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Research Article

Efficacy of different doses of atracurium on intubating conditions of burned patients

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KEYWORDS

Atracurium;
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Intubation conditions and onset time

Abstract *Background:* Burned patients exhibit resistant response to nondepolarizing muscle relaxants. This study was designed to investigate the efficacy of high dose atracurium (3 and 4 times ED95) with and without application of the priming principle on the intubating conditions and the onset times in burned patients.

Methods: ASA physical status I and II patients undergoing burn related surgery, were randomly allocated into one of four groups of 20 patients each. Group I received 1 ml placebo followed 3 min later by atracurium 0.75 mg/kg, group II received atracurium 0.04 mg/kg as the priming dose followed 3 min later by atracurium 0.71 mg/kg, group III received 1 ml placebo followed 3 min later by atracurium 1 mg/kg and group IV received atracurium 0.04 mg/kg as the priming dose followed 3 min later by atracurium 0.96 mg/kg. Datex relaxograph was used at the adductor pollicis to monitor and record the twitch response to the train of four (TOF) stimulation.

Results: The conditions for intubation improved significantly with increasing the dose of atracurium, as we seen, when comparing patients in group IV and group I. Onset times were significantly delayed in groups I and II compared with groups III and IV.

Conclusion: Combinations of 4 times ED95 of atracurium together with the application of the priming principle are required to overcome the resistance and produce satisfactory intubating conditions in burned patients.

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1. Introduction

Patients with thermal injury usually demonstrate resistant response to nondepolarizing muscle relaxants (NDMRs) and this manifests itself clinically by increasing the dose of NDMRs to produce the desired effect [1]. This type of resistance usually seen when burn involves more than 20% of total body surface area (TBSA). It was found that peri-junctional proliferation and the expression of immature acetylcholine

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receptors on the muscle membrane are the main causes of resistance [2,3].

Succinylcholine is contraindicated in burned patients, as it may be associated with life threatening hyperkalemia. Alternative methods can be used in patients with thermal injury to produce faster onset of neuromuscular effect including; the use of high dosage of NDMRs, the combination of two structurally different NDMRs or the use of the priming principle [4].

This study was conducted to compare the effect of high dose atracurium (3 and 4 times ED95 (Effective Dose 95%)) with and without application of the priming principle on the onset times and the intubating conditions in burned patients.

2. Patients and methods

The study protocol was reviewed and approved by local hospital ethics committee. Written informed consent was obtained from each patient. Eighty ASA I and ASA II patients with history of burns more than 20% total body surface area(TBSA), aged 20–60 years, undergoing burn-related surgery lasting more than one hour, at 21–90 days after the injury, were enrolled in the study at Mansoura University burn and plastic surgery center.

Patients with history of using drugs known to influence neuromuscular transmission or those with any disorder of renal, hepatic, neurological, neuromuscular, or cardiovascular system were excluded from the study. Patients were also excluded if having history of asthma, difficult intubation or requiring a rapid sequence procedure.

Patients were premedicated using midazolam 0.04 mg/kg I.V. Routine monitors were applied upon arrival to the operating theater including electrocardiogram, noninvasive arterial blood pressure, and pulse oximetry. Datex relaxograph was used at the adductor pollicis to monitor and record the twitch response to the train of four (TOF) stimulation. All patients were preoxygenated with 100% oxygen for 3 min before induction of anesthesia.

Patients were randomly assigned according to predetermined randomization code to four equal groups. The studied patients received atracurium either at 3 ED95 (groups I and II) or 4 ED95 (groups III and IV) with and without priming as follow; group I – received 1 ml normal saline given I.V. (intravenously) simulating the priming dose (placebo with saline) followed 3 min later by atracurium 0.75 mg/kg I.V. over 75 s, group II – received atracurium 0.04 mg/kg I.V. as the priming dose followed 3 min later by atracurium 0.71 mg/kg I.V. over 75 s, group III – received 1 ml normal saline given I.V. simulating the priming dose (placebo with saline) followed 3 min later by atracurium 1 mg/kg I.V. over 75 s and group IV – received atracurium 0.04 mg/kg I.V. as the priming dose followed 3 min later by atracurium 0.96 mg/kg I.V. over 75 s.

General anesthesia was induced in the studied groups with propofol 1.5–2.5 mg/kg I.V. and fentanyl 1–2 μg/kg I.V. 3 min after administration of the priming dose (atracurium or saline). The patients in group I and II received (3 ED95)0.75 mg/kg atracurium and those in group III and IV received (4 ED95)1 mg/kg atracurium.

Neuromuscular monitoring was initiated after obtaining the control values by supramaximal stimulus square wave stimuli applied to the ulnar nerve at 2 Hz with pulse width 0.2 ms repeated every 15 s. After TOF stabilization, the muscle relaxant was given as previously mentioned for each group.

After induction of anesthesia and while TOF monitoring was established, the airway was maintained with oral airway. Manual ventilation was performed with 100% oxygen via facemask. The end tidal CO_2 was kept within the normocarbic range during this period. Onset time was noted (the interval from the end of muscle relaxant bolus injection until the maximal suppression of T_1 %).

Two minutes after injection of the intubating dose, endotracheal intubation was attempted by laryngoscopist who was blinded to the induction technique. The condition of intubation was assessed and scored on a scale described by Clarke and Mirakhur. Possible tracheal intubation conditions were excellent (jaw relaxed, vocal cords apart and immobile, no diaphragmatic movement), good (jaw relaxed, vocal cords apart and immobile, some diaphragmatic movement), poor (jaw relaxed, vocal cords moving and substantial diaphragmatic movement), or inadequate (jaw not relaxed, vocal cords closed) [5].

Anesthesia was maintained with 100% oxygen and isoflourane (1–1.5 MAC (Minimum Alveolar Concentration)), boluses of the muscle relaxant (10% of the initial dose) with 25% recovery of response to T_1 % and ventilation was controlled by the Datex-Ohmeda ventilator to adjust end tidal CO_2 at (30–35 mmHg).

At the end of operation, the block was reversed with neostigmine and atropine mixture (2.5 mg neostigmine: 1 mg atropine) through slow IV injection if TOF-ratio was less than 70%.

The heart rate (HR), mean arterial blood pressure (MABP) were noted before administration of atracurium and 1, 5, 10, 15 and 20 min after intubation. An observer blinded to randomization schedule recorded signs of histamine release such as flushing (redness >2 min) or presence of any hemodynamic changes or bronchospasm.

2.1. Statistical analysis

The statistical analysis of data was done by using excel program for figures and SPSS program statistical package for social science; SPSS Inc., Chicago, IL. The description of the data was done in form of mean ± SD for quantitative data, and frequency and proportion for qualitative data. The analysis of data was done to test statistical significant difference between groups. One way ANOVA was used to compare more than two groups followed by post hoc least significant difference (LSD) test if subtraction between two means gives $\geqslant$LSD this means significant difference between the two means. Chi square test was used for qualitative data. P is considered significant if $<$ or $=$ 0.05 at confidence interval 95%.

Power analysis was not performed to determine sample size because we did not have preliminary data on onset, maximum block and duration of atracurium in burned patients with different priming regimen. However this study could be considered an exploratory pilot study rather than a formal test of hypothesis. The sample size of 80 (20 in each group) was chosen arbitrarily.

3. Results

All groups were comparable with respect to age, sex, height, weight, extent of burn injury and the time of the study after

Table 1 Demographic data of the four groups.

	Group I	Group II	Group III	Group IV
Age (years)	38.75 ± 9.8	35.25 ± 5.3	37.6 ± 8.3	39.3 ± 10.1
Sex (M/F)	13/7	14/6	12/8	13/7
Weight (kg)	77.9 ± 6.6	73.5 ± 7.7	80.3 ± 7.6	76.8 ± 5.9
Height (cm)	168.7 ± 5.5	167.8 ± 7.9	169.7 ± 4.5	171.8 ± 4.8
Burn area[a]	31.8 ± 6.9	31.2 ± 6.4	30.5 ± 7.1	32.1 ± 6.7
Days since burn injury	32.9 ± 13.9	35.2 ± 16.6	33.7 ± 14.1	34.6 ± 15.3

Group I (3 ED95 without priming), group II (3 ED95 with priming), Group III (4 ED95 without priming), Group IV (4 ED95 with priming). Values are mean ± SD or number. No significant differences between groups ($p > 0.05\%$).

[a] % Of total body surface area.

injury (Table 1). Onset times were significantly delayed in groups I and II, compared with groups III and IV. The neuromuscular block obtained in groups I and II, was incomplete, however, doses of atracurium in groups III and IV were sufficient to produce complete block ($p < 0.001$) (Table 2).

In all patients, the tracheas were intubated at the first laryngeoscopy, and intubating conditions were noted as excellent in 8 (40%), 10 (50%), 12 (60%), and 15 (75%); good in 7 (35%), 8 (40%), 8 (40%), and 5 (25%) and poor in 5 (25%), 2 (10%), 0, and 0 in group I, II, III and IV respectively (Table 3). The conditions for intubation improved significantly with increasing the dose of atracurium when comparing patients in group IV and group I (excellent in 15 of 20 versus excellent in 8 of 20, $p < 0.05$).

The mean arterial blood pressure and the heart rate were significantly more at 1 min after intubation in all groups ($p < 0.05$), but at 5 min and thereafter, they had come near the baseline(Tables 4 and 5). Signs of histamine release were noted in 27 patients (33.75%) in the form of cutaneous flushing. The incidence of cutaneous flushing seemed to be dose dependent (25% (5), 25% (5), 40% (8), and 45% (9)) for groups I, II, III and IV respectively with no significant differences among the four groups ($p > 0.05\%$). No patient in the studied groups, developed bronchospasm or hypotension (see Table 6).

4. Discussion

The results of this study have confirmed previous findings [6] that giving priming dose shortly before a larger bolus dose improved both onset of paralysis and the intubating conditions compared with the same single bolus dose; as in group II (0.04 + 0.71 mg/kg) versus group I (0.75 mg/kg) and group IV (0.04 + 0.96 mg/kg) versus group III (1 mg/kg), however, no statistically significant difference exists between either groups II and I or groups IV and III.

The priming dose of NDMRs is usually 20% of ED_{95}. This dose accelerates the onset of action and improves onset times by 10–40% with the fewest side-effects [7]. In this study we chose relatively small priming dose of atracurium 0.04 mg/kg (16% of ED_{95}) to avoid occurrence of any respiratory difficulties. No patient in the primed groups (II and IV) complained of diplopia or any evidence of hypoventilation after receiving the priming dose.

In the current study, priming interval was kept at 3 min simply because, it was found that 3 min priming interval gave the optimum intubating conditions and waiting for 5 min gave no added benefits [8].

In accordance with other studies [9], increasing the dose of atracurium from 3 ED95 (0.75 mg/kg) to 4 ED95 (1 mg/kg) accelerated the onset times significantly in groups III and IV (1 mg/kg) when compared with groups I and II (0.75 mg/kg).

We did not study the duration of action of high dose atracurium as this was not the aim of our study and thus we limited the study to burn related surgery lasting more than one hour simply because Mirakhur et al., found that the duration of high dose atracurium 1 mg/kg was about 57 min [10].

Regarding intubating conditions, no significant differences exist among groups apart from the intubating conditions in group IV which were developed significantly faster (4 times ED95 with application of priming principle) when compared with group I (3 times ED95 with no priming). This study is consistent with previous studies showing that burned patients have resistance to atracurium and this was evidenced by failure to obtain complete neuromuscular block in groups I and II. Causes of resistance to NDMRs in burned patients may be due to enhanced protein binding or increased clearance kinetics and most importantly upregulation of acetylcholine receptors [11].

The heart rate and the mean arterial blood pressure increased in all groups significantly at 1 min after intubation due to the stress response, however, HR and MABP returned near the base line at 5 min and this is consistent with another

Table 2 Onset of neuromuscular blockade after administration of atracurium in the studied groups.

	Group I	Group II	Group III	Group IV	*P*	LSD
Onset time (s)	227.3 ± 4.4	217 ± 4.1	178.1[†,*] ± 3.7	167.4[†,*] ± 5.8	< 0.001	38.9
Maximm block (%)	97.7 ± 1.6	98.25 ± 1.1	100[†,*]	100[†,*]	< 0.001	1.75

Group I (3 ED95 without priming), group II (3 ED95 with priming), group III (4 ED95 without priming), group IV (4 ED95 with priming). Values are mean ± SD or number.

[*] Statistically significant difference versus group I ($p < 0.001$).

[†] Statistically significant difference versus group II ($p < 0.001$). Least significant difference (LSD).

Table 3 Intubating conditions 2 min after administration of atracurium.

Score	Group I	Group II	Group III	Group IV
Excellent	8 (40%)	10 (50%)	12 (60%)	15* (75%)
Good	7 (35%)	8 (40%)	8 (40%)	5 (25%)
Poor	5 (25%)	2 (10%)	0 (0%)	0 (0%)
Inadequate	0 (0%)	0 (0%)	0 (0%)	0 (0%)

Group I (3 ED95 without priming), group II (3 ED95 with priming), group III (4 ED95 without priming), group IV (4 ED95 with priming). Values are number or %.
* Statistically significant difference versus group ($p < 0.05$).

Table 4 Heart rate (HR) changes before and after injection of atracurium.

	Group I	Group II	Group III	Group IV
Basal	72.5 ± 5.9	72.3 ± 6.1	73.3 ± 4.2	72.2 ± 6.4
1 min after intubation	83.1 ± 6.9*	84.4 ± 5.7*	85.2 ± 3.7*	86.6 ± 5.1*
5 min	75.2 ± 8.1	76.1 ± 6.5	73.1 ± 3.9	73.6 ± 6.9
10 min	74.4 ± 6.8	75.3 ± 6.4	74.2 ± 5.1	73.3 ± 5.8
15 min	75.1 ± 7.3	74.9 ± 5.9	73.3 ± 4.4	74.4 ± 5.4
20min	74.7 ± 7.8	74.8 ± 6.4	74.5 ± 3.8	73.8 ± 6.6

Group I (3 ED95 without priming), group II (3 ED95 with priming), group III (4 ED95 without priming), group IV (4 ED95 with priming). Values are mean ± SD or number. Values are mean ± SD.
* Statistically significant difference versus baseline reading ($p < 0.05$).

Table 5 Mean arterial blood pressure (MABP in mmHg) changes before and after injection of atracurium.

	Group I	Group II	Group III	Group IV
Basal	81.3 ± 8.4	80.8 ± 9.4	81.9 ± 9.5	80.3 ± 10.7
1 min after intubation	92.6 ± 7.4*	91.7 ± 6.9*	91.8 ± 8.1*	90.9 ± 7.9*
5 min	85.4 ± 6.9	84.6 ± 8.1	84.7 ± 8.2	85.2 ± 9.1
10 min	83.6 ± 7.1	84.5 ± 8.4	84.9 ± 8.9	85.7 ± 8.3
15 min	82.5 ± 8.6	83.6 ± 9.1	83.8 ± 7.8	84.5 ± 8.7
20 min	81.9 ± 7.6	84.4 ± 8.9	83.7 ± 9.1	83.9 ± 8.8

Group I (3 ED95 without priming), group II (3 ED95 with priming), group III (4 ED95 without priming), group IV (4 ED95 with priming). Values are mean ± SD.
* Statistically significant difference versus baseline reading ($p < 0.05$).

Table 6 Incidence of cutaneous flushing after administration of atracurium in the studied groups.

	Group I	Group II	Group III	Group IV	χ^2	p
Cutaneous flushing	5 (25%)	5 (25%)	8 (40%)	9 (45%)	2.85	0.41

Group I (3 ED95 without priming), group II (3 ED95 with priming), group III (4 ED95 without priming), group IV (4 ED95 with priming). Values are number or %. No significant differences between groups ($p > 0.05\%$). χ^2 = Chi square test.

study which reported no changes in the HR or the arterial blood pressure when atracurium was given in a dose up to 1 mg/kg [10] and also as we injected the bolus dose of atracurium over 75 s preventing significant increase in the plasma histamine release and this was in agreement with another study done by Scott et al. [12].

Flushing is a cutaneous manifestation resulting from skin histamine release and is not always associated with increased plasma histamine level [13]. The incidence of flushing in our study was similar to those obtained by other authors at comparable doses and was dose related [10].

Limitation of this study, we did not examine the effects of burn size and time after burn on the neuromuscular effects of atracurium.

In conclusion, combinations of 4 times ED95 of atracurium together with the application of the priming principle are required to overcome the resistance and produce satisfactory intubating conditions in burned patients.

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