50

Table 12: Recovery Score of Group I Patients in whom Reversal was done in O.T.

Recovery Score	Number of Patients	
	Just After Reversal	10 Mts. Later
Spont Recovery		
11- 15	44	50
06 – 10	06	00
01 – 05	00	00
Total	50	50

Table 13: Recovery Score in Recovery Room (Group 1 Patient)

Recovery Score	Number of Patients	
	Arrival in R.R.	30 mts. Later
Spont Recovery		
11- 15	50 (100%)	50 (100%)
06 – 10	00	00
01 – 05	00	00
Total	50	50

Table 14: Recovery Score in O.T. in whom Reversal was done (Group II Patients)

Recovery Score	Number of Patients	
	Arrival In R.R.	30 mts. Later
Spont Recovery		
11- 15	45 (100%)	50 (100%)
06 – 10	00	00
01 – 05	00	00
Total	50	50

Table 15: Recovery Score in Recovery Room (Group II Patients)

Recovery Score	Number of Patients	
	Arrival in R.R.	30 mts. Later
Spont Recovery		
11- 15	50(100%)	50 (100%)
06 – 10	00	00
01 – 05	00	00
Total	50	50

DISCUSSION

The present study was undertaken with an object to evaluate efficacy of Pipecuronium bromide and to compare it with pancuronium bromide.

In our study, we have compared the intubating conditions, hemodynamic changes and reversal conditions of pipecuronium bromide and Pancuronium bromide.

Total hundred patients of various age groups and both sexes, scheduled for various surgical interventions were included in this study. All patients belonged to ASA grade I and II.

Intubating Conditions

In 76% patients, who received pipecuronium, the time for onset of apnoea was between 61 to 90 seconds and in 24% cases, it was between 91 to 120 seconds. The mean apnoea time was 91.64 seconds 13.59 sec. In 78% patients, the intubating time was between 91 to 120 seconds and in 22% cases, it was 121 to 150 seconds. The mean intubating time was 126.60 seconds $\pm$12.55 seconds.

The intubating conditions were excellent in 98% cases and satisfactory in 2% cases. Our findings co-relate with these of the following workers.

Lirijani *et al.* used this drug in a dose of 70 to 85 micro gram/ kg. Body weight and found complete block in 2 to 2.5 mts. [4].

Tassonyi E *et al.*, found that the intubation can be carried out within 23 minutes, where 70 to 80 micro gram/kg. body weight is given [13].

Azad SS *et al.* concluded that pipecuronium has relatively rapid onset and trachea could be intubated successfully in 1.5 minutes with a dose of either 0.07 mg/kg body with or 0.10 mg/kg body wt. [6].

When pipecuronium was used, the mean time for onset of apnoea was 118.84 ±12.53 seconds. Intubation was not possible before 90 seconds in any of the patients. 30% patients could be intubated between 91 to 120 seconds, 58% between 121 to 150 seconds and 12% between 151 to 180 seconds. The mean intubation time was 144.60 ±22.8 seconds.
Excellent intubating conditions were available in 84% cases and satisfactory condition in 16% cases. The above results suggest that pipecuronium bromide provides favourable intubating conditions with a mean intubating time of 126.60 ± 12.55 seconds.

In majority of patients, as compared to pancuronium bromide, which is having a mean intubation time 144.60 ±22.87 seconds.

The intubating condition was also excellent in 98% cases in pipecuronium group as compared to 84% cases in pancuronium group.

Larijani GE *et al.* concluded that pipecuronium provided good to excellent intubating conditions within 3 minutes after the administration of 70 Mcg '/ kg. dose [4].

Cardiovascular Responses

In this study cardiovascular responses to tracheal intubation i.e. tachycardia and hypertension were seen with pipecuronium bromide and pancuronium bromide but they were of very lesser magnitude and shorter duration with pipecuronium as compared with pancuronium.

Refer to chapter observation (Table No. 6 & 7). The hemodynamic effects of pipecuronium returned to the preoperative value with in 10 mts. But with pancuronium the mean pulse rate and systolic blood pressure continue to be raised even 30 mts. after administration of the Pancuronium.

The finding of our study is supported by those of Kelman and Kennedy [7], who studied the cardiovascular effects of pancuronium in men. They demonstrated that pancuronium does cause a marked rise in the heart rate accompanied by a lesser increase in cardiac output and mean arterial pressure.

Brankay *et al.* [8] reported that a potency of pipecuronium is similar to pancuronium bromide with minimal cardiovascular effects.

Bunjatjian A.A *et al.*, [9] concluded that unlike pancuronium however pipecuronium had no unwanted circulatory side effects. Boros M *et al.* [10] made similar observation.

Tassonyi E *et al.* [13] reported that the main advantage of pipecuronium is that, It has no cardiovascular side effects as has also been proven with invasive methods.

Tassonyi E *et al.* [5] made a comparison of pipecuronium with pancuronium for cardiovascular effects in patients undergoing C.A.B.G. (Coronary Artery Bypass Grafting). They concluded that pipecuronium does not change significant hemodynamic effects as compared to pancuronium. Although some degree of bradycardia have occasionally been reported.

Larijani GE *et al.* [4] also reported that there is no significant change in heart rate, systolic and diastolic blood pressure after the administration of pipecuronium.

Neuromuscular Blocking Properties
Initial Dose

The mean duration of action of initial dose of pipecuronium was 78.64± 8.97 mts. and 42.63 ±5.57 mts. with pancuronium. Pipecuronium bromide is thus a long acting neuromuscular blocking agent as compared to pancuronium.

Incremental Dose

The duration of action of the incremental dose of pipecuronium bromide was 45.08 ±7.19 mts., and that of pancuronium was 27.06± 5.01 mts.

The findings of our study are in agreement with those of Boros *et al.* [10] Brankay *et al.* [8], made similar observation.

Tassonyi E *et al.* [13] compared pipecuronium bromide with pancuronium and reported that it is more potent than pancuronium bromide. Larger doses of pipecuronium bromide produced prolonged neuromuscular blockage upto 80 to 100 mts. For maintenance of muscle relaxants 12 to 14 u/kg. can be used without danger of cumulation.

Findings of our study do not corelate with those of Caldwell JE *et al.* [11] who did a comparative study of pipecuronium and pancuronium and reported a rapid plasma clearance and a shorter duration of action of pipecuronium as compared to pancuronium.

The interpretation of duration of action of their study was complicated by the fact that, in some cases surgery was completed before the twitch response recovered to 25%.

Larijani GE *et al.* [4] concluded that pipecuronium provides clinical neuromuscular relaxation of 1-2 hour duration. He also found that there is wide variation in the duration of action of pipecuronium related dose.

Sugai N *et al.* [12] found that pipecuronium bromide is more potent than Pancuronium bromide and the duration of action is longer.

Reversal Character and Recovery Score

In group 1 patients, who were given pipecuronium showed a recovery score between 11-15 in 88% cases aned 12% patients had recovery score between 6.10, just after reversal and all patient had recovery score between 11-15. Ten min. later no patient showed sponsaneous recovery.

In 90% patients, who received pancuronium bromide showed a recovery score between 11-15 and 10% between 6-10 just after reversal and 100% of patients had recovery score between 11-15. 10 min. later no patient showed spontaneous recovery.

Findings of our study are in agreement with those of Tassonyi *et al.* [13]. Larijani GE *et al.* [4] reported that full recovery of neuromuscular junction after neostigmine 2.5 mg administration was observed within 10 min. in the majority of patients. Foldes FF *et al.* [14] reported that the recovery indices of pipecuronium were similar, and our findings are in agreement with this study. Youssef SA *et al.* [15] compared pipecuronium with pancuronium on rats and concluded that neostigmine rapidly and completely antagonises the neuromuscular blockage caused by pipecuronium and pancuronium.

Thus from the above discussion, it is evident that pipecuronium provided better conditions for endotracheal intubation earlier, showed minimal cardiovascular disturbances following endotracheal intubation and a longer duration of action as compared to pancuronium bromide. Reversal characteristics were similar with both the drugs.

SUMMARY AND CONCLUSIONS

The study was carried out with the aim of comparing the intubating conditions, cardiovascular responses, neuromuscular blocking properties, and reversal characterstics of popecuronium bromide and pancuronium bromide.

The partients belongs to the age group (18-70 yrs). and were of both sakes. The patients were premedicated with injection atropine 0.01 mg/kg. body weight and injection pentazocine lactate in dose of 0.5 mg/kg body weight (maximum 30 mg) intramuscular 45 min. before induction of anaesthesia.

The patients were induced with thiopental sodium followed by muscle relaxants. IPPR was done and patients were intubated, and anaesthesia was maintained with 33% oxygen and 66% nitrous oxide and maintenance dose of muscle relaxant.

At the end of surgical procedure, reversal of neuromuscular blockage was done with injection atropine and injection neostigmine. The preoperative pulse rate and blood pressure were recorded and compared with the records of pulse rate and systolic blood pressure after administration of muscle relaxant just after intubation and then every 10 min.
Intubating conditions, onset of action, duration of action of the initial dose and maintenance dose reversal characteristics and recovery score were also noted.

The findings of our study were thoroughly discussed with the available literature. Now, following conclusion can be drawn from the present study.

- Time for onset of apnoea for pipecuronium and pancuronium were 91.64$\pm$3.59 sec. and 118.84$\pm$12.53 sec. respectively.
- Intubating conditions: Excellent conditions for intubation were available within 120 sec. in 78% cases of group I, while 58% cases of group II could be intubated after 2-2.5 while 58% cases of group II could be intubated after 2-2.5 min. The mean time for intubation was 126.60 $\pm$12.55 sec. and 144.60 $\pm$ 22.87 sec. with pipecuronium and pancuronium respectively.
- The duration of action of initial dose: In 40% of group I patients, the duration of initial dose was between 81-90 min., while mean duration of block was 78.64 $\pm$ 8.97 min. In 38% of group II cases, the block lasted from $\pm$36-40 min. with a mean duration of block 41.60$\pm$ 5.57 min.
- Duration of maintenance dose: The mean duration of maintenance dose in group I cases was 45.08 $\pm$ 7.19 min., while it was 27.06 $\pm$ 5.01 min. in group II' s cases.
- Cardiovascular effects : Group I patients did not show significant hemodynamic changes while hemodynamic changes were seen with group II patients due to mild atropine like and sympathomimetic action of pancuronium.

- Recovery: There was no spontaneous recovery in both group of patients. All patients required titrated dosage of atropine / neostigmine.
- In group I patients, after reversal , 90% of patients had adequate recovery and scored a high score between 11-15 (Badve and Mirakhur 1975) . In group II patients , after reversal, 88% had adequate recovery and scored a high score between 11-15.

Thus from the above data, it is evident that pipecuronium bromide provided excellent intubating conditions, negligible cardiovascular disturbances, longer duration of action, lack of cumulative action, easy reversibility of neuromuscular block with high postoperative recovery score. Thus it proves to be the ideal muscle relaxant of choice in the long surgical procedure.

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