

# Onset and effectiveness of rocuronium for rapid onset of paralysis in patients with major burns: priming or large bolus

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**Background.** Burn injury leads to resistance to the effects of non-depolarizing muscle relaxants. We tested the hypothesis that a larger bolus dose is as effective as priming for rapid onset of paralysis after burns.

**Methods.** Ninety adults, aged 18–59 yr with 40 (2)% [mean (SE)] burn and 30 (2) days after injury, received rocuronium as a priming dose followed by bolus ( $0.06+0.94$  mg kg<sup>-1</sup>), or single bolus of either 1.0 or 1.5 mg kg<sup>-1</sup>. Sixty-one non-burned, receiving 1.0 mg kg<sup>-1</sup> as a primed ( $0.06+0.94$  mg kg<sup>-1</sup>) or full bolus dose, served as controls. Acceleromyography measured the onset times.

**Results.** Priming when compared with 1.0 mg kg<sup>-1</sup> bolus in burned patients shortened the time to first appearance of twitch depression (30 vs 45 s,  $P<0.05$ ) and time to maximum twitch inhibition (135 vs 210 s,  $P<0.05$ ). The onset times between priming and higher bolus dose (1.5 mg kg<sup>-1</sup>) were not different (30 vs 30 s for first twitch depression and 135 vs 135 s for maximal depression, respectively). The onset times in controls, however, were significantly ( $P<0.05$ ) faster than burns both for priming and for full bolus (15 and 15 s, respectively, for first twitch depression and 75 and 75 s for maximal depression). Priming caused respiratory distress in 10% of patients in both groups. Intubating conditions in burns were significantly better with 1.5 mg kg<sup>-1</sup> than with priming or full 1.0 mg kg<sup>-1</sup> bolus.

**Conclusions.** A dose of 1.5 mg kg<sup>-1</sup> not only produces an initial onset of paralysis as early as 30 s, which we speculate could be a reasonable onset time for relief of laryngospasm, but also has an onset as fast as priming with superior intubating conditions and no respiratory side-effects.

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Resistance to the neuromuscular effects of non-depolarizing muscle relaxants (NDMRs) after major burns takes several days to develop, and may persist for several months after wound healing.<sup>1–3</sup> This resistance is usually observed when burn injury exceeds 20% of total body surface area (TBSA), and is manifested as a slower onset of paralysis, inadequate paralysis or faster recovery, when normal doses are administered to these patients.<sup>4</sup> The perijunctional proliferation and the expression of immature, fetal type, or both  $\alpha 7$  neuronal acetylcholine receptors (AChRs) on the muscle membrane probably play a major role in the altered neuromuscular pharmacodynamics.<sup>5–7</sup>

Methods to produce a faster onset of neuromuscular effect in non-burned patients include the use of larger doses, the combination of two structurally different classes of compounds, or the use of the priming principle.<sup>8,9</sup> Rocuronium (Esmeron<sup>®</sup>, Organon International, Inc., USA), with a relatively fast onset of paralysis and no potential for hyperkalaemia, may be a suitable alternative for effecting rapid onset of neuromuscular paralysis in burned patients because succinylcholine is contraindicated.<sup>5</sup> The utility of single high bolus dose of rocuronium compared with priming for producing rapid onset of neuromuscular paralysis in burned patients has not been tested.

In this prospective study, we tested the hypothesis that a higher bolus dose of rocuronium would be as effective as priming with normal doses to produce rapid onset of paralysis in burned patients. The neuromuscular pharmacodynamics of priming followed by bolus of rocuronium was compared with the same total dose given as a bolus and to a larger dose given as a bolus.

## Methods

The study protocol was reviewed and approved by the Institutional Ethics Committee for Human Research. After careful explanation and discussion, written informed consent was obtained from each patient or guardian. Adult patients with major burns (>20% TBSA), aged 18–59 yr, undergoing burn-related surgery, at 6–92 days after the injury, were studied. Ninety-three burned patients were recruited and assigned to either rocuronium priming  $0.06+0.94 \text{ mg kg}^{-1}$  ( $n=29$ ) or rocuronium  $1.0 \text{ mg kg}^{-1}$  single bolus ( $n=29$ ) groups. Rocuronium  $1.5 \text{ mg kg}^{-1}$  single bolus dose ( $n=35$ ) in burns was studied as an additional group after data collection of priming and  $1 \text{ mg kg}^{-1}$  bolus were completed. Non-burned patients receiving either rocuronium priming  $0.06+0.94 \text{ mg kg}^{-1}$  ( $n=32$ ) or rocuronium bolus dose of  $1.0 \text{ mg kg}^{-1}$  ( $n=29$ ) served as controls. A bolus dose of rocuronium  $1.5 \text{ mg kg}^{-1}$  was not tested in the control group in view of the anticipated prolonged duration of paralysis.

Patient characteristics recorded included age, sex distribution, height in centimetres, weight in kilograms, American Society of Anesthesiologists physical status classification, types and extent of burn injury, and the number of days from the injury to the study. The studies were performed during the subacute hyperdynamic phase of injury when most of the patients were confined to bed and continued to lose weight, but had no serious respiratory problems requiring mechanical ventilation. Patients in whom difficulty in mask ventilation or tracheal intubation was anticipated were not recruited. Patients who were 30% above or below ideal body weight, with a cardiac pacemaker, or history of allergic reaction to neuromuscular blocking agents were excluded, as were those with evidence of hepatic, renal, neuromuscular, or endocrine disease, marked electrolyte imbalance, myasthenia gravis, or the use of drugs (e.g. anticonvulsants) that might affect neuromuscular transmission.

One hour before the anticipated induction of anaesthesia, an 18 or 20 gauge i.v. catheter was inserted. Routine monitors, including ECG, non-invasive blood pressure, and pulse oximetry, were applied in the operating theatre. The arm used for monitoring neuromuscular paralysis, free of blood pressure cuff or i.v. fluid infusion, was secured on an arm board, with the thumb left freely mobile, whereas the other fingers were loosely immobilized with tape. Neuromuscular block was monitored with an

acceleromyography, TOF-Watch<sup>®</sup> (NV Organon, Oss, The Netherlands). To stimulate the ulnar nerve, two surface electrodes were placed in parallel over the flexor carpi ulnaris tendon and connected to the negative electrode distally and positive electrode proximally. The acceleration transducer was attached to the volar aspect of the distal phalanx of thumb.

Midazolam  $2 \text{ mg}$  was i.v. administered. Having informed the patient of the initiation of nerve stimulation, a brief period of initial TOF-Watch<sup>®</sup> calibration was followed by a tetanic stimulation for 10 s as a recruitment manoeuvre for the neuromuscular junction. This was followed by train-of-four (TOF) stimuli for 1 min. TOF-Watch<sup>®</sup> was programmed to deliver impulses at 2 Hz, pulse width 200 ms, square wave for 1.5 s, repeated every 15 s at 50 mA. After TOF stabilization, before the administration of normal saline or rocuronium priming, the first twitch response (T1) of the TOF was considered the baseline twitch height. The twitch responses shown in the TOF-Watch<sup>®</sup> monitor screen and the time of each twitch response, measured by a digital stopwatch, were recorded serially.

The study groups with burns received one of the three treatments. The priming group received rocuronium  $0.06 \text{ mg kg}^{-1}$  as the priming dose, followed 3 min later by rocuronium  $0.94 \text{ mg kg}^{-1}$  bolus over 5 s. The other group received normal saline 1 ml, mimicking the priming dose, followed 3 min later by a bolus dose of rocuronium  $1.0 \text{ mg kg}^{-1}$  given over 5 s. The third group of burned patients received rocuronium  $1.5 \text{ mg kg}^{-1}$ . Control patients only received one of the two treatments, either rocuronium  $0.06 \text{ mg kg}^{-1}$  of rocuronium as the priming dose, followed 3 min later by rocuronium  $0.94 \text{ mg kg}^{-1}$  bolus, or normal saline 1 ml mimicking the priming dose, followed 3 min later by rocuronium  $1.0 \text{ mg kg}^{-1}$  bolus given over 5 s.

The same anaesthesia induction regimen was used in both the burned and the control groups. Approximately 2 min after priming (rocuronium or saline), anaesthesia was induced with i.v. propofol  $2.0\text{--}2.5 \text{ mg kg}^{-1}$  and fentanyl  $1\text{--}2 \mu\text{g kg}^{-1}$ , followed 1 min later by the bolus of rocuronium  $0.94$  or  $1.0$ . Burned patients in the rocuronium  $1.5 \text{ mg kg}^{-1}$  group received the rocuronium 1 min after propofol and fentanyl. The time from the beginning of rocuronium bolus administration to the earliest sign of twitch depression, and to 90%, and complete twitch depression of twitch height were noted. During this time, anaesthesia was maintained with an oral airway and facemask ventilation. The end-tidal  $\text{CO}_2$  was controlled within the normocarbic range during this period. An anaesthesiologist, unaware of the priming technique and dosage, performed tracheal intubation when the twitch suppression was completely ablated or maximal. The intubation was carried out by anaesthesiologists, experienced in the assessment of intubating condition, which was graded as excellent, good, or poor, as per the guidelines for Good Clinical Research

Practice in Pharmacodynamic Studies of Neuromuscular Blocking Agents.<sup>10</sup>

SPSS version 11 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. All data are presented as mean (SE) or median with range (min–max) whenever appropriate. Differences in patient characteristics among the groups were examined with one-way analysis of variance (ANOVA). Non-parametric Kruskal–Wallis one-way ANOVA with Dunn’s *post hoc* method examined differences in onset times between priming and bolus groups in both burned and non-burned groups. Fisher’s exact test compared intubating conditions among the groups. A value of  $P < 0.05$  was considered statistically significant.

**Results**

One patient in the priming group and two in the rocuronium 1.0 mg kg<sup>-1</sup> bolus were excluded from the final analysis because the burn size turned out to be <20% TBSA. Two burned patients in the rocuronium 1.0 mg kg<sup>-1</sup> bolus group had 90% twitch suppression, but not complete inhibition. In these two patients, the intubation was performed at maximal twitch suppression, assessed by three consecutive unchanged twitch responses. All 35 patients in the rocuronium 1.5 mg kg<sup>-1</sup> bolus group completed the study and were included in the final analysis. The five groups, including the non-burned, were comparable with respect to the age, sex, height, and weight (Table 1). Among the burned, the extent of injury and the time of study after injury were comparable. The types of surgery for both the burned and the non-burned groups are tabulated in Table 2. Split thickness skin graft in burns and orthopaedic procedures in non-burns were the most common types of surgery (Table 2).

Three patients (~10%) in each priming group reported subjective sensations of respiratory difficulties, described as chest tightness, choking sensation, or difficulty in breathing. The corresponding TOF values at the adductor pollicis at this time were 87%, 100%, and 98% for the burned and 71%, 77%, and 100% for the control, respectively.

**Table 1** Patient characteristics. Values are expressed as mean (range) or mean (SE). Data were compared by one-way ANOVA. ASA, American Society of Anesthesiologists; TBSA, total body surface area; N/A, not applicable; n, numbers

Groups	Burned			Non-burned	
	Priming 0.06+0.94 (n=28)	Bolus 1.0 (n=27)	Bolus 1.5 (n=35)	Priming 0.06+0.94 (n=32)	Bolus 1.0 (n=29)
Age (yr)	40.9 (20–75)	39.0 (20–65)	38.5 (23–66)	42.4 (20–75)	41.0 (20–76)
Sex (M/F)	25/3	22/5	31/4	27/5	26/3
Weight (kg)	66.3 (2)	64.5 (2)	66.0 (2)	67.6 (2)	67.9 (2)
Height (cm)	171 (1)	168 (1)	170 (1)	167 (1)	169 (1)
ASA class (I/II/III)	0/28/0	0/23/4	0/31/4	19/13/0	22/7/0
TBSA (%)	36 (3)	39 (3)	43 (2)	N/A	N/A
Time after burn (days)	28 (3)	30 (3)	33 (3)	N/A	N/A

**Table 2** Types of surgery in patients with or without major burn. Miscellaneous include line placement, dressing changes, etc

Groups	Burned			Not burned	
	Priming 0.06+0.94 (n=28)	Bolus 1.0 (n=27)	Bolus 1.5 (n=35)	Priming 0.06+0.94 (n=32)	Bolus 1.0 (n=29)
Burn grafting	16	19	25	0	0
Escharectomy	2	1	1	0	0
ENT				4	6
Orthopaedic	10	7	9	15	13
Plastics				3	0
General surgery				4	5
Miscellaneous				6	5

In the control group, no differences were demonstrated between priming and bolus techniques for onset of initial appearance of twitch depression, 90%, or complete twitch inhibition. Irrespective of technique or dose, burned patients had significantly prolonged onset time in all pharmacodynamic variables enumerated above compared with controls (Table 3). Among the burned, priming significantly shortened the onset of initial twitch depression, 90%, and 100% twitch inhibition, compared with the rocuronium 1.0 mg kg<sup>-1</sup> bolus group. When rocuronium 1.5 mg kg<sup>-1</sup> bolus dose was compared with priming, there were no significant differences in all onset times. However, rocuronium 1.5 mg kg<sup>-1</sup> produced significantly faster onset times for 90% and 100% twitch depression than rocuronium 1.0 mg kg<sup>-1</sup> single bolus dose (Table 3).

In the rocuronium 1.0 mg kg<sup>-1</sup> bolus burned group, intubation was very difficult in one patient and unsuccessful in another, due to inadequate relaxation, despite the complete twitch ablation at the adductor pollicis, assessed by the TOF-Watch® screen. These patients did not have any difficult airway anatomy. The intubating conditions were excellent in 71% and 56% of patients receiving rocuronium priming and 1.0 mg kg<sup>-1</sup> bolus doses, respectively, albeit not significantly different. Thus, priming did not significantly improve the potential for excellent intubation conditions compared with the rocuronium 1.0 mg kg<sup>-1</sup> bolus in the burned patients. However, the intubating conditions in burned patients were greatly enhanced by increasing the rocuronium bolus dose to 1.5 mg kg<sup>-1</sup> (Table 4). Approximately 40% (n=36) of the burned patients (rocuronium priming vs bolus 1.0 vs 1.5 mg kg<sup>-1</sup>=14/28 vs 17/27 vs 5/35, respectively) had some form of diaphragmatic movement, non-sustained cough, or slight movements in the upper extremities at the time of intubation, in spite of reportedly easy laryngoscopy. The incidence of diaphragmatic movement in burns was lowest (16%) in the rocuronium 1.5 mg kg<sup>-1</sup> group compared with ~50–60% in the other two groups. In patients without burn injury, the provision of excellent intubating conditions was similar between priming and bolus technique (Table 4). Diaphragmatic movement was not observed in controls.

**Table 3** Pharmacodynamics of onset of paralysis after rocuronium priming or bolus in patients with and without major burn. Values are expressed as median with range (min–max). *n*, numbers. Data were compared by non-parametric Kruskal–Wallis one-way ANOVA with Dunn's *post hoc* method. The times were rounded off to the closest second. \**P*<0.05 when patients with bolus vs priming of same total dose were compared in burns. †*P*<0.05 when burns patients were compared with non-burns in the same dosing regimen. ‡*P*<0.05 when bolus of 1.0 vs 1.5 mg kg<sup>-1</sup> was compared in burns. The priming technique facilitates the onset times in the burned group. Priming had no effect on onset times in the non-burned group

Groups	Burned			Non-burned	
	Priming 0.06+0.94 ( <i>n</i> =28)	Bolus 1.0 ( <i>n</i> =27)	Bolus 1.5 ( <i>n</i> =35)	Priming 0.06+0.94 ( <i>n</i> =32)	Bolus 1.0 ( <i>n</i> =29)
Time (s) to					
First appearance of twitch depression	30 (15–75)*,†	45 (15–120)†	30 (15–90)	15 (15–45)	15 (15–30)
90% twitch depression	60 (30–135)*,†	120 (60–270)†	75 (30–165)‡	45 (15–75)	45 (30–90)
100% twitch inhibition	135 (45–285)*,†	210 (105–540)†	135 (90–450)‡	75 (45–150)	75 (30–105)

**Table 4** Tracheal intubating conditions after rocuronium priming vs bolus in burned and control patients. Data compared by Fisher's exact test. *n*, numbers. The grading system was adopted from the guidelines for Good Clinical Research Practice in Pharmacodynamic Studies of Neuromuscular Blocking Agents.<sup>10</sup> \**P*<0.05, when 1.5 mg kg<sup>-1</sup> compared with the priming group and 1.0 mg kg<sup>-1</sup> group with burns

Groups	Burned			Not burned	
	Priming 0.06+0.94 ( <i>n</i> =28)	Bolus 1.0 ( <i>n</i> =27)	Bolus 1.5 ( <i>n</i> =35)	Priming 0.06+0.94 ( <i>n</i> =32)	Bolus 1.0 ( <i>n</i> =29)
Excellent	20 (71%)	15 (56%)	32 (91%)*	28 (87%)	27 (93%)
Good	8 (29%)	10 (36%)	3 (9%)	4 (13%)	2 (7%)
Poor	0	1 (4%)	0	0	0
Failed	0	1 (4%)	0	0	0

## Discussion

This study in burned patients quantifies that a priming dose of rocuronium shortly before a larger bolus dose significantly accelerated the onset of paralysis compared with the same total dose given as a single bolus (Table 3). Increasing the rocuronium bolus to 1.5 mg kg<sup>-1</sup> produced an onset time similar to that of priming. The latter dose, however, was different in its effects from those of the other two burned groups in that it resulted in excellent intubating conditions in a greater than 90% of burned patients and at a time significantly faster than a dose of 1.0 mg kg<sup>-1</sup>. Neither priming nor the higher bolus dose achieved the onset times seen in non-burned controls. The intubating conditions of the non-burned patients were comparable with those of the high-dose (1.5 mg kg<sup>-1</sup>) burned group (Table 4). Of note, priming produced respiratory difficulties in 10% of burned and non-burned patients.

The priming dose of NDMRs is usually 10–20% of ED<sub>95</sub>. This dose achieves the shortest onset of action with the fewest side-effects and improves onset times by 10–40%.<sup>8 11–18</sup> On the basis of well-known resistance to NDMRs in patients with major burns,<sup>1–4</sup> we chose rocuronium 0.06 mg kg<sup>-1</sup> (20% of ED<sub>95</sub>) for priming. The objective was to determine whether the onset time of rocuronium could be reduced to <1 min, and match the onset time reported in non-burn patients. The priming dose of 20% of ED<sub>95</sub> is relatively large for the controls,

perhaps more than needed, and the ceiling effect of the higher priming dose may explain the lack of difference between priming and bolus in controls.<sup>4</sup>

The downside of priming also became apparent in our studies. Approximately 10% of patients even with burns exhibited respiratory symptoms possibly related to the weakness of airway muscles. This is consistent with the reports that upper airway muscles are relatively more sensitive to the neuromuscular effect of relaxants.<sup>19</sup> In our study, the appearance of unpleasant respiratory symptoms with the dose administered (rocuronium 0.06 mg kg<sup>-1</sup>) suggests that this technique may not be applicable for rapid onset of paralysis, particularly in patients with full stomach; even the mild weakness of airway muscle could potentially lead to aspiration of gastric contents.<sup>15 16 19</sup> Thus, this study confirms the futility of using priming technique in burns for rapid onset of effect.

One may argue that cardiac output is a major factor in determining the onset of neuromuscular block as the increased blood flow is likely to deliver the NDMRs faster to the biophase (neuromuscular junction). If the cardiac output were indeed the only determining factor, then burned patients, whose cardiac outputs are usually elevated in the hyperdynamic subacute convalescence of the injury,<sup>20 21</sup> should have the faster onset times. This was not the case in our study. Thus, in the burned, onset times appear to be ultimately determined by the pharmacodynamic interaction between the drug and the receptors, and not by the cardiac output. The AChR changes associated with burns may explain the pharmacodynamic resistance.<sup>1–7</sup> However, the fluid resuscitation and tissue oedema in burned patients may contribute to the increased volume of distribution, causing a dilutional effect.

We did not measure the duration of action for the different groups. The main objective of the study was to compare onset times with priming and bolus doses since succinylcholine cannot be used in burns for rapid sequence induction or treatment for laryngospasm. Priming has been shown not to prolong the clinical duration of action of NDMRs in comparison with non-priming technique.<sup>8 18</sup> In a previous study,<sup>4</sup> we have already shown that 25% recovery of twitch height took about 90 (19) min with



0.9 mg kg<sup>-1</sup> and 115 (15) min with 1.2 mg kg<sup>-1</sup> bolus for controls. Therefore, a dose of 1.5 mg kg<sup>-1</sup> to controls would have probably resulted in paralysis longer than 2 h. It is for this reason a larger dose (1.5 mg kg<sup>-1</sup>) was not attempted in controls. The decision to study the pharmacodynamics of 1.5 mg kg<sup>-1</sup> was made after the observation that the onset time even with priming was about 1.5 times longer than controls. It is, however, notable that even with 1.5 mg kg<sup>-1</sup>, the onset times never matched that of controls (Table 3).

Another clinical scenario when rapid onset of paralysis is necessary would be a patient in laryngospasm. It is important to state that priming is of no value in treating this condition. One cannot wait for 2–3 min of priming before bolus. Burned patients usually have poor lung function. This together with their hypermetabolic state and increased oxygen consumption will lead to faster oxygen desaturation compared with non-burned patients in the absence of air exchange due to laryngospasm. No study has evaluated the utility of any muscle relaxant to treat laryngospasm. However, a rapid onset of neuromuscular effect is necessary when treating this complication in burned patients. Because of the potential for hyperkalaemia, succinylcholine is not the drug of choice in this scenario. Although the effect of rocuronium 1.5 mg kg<sup>-1</sup> on laryngeal muscles or laryngospasm was not studied by us, it is noteworthy that the onset of the first paralytic effect was seen as early as 30 s with rocuronium 1.5 mg kg<sup>-1</sup> compared with 45 s with rocuronium 1.0 mg kg<sup>-1</sup> (Table 3). Therefore, the higher dose of rocuronium probably can produce some paralysis of the laryngeal muscles as early as 30 s. This speculation is plausible in view of the increased sensitivity of the upper airway muscles to muscle relaxants.<sup>19</sup>

Intubating conditions were also improved by increasing the dose to rocuronium 1.5 mg kg<sup>-1</sup> in the burned patients compared with the priming technique or the bolus dose of 1.0 mg kg<sup>-1</sup> (Table 4). Onset time is more objective, based on twitch response to TOF stimulation, while the assessment of intubating conditions can be quite subjective with interindividual variability. Despite this limitation, the similar onset time between rocuronium 1.5 mg kg<sup>-1</sup> and priming but the better intubating conditions with the former may seem contradictory. This discrepancy may be due to the fact that twitch tension that we recorded measures the effect at the adductor pollicis, while intubating conditions are related to pharyngeal and respiratory muscles. Not only burned but also critically ill trauma, septic, and immobilized patients have resistance to neuromuscular effects of NDMRs and can develop hyperkalaemia with succinylcholine.<sup>1</sup> Whether our results in burned patients could be applied to these categories of patients needs further study.

The risk of paralysis is ever present even with small dose of NDMRs. Priming doses were carefully administered with special attention to the patient during the interval between

priming and full dose. Our study during elective operations in fasted patients documents the risk of priming, a technique not previously studied in the burned patients. Despite the known resistance to NDMRs in burns, the burned patients still do show unpleasant respiratory side-effects. An important message and conclusion from the study is that the priming is an inferior technique even in burns as much as in non-burns. More importantly, the priming technique could be potentially risky for patients with full stomach. A dose of rocuronium 1.5 mg kg<sup>-1</sup> appears to be the best and safest method for not only rapid onset of paralysis but also for superior intubating conditions in major burns. The downside of such a large dose is the potential for prolonged duration of the paralytic effect.

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