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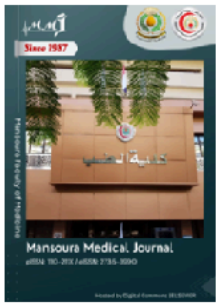

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# EVALUATION OF NEUROMUSCULAR PROFILE OF PIPECURONIUM AND ATRACURIUM COMBINATION

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## ABSTRACT

This study was designed to evaluate hemodynamic and neuromuscular blocking effects of different doses of pipecuronium and atracurium combination. Sixty patients of either sex were included in this study.The patients were scheduled for major abdominal surgery and they were classified into three groups (each of 20).According to muscle relaxant given :Group (A) received 0.08 mg /kg pipecuronium alone and Group (B) received a combination of pipecuronium and atracurium in a dose of 0.04 and 0.25 mg/kg respectively .Group (C) received the same combination but in a dose of 0.026 and 0.166 mg/kg respectively .All the patients were premedicated with 0.03 mg/kg midazolam and maintenance of anesthesia was done by N2O in oxygen (2:1) and isoflurane 1:1.5 %. Neuromuscular monitoring including onset of action of muscle relaxant ,assessment of intubation condition using intubation condition score,duration of bolus dose, number of redoses, duration of each, recovery times and total dose of muscle relaxant. Combination of both pipecuronium and atracurium in half the intubating dose (group B) produced clinical effective neuromuscular blockade with acceptable onset time similar to that of pipecuronium alone, and the duration of clinical relaxation of the first redose displayed a potentiating effect. The clinical duration and recovery times of the combined drugs in group C were shorter than those of A & B

*Key Words:* Neuromuscular relaxants : pipecuronium and atracurium,

drug combination, clinical relaxation & recovery times

## INTRODUCTION

There have been numerous studies both in adults and children which had documented prolonged neuromuscular blockade that extended into the post anesthesia recovery period despite diligent intraoperative monitoring and seemingly adequate reversal. The incidence of impaired neuromuscular function upon arrival in the recovery room has been shown to be approximately 40% following the use of long acting steroidal compound e.g, pancuronium, but less than 5% after vecrunium or atracurium suggesting the greater safety of these intermediate acting muscle relaxants[1].

Neuromuscular blocking drug combination had been tried to achieve the desired degree of relaxation, speed of onset and duration of block for a given clinical situation. It was demonstrated that significant potentiation of neuromuscular blockade occurred when pancuronium and metocurine or pancuronium and d-tubocurarine were administered in combination [2].

According to the available literature, the combination of pipecuronium and atracurium had not been tried before, so, this study was undertaken to compare the hemodynamic and neuromuscular blocking effects of different doses of pipecuronium and atracurium combination over pipecuronium alone in patients submitted for major abdominal surgery.

## PATIENS AND METHODS

The protocol was approved by our local Ethics Committee, a written informed consent was secured from all patients before the study. Sixty ASA physical status I or II patients, scheduled for elective major abdominal surgery were recruited in this study at Mansoura Gastroenterology Center. Patients with a history of renal, hepatic or neuromuscular disease were excluded as those with diabetes, anticipated difficult airway or any patients receiving medication known to affect myoneuronal junction.

All patients received oral diazepam 5 mg the night before surgery. An infusion of lactated Ringer's solution were started at a rate of 4-6mg. $Kg^{-1}.h^{-1}$ before induction of anesthesia in the arm contra lateral to that used to monitor neuromuscular function. Meanwhile, the forearm and the

hand of patients were cleaned with alcohol and left to dry, then three surface electrodes of Datex angstrom M.NMT sensor were applied over the ulnar nerve at wrist.

Patients received midazolam 0.03 mg.Kg-1, fentanyl 1µg.Kg-1 intravenously before induction of anesthesia, then patients were randomized according to neuromuscular drug protocol by sealed unmarked envelops to one of three groups (20 patients each) :

**Group A { P } :** received pipecuronium in a dose of 0.08 mg.Kg-1.

**Group B { P1T1} :** received pipecuronium-atracurium combination in a dose of 0.04 mg.Kg-1, and 0.25 mg.Kg-1 respectively" one half of the intubating dose".

**Group C {P2T2} :** received pipecuronium-atracurium combination in a dose of 0.026 mg.Kg-1 , and 0.166mg.Kg-1 respectively" one third of the intubating dose".

Then anesthesia was induced with thiopentone Na, in a dose sufficient to abolish the eye lash reflex. Laryngoscopy and tracheal intubation were performed when T1 ratio reached 10%. Anesthesia was maintained with $N_2O$ in oxygen (2:1) and Isoflurane (1-1.5 %). Ventilation was controlled to maintain end tidal $CO_2$ around 30 mmHg. Further increments (1/10 of the intubating dose) of neuromuscular blocker or their combination were administered when T2 response of TOF was first detected," it corresponds to 25% recovery of single muscle twitch height (T1/T Control = 25%).

*Recovery :* when two palpable twitches in response to TOF were detected, reversal agents were given to the patients in a dose of neostigmene 0.04 mg.Kg-1 mixed with atropine 0.02 mg.Kg-1. When T4 of TOF was first detected, DBS pattern was set every 30 sec. until two equal contractions were felt (i.e absence of DBS fade) and in addition to the presence of other criteria for extubation, extubation was done.

The recorded parameters included:

*(a) : Parameters of muscle relaxation :*

- Onset of action ( time from injection of neuromuscular blocking drug or drug combination till T1 ratio reached 10% ).
- Time of successful intubation.
- Assessment of intubating condition

using intubating condition score (table 1), and incidence of signs of inadequate relaxation.

- Duration of the neuromuscular block of the bolus dose of relaxant, or the combination (time from injection till T1 ratio of 25%).
- Number of redoses and duration of each.
- Recovery times: - recovery time 1 (time from last incremental dose to first detection of T2. – recovery time 2a: time from neostigmine injection to first detection of T4, - recovery time 2b: time from neostigmine injection to full detection of equal contraction of DBS.
- Total dose requirement of pipecuronium alone or in combination with atracurium and total dose of atracurium in μg / kg.

(b) Heart rate, mean arterial blood pressure, using Datex Ohmeda monitor , temperature was monitored by nasopharyngeal thermistor and maintained at 36.5 ± 0.5 $^{o}$C, also skin temperature over the thenar eminence and forehead was maintained at a level of 32$^{o}$ - 33$^{o}$C.

© Any concomitant complication e.g signs of histamine release, cutaneous rashes, hypotension were recorded.

## STATISTICAL ANALYSIS

Statistical analysis was carried out using SPSS Statistical Package. Mann-Whitney u test was used to test for significant difference in quantitative variables between each two groups. Wilcoxon – matched pairs test was used to test significance of difference of changes in each variable in the same group. Differences were considered to be significant when $P < 0.05$.

## RESULTS

Patients characteristics and duration of surgery were comparable among groups (Table 2). Onset time was nearly similar in the three groups of the study, time of successful intubation showed no significant differences in the studied groups (Table 3)

Intubation condition were excellent or good in the three groups except for 2 patients in group A, when intubation was poor due to patients anomalies they were excluded from the study (Table 4).

Table (5): shows that the signs of incidence of inadequate relaxation were more in group A & C, three patients in group A bucked on the tube. The surgeons complained of in

adequate relaxation of 5 patients in group C.

The duration of clinical relaxation of either the bolus dose or the incremental ones in group C were significantly short compared with those of group B. While in comparison with group A, the duration of clinical relaxation of the bolus dose, the third, and the fourth incremental ones displayed a significant decline. The duration of the neuromuscular blockade of the first redose in group B was significantly longer than those of group A (Table 6).

Table (7) shows that recovery time 1(time from last incremental dose to first detection of T2) from muscle relaxants in group C was significantly short compared with those of group A and B. Time from neostigmine injection to first detection of T4, and time from neostigmine injection to full detection of equal contraction of DBS showed no significant differences among the three groups.

Total dose requirements of atracurium calculated in microgram / kg / min. showed no significant differences in both groups B and C, and pipicuronium requirement in both groups were significantly less than group A requirement.

Heart rate monitoring revealed stability in heart rate values in group B throughout the procedure. In comparison with group A, group B showed significant decrease in heart rate values throughout the intraoperative time and immediately postoperative. Patients of group C showed a significant decrease in the intraoperative heart rate values in comparison to group A, 10 minutes after intubation, and extending throughout the operative time. However the same values were significantly higher compared to group B at preoperative basal values, at induction, intubation, and 30 min. after intubation. Compared with the preoperative values, only group B showed significant decrease of the heart rate at induction time, intubation, 30 minutes after intubation, and immediately postoperatively (Table 8).

There was a significant decrease in perioperative mean arterial blood pressure in group B and C compared with group A except at 30 minutes after intubation. Comparing with the preoperative basal values, group A showed a significant decrease in

mean arterial blood pressure at time of induction and at 30 minutes after intubation. Group B demonstrated a significant decrease at the time of induction only, meanwhile group C showed the same findings 10 minutes after intubation (Table 9). No signs of histamine release were recorded.

Table (1): Intubation Condition Score [3]

| **Assessment:**<br>-Vocal cords<br>-Coughing<br>-Laryngoscopy<br>-Point | Open<br>Non<br>Easy<br>1 | Moving<br>With Diaphragm<br>Fair<br>2 | Closing<br>Clear<br>Difficult<br>3 | Closed<br>Sever<br>Impossible<br>4 |
|---|---|---|---|---|
| **Classification:**<br>-Points<br>-Intubating condition | 3-4<br>Excellent | 5-7<br>good | 8-10<br>Poor | 11-12<br>Inadequate |

Table (2): Patients characteristics and duration of surgery [Mean ± SD]

| | Group (A)<br>n = 20 | Group (B)<br>n = 20 | Group C<br>n = 20 |
|---|---|---|---|
| Age (years) | 48.0 ± 11 | 54.0 ± 11 | 49.0 ± 11 |
| Sex ( M/F) | 4 : 1 | 3 : 1 | 1 : 1 |
| Weight (Kg) | 69.5 ± 14.6 | 75.5 ± 9.73 | 71.5 ± 10.55 |
| Duration of surgery (min.) | 186 ± 64 | 226 ± 76 | 187 ± 41 |

Group A = Pipecuronium 0.08 mg.kg $^{-1}$; Group B = Pipecuronium 0.04 mg.kg$^{-1}$ + Atracurium 0.25 mg.kg$^{-1}$; Group C = Pipecuronium 0.026 mg.kg$^{-1}$ + Atracurium 0.166 mg.kg$^{-1}$

Table (3): Onset of action and time of successful intubation [Mean ± SD]

| | Group A n = 20 | Group B n = 20 | Group C n = 20 |
|---|---|---|---|
| Onset of action ( min.) | 3.7 ± 0.6 | 3.7 ± 0.5 | 3.6 ± 0.6 |
| Time of successful Intubation (seconds) | 60.3 ± 2 | 58.3 ± 4.3 | 57.3 ± 3.6 |

Group A = Pipecuronium 0.08 mg.kg $^{-1}$; Group B = Pipecuronium 0.04 mg.kg$^{-1}$ + Atracurium 0.25 mg.kg$^{-1}$; Group C = Pipecuronium 0.026 mg.kg$^{-1}$ + Atracurium 0.166 mg.kg$^{-1}$

Table (4): Intubating condition score

| | Group A n = 20 (%) | Group B n = 20 (%) | Group C n = 20 (%) |
|---|---|---|---|
| Excellent | 18 (90) | 19 (95) | 18 (90) |
| Good | 2 (10) | 1 (5) | 2 (10) |
| Poor | 0 (0) | 0 (0) | 0 (0) |
| Inadequate | 0 (0) | 0(0) | 0(0) |

Group A = Pipecuronium 0.08 mg.kg $^{-1}$; Group B = Pipecuronium 0.04 mg.kg$^{-1}$ + Atracurium 0.25 mg.kg$^{-1}$; Group C = Pipecuronium 0.026 mg.kg$^{-1}$ + Atracurium 0.166 mg.kg$^{-1}$

Table (5): Incidence of signs of inadequate muscle relaxation

| Condition | Group A No. (%) | Group B No. (%) | Group C No. (%) |
|---|---|---|---|
| Limb movement | 0 | 0 | 0 |
| Bucking on tube | 3 (15) | 0 | 0 |
| Surgeon complaint of inadequate relaxation | 0 | 0 | 5 (25) |

Group A = Pipecuronium 0.08 mg.kg $^{-1}$; Group B = Pipecuronium 0.04 mg.kg$^{-1}$ + Atracurium 0.25 mg.kg$^{-1}$; Group C = Pipecuronium 0.026 mg.kg$^{-1}$ + Atracurium 0.166 mg.kg$^{-1}$

Table (6): Neuromuscular Transmission Data During Maintenance Of Anesthesia (Mean ± SD)

| Duration of relaxation of each dose (min.) | Group A (n = 20) | Group B (n = 20) | Group C (n = 20) |
|---|---|---|---|
| Bolus dose (min.) Number of patients | 58.0 ± 19.5 (20) | 58.3 ± 15.4 (20) | 51.0 ± 11.8 *† (20) |
| Number of Redoses | 2.9 ± 0.7 | 2.5 ± 1.1 | 2.7 ± 0.8 |
| 1st redose. Number of patients | 53 ± 10 (20) | 59.7 ± 8 * (19) | 50 ± 10 † (20) |
| 2nd redose Number of patients | 52 ± 10 (19) | 55 ± 11 (18) | 50.5 ± 13† (20) |
| 3rd redose Number of patients | 66.0 ± 2 (10) | 57.7 ± 10.8 10 | 45.0 ± 12* † (13) |
| 4th redose Number of patients | 60.0 ± 0.0 (4) | 60 ± 0.0 (1) | 40 ± 7.7 *† (5) |

Group A = Pipecuronium 0.08 mg.kg $^{-1}$; Group B = Pipecuronium 0.04 mg.kg$^{-1}$ + Atracurium 0.25 mg.kg$^{-1}$; Group C = Pipecuronium 0.026 mg.kg$^{-1}$ + Atracurium 0.166 mg.kg$^{-1}$

*Significant compared with A ( $P < 0.05$)
† Significant compared with B ( $P < 0.05$)

Table (7): Recovery Pattern and Total Dose Requirement (Mean ± SD)

| | A n = 20 | B n = 20 | C N = 20 |
|---|---|---|---|
| Recovery time 1 (min.) | 54.0 ± 15.7 | 60.6 ± 12.9 | 48.6 ± 13.5 *† |
| Recovery time 2 (min.) (a) (b) | 4.3 ± 0.8 4.6 ± 0.7 | 4.0 ± 0.8 4.3 ± 0.9 | 3.9 ± 0.8 4.0 ± 0.8 |
| Total dose requirement of pipicuronium in µg / kg / min. | 0.74 ± 0.24 | 0.32 ± 0.08 * | 0.31 ± 0.08 * |
| Total dose requirement of Atracuirium in µg / kg / min. | — | 1.95 ± 0.48 | 1.87 ± 0.49 |

*Significant compared with A (P < 0.05)
†Significant compared with B ( P < 0.05)

Table (8): Perioperative heart rate changes (beat / min.){ Mean ± SD}

| Group | Basal Preop. | Induction time | Intubation Time | After Intubation 10 min. | 30 min. | 60 min. | 120 min. | Immed. P. O. |
|---|---|---|---|---|---|---|---|---|
| A (n =20) | 89.5 ± 14.8 | 87.0 ± 14.4 | 93.5 ± 12.4 | 92.0 ± 11.7 | 90.6 ± 13.8 | 91.8 ± 12.3 | 89.9 ± 11.5 | 94.8 ± 10.0 |
| B (n=20) | 81.0* ± 12.5 | 72.6*# ± 11.5 | 71.5*# ± 10.7 | 79.0* ± 10.4 | 71.0*# ± 8.7 | 77.0* ± 9.0 | 77.4* ± 7.6 | 80.5*# ± 9.4 |
| C (n=20) | 87.3† ± 18.6 | 89.0† ± 15.9 | 92.0† ± 14.9 | 81.6* ± 12.4 | 80.6*† ± 13.4 | 80.9* ± 15.4 | 78.7* ± 12.3 | 89.9 ± 13.8 |

Group A = Pipecuronium 0.08 mg.kg $^{-1}$; Group B = Pipecuronium 0.04 mg.kg$^{-1}$ + Atracurium 0.25 mg.kg$^{-1}$; Group C = Pipecuronium 0.026 mg.kg$^{-1}$ + Atracurium 0.166 mg.kg$^{-1}$

* Significant compared with A ( P < 0.05)
† Significant compared with B ( P < 0.05)
# Significant compared with basal ( P < 0.05 )

Table (9): Perioperative Mean Arterial Blood Pressure (mm Hg.){ Mean ± SD}

| Group | Basal Preop. | Induction time | Intubation Time | After Intubation 10 min. | 30 min. | 60 min. | 120 min. | Immed. P. O. |
|---|---|---|---|---|---|---|---|---|
| A (n =20) | 101 ± 8.2 | 98.0# ± 7.3 | 101.7 ± 10.2 | 102.2 ± 6.8 | 93.6# ± 12.5 | 99.8 ± 22.5 | 102.4 ± 8.2 | 100.9 ± 5.4 |
| B (n=20) | 89.0* ± 12.9 | 84.3*# ± 11.8 | 84.2* ± 14.8 | 91.2* ± 9.2 | 87.9 ± 10.4 | 84.4* ± 13.2 | 85.1* ± 11.1 | 88.6* ± 10.2 |
| C (n=20) | 90.2* ± 11.7 | 88.0* ± 9.8 | 87.5* ± 12.3 | 84.1*†# ± 12.6 | 87.0 ± 11.2 | 84.6* ± 10.6 | 87.2* ± 10.7 | 87.9* ± 9.6 |

Group A = Pipecuronium 0.08 mg.kg $^{-1}$; Group B = Pipecuronium 0.04 mg.kg$^{-1}$ + Atracurium 0.25 mg.kg$^{-1}$; Group C = Pipecuronium 0.026 mg.kg$^{-1}$ + Atracurium 0.166 mg.kg$^{-1}$

* Significant compared with A ( P < 0.05)
† Significant compared with B ( P < 0.05)
# Significant compared with basal ( P < 0.05 )

## DISCUSSION

There are two important safety issues in practice with muscle relaxant, cardiovascular side effects and adequacy of recovery to normal neuromuscular function. The latter is by far the more important. It was difficult to demonstrate that one muscle relaxant is truly safer than another, to avoid prolonged residual block , the main goal should be to use the lowest possible dose that will provide adequate relaxation for surgery [4]. Currently available non-depolarizing neuromuscular blocking drugs, all cause alteration in cardiovascular performance when used in clinical effective doses, such cardiovascular changes are largely dose dependant. [5] .

As reported by David et al [6] atracurium at high dose ranges cause a moderate histamine release and significant fall in blood pressure. Bradycardia during anaesthesia may be more common with atracurium than with other muscle relaxants, since atracurium has no clinical significant effects on heart rate in the recommended dosage range. It will not counteract bradycardia or vagal stimulation during anaesthesia.

Pipecuronium is a long acting aminosteroid muscle relaxant which is devoid of ganglion blocking activity and does not block the muscarinic cardiac receptors by the myoparalytic dose range. It has very wide safety margin, and the dose of the drug that causes vagal blockade showed to be around 131 times higher than the neuromuscular blocking doses [7].

Wierda et al [8] reported that, pipecronium has no cumulative tendency in contrast to that of pancuronium. However, cumulative effects can always be demonstrated by increasing the maintenance doses or shortening the time period between the doses. Because these side effects are largely dose related, autonomic and cardiovascular alterations can be minimized by giving relatively small dose of neuromuscular blockers. So, this study was designed to evaluate hemodynamic and the neuromuscular blocking profiles of pipecuronium given alone or combined with atracurium .

Detailed neuromuscular pattern and recovery characteristics of pipecuronium and atracurium combination had not been studied previously, however, we relied on comparison with other non-depolarizing neuromuscular

blockers within the same category with similar chemical structure of the studied drugs.

This study shows that combination of pipecuronium and atracurium in different doses provides onset characteristics and intubating conditions comparable to those associated with pipecuronium alone. The same results were obtained with d-tubocurarine and pancuronium combination [9]. Lebowitz et al [2] found comparable results to the present study with pancuronium and metocurine combination. They reported that, the onset time and intubation condition were similar when pancuronium used alone in a dose of 0.1mg/kg (twice the ED95) or used with metocuraine giving as (ED95) of both drugs. On the other hand, Motamed and donati [10] reported that, with mivacurium and rocurinum combination, the onset has been reported to be as rapid as that of rocuronium and duration as short as mivacurium. They added also that, the combination of muscle relaxant keeps the desired features of each agent.

In the present study there was no observed signs of histamine release as hypotension or flushing. Similar results concerning haemodynamic stability with vecuronium and d-tubocurarine combination were observed although d-tubocurane is a more potent histamine releaser than atracurium [11]. David et al [6] documented that, the use of atracuruim in high dose (0.6 ml/kg) was associated with hypotension and other signs of histamine release as tachycardia and allergic reactions. they recommended to administer an initial lower dose (0.3 –0.4 mg / kg) slowly or in divided doses over 1 min.

The drug combination calculated in half the intubated dose represented in group B resulted in clinical duration of action and recovery times comparable to those of pipecuronium alone(group A). The clinical duration and recovery times of the combined drugs in group C were shorter than group A and group B. This is in parallel with Naguib et al [12] study who reported that clinical profiles and complete spontaneous recovery of T1, and TOF ratio with subparalyzing doses of rocuronium-cisatracurium combination was significantly shorter than that observed with equipotent doses of cistracurium. This finding was explained by lobewitiz et al [2] who reported that such low dose of combina-

tion (pancuronium and metocurine) as compared with pancuronium alone resulted in redistribution kinetics with earlier reduction in the level of each neuromuscular blocking drug at its pre-or postsynaptic site of action and consequently early restoration of normal neuromuscular transmission.

In this study pipecuronium-atracurium combination in group B resulted in synergistic rather than additive effect, it is observed in the duration of neuromuscular blockade of the bolus dose which is nearly similar to pipecuronuim alone, and the duration of the first redose was significantly longer than those of group A and C. concerning the adequacy of muscle relaxation, patients of group B were more comfortable to surgeon in respect of surgical relaxation than other groups.

Pararell with this study, Pollard and Jones[13] reported that a combination of d-tubocurane with pancuronium has been shown to result in a greater than additive effect both in animal preparation and in human.

The potentiation effects of those combination was explained by Mirakhur et al., [11] who excluded the differences in protein binding and alteration in tissue blood flow to be a contributing factor in this potentiation, and attributed this synergistic action to the different sites of action of the combined drug. They reported that the more plausible reason for the potentiation of d-tubocurane and vecuronium may be the action of these two drugs occurring at more than one site to different degrees, possibly a prejunctional action to impair transmitter release occurs as well as the more familiar postjunctional receptor block.

Naguib and Abdulatif [14] confirmed these results and added that interaction between pipecuronium and vecuronium was found to be additive( both have the similar chemical structure).Further studies by Naguib et al., [15], postulated that combination of structurally similar neuromuscular blocking drugs produce an additive response in human but combination of structurally dissimilar neuromuscular blocking drugs resulted in potentiating effect.

A practical advantage of using a combination of pipecuronium and atracurium is hemodynamic stability observed in-group B compared with those of group A and C. Another economic advantage is that this

combination generally requires 30-50 % less total drug for a similar clinical effect compared to either drug used separately, it may be possible to use these synergistic combination in some clinical situation to achieve substantial cost saving because less total drug is used.

In this study we are lacking to investigate the neuromuscular profile of atracurium because our operation is somewhat long about (more than 3 hrs). so, atracurium is not a suitable choice for these procedures.

In conclusion, Combination of atracurium and pipecuronium (half the intubating dose) can be used to obtain acceptable onset times with duration of action similar to that of pipecuronium. Also, combination in group C ( using one third of the intubating dose) can be suitable especially when the anticipated duration is about 1-2 hours. But in longer procedures it is preferable to use combination of both drugs in half the intubating dose.

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