Change in jaw occlusive power by paralysis of masseter muscle with a neuromuscular blocker: Sion’s masseter muscle paralysis

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Abstract:
STUDY OBJECTIVE: We aimed to determine whether jaw occlusive power decreases with the injection of neuromuscular blocking agents in masseter muscle – a method we named Sion’s masseter muscle paralysis (SMP).

METHODS: A randomized, placebo-controlled animal study was conducted in which researchers were blinded to group allocation. We used 12 male mongrel dogs aged 10–12 months and weighing 30–35 kg. Four groups were formed: a conventional dose (CD) group (0.004 mg/kg succinylcholine in 4 ml normal saline [NS]); a high dose (HD) group (0.04 mg/kg succinylcholine in 4 ml NS); a placebo group (4 ml NS); and no intervention group. To measure the jaw occlusive power, 1 kg weight was hung sequentially on a specifically designed device on the animal’s lower jaw. At −4, −2, 0’, +2, +4, +6, +8, +10, +20, and +30 min, we measured the jaw occlusive power, oxygen saturation (SpO₂), and end-tidal carbon dioxide (ETCO₂).

RESULTS: After SMP, jaw occlusive power began to decline in CD and HD group. The arithmetical mean jaw occlusive power values at −4, −2, 0’, +2, +4, +6, +8, +10, +20, and +30 min were 9.7, 9.7, 9.7, 8.7, 8.3, 7.3, 6.7, and 6.3 kgw in the CD group and 9.7, 9.3, 8.7, 8.0, 6.7, 5.0, and 5.3 kgw in the HD group. No abnormalities in SpO₂ or ETCO₂ were detected.

CONCLUSION: Jaw occlusive power was decreased after SMP with succinylcholine, without inducing respiratory complication.

Keywords: Jaw occlusive power, masseter muscle, Sion’s Masseter muscle paralysis, succinylcholine

Introduction

Neuromuscular-blocking agents (NMBAs) are used to paralyze skeletal muscles. When nerve impulses reach the nerve terminal, acetylcholine (ACh) is released into the synaptic cleft, diffuses across the synaptic cleft, and attaches to nicotinic receptors on motor endplates to produce an action potential, causing the skeletal muscle to contract. Structurally related to ACh, currently available NMBAs interfere with the binding of ACh to the motor endplate and are used during general anesthesia and mechanical ventilation. NMBAs are particularly useful in the emergency department, where they are frequently used to facilitate emergency rapid sequence intubation (RSI).[1,2] For RSI, sedative agents and NMBAs are administered to make a patient rapidly unconscious and flaccid after oxygen loading. However, adverse effects such as prolonged paralysis have made physicians
reluctant to use NMBAs, despite the knowledge that intubation without paralysis produces worse outcomes.\[3\] Given that the adverse effects of NMBAs arise from intravascular or deep intramuscular (IM) injection (e.g., in the gluteus medius), we hypothesized that selective administration of low doses to target sites could avoid or limit systemic adverse effects.

During intubation with an endotracheal tube, opening the patient’s mouth and lifting the lower jaw upward to visualize the vocal cords requires the application of considerable force. Thus, lowering the jaw occlusive power could aid endotracheal intubation and because occlusive power mainly comes from the contraction of the masseter muscle, isolated paralysis of this muscle, rather than inducing whole body paralysis, could be an effective strategy. Based on this assumption, we designed a method of selective NMBA administration by IM injection in the masseter muscle to induce paralysis, which we named Sion’s masseter muscle paralysis (SMP) after the first designer. At present, only the depolarizing agent succinylcholine is available for injection through the IM route, so this was used for SMP.

We aimed to determine whether the jaw occlusive power decreased when using the SMP in a canine model. We also aimed to detect whether a systemic adverse effect occurred that resulted in hypoxia or hypercapnia.

**Methods**

**Study design**

This experimental study was performed in healthy adult canines after receiving approval from the Institutional Animal Care and Use Committee at the study site (CRONEX-IACUC-170600). Experiments were carried out in accordance with the guidelines for the care and use of laboratory animals of the Institutional Ethical Committee and the study adhered to the Animal Research: Reporting of in vivo experiments guidelines.\[4\] Finally, we used a blinded, randomized, placebo-controlled study design. In the present study, 12 male mongrel dogs (age 10–12 months, weight 30–35 kg) were randomized into four groups: no intervention (NI) group (n = 3), a placebo group (n = 3), a conventional dose (CD) group (n = 3), and a high dose (HD) group (n = 3).

We developed a model for the measurement of jaw occlusive power. In this, a specifically designed device was placed on the animal’s lower jaw and was linked and fixed to allow weights to be hung. Jaw occlusive power was then measured as the weights were hung one at a time until the animal could not maintain the jaw occlusion. Given that each weight was 1 kg, the scale increment was 1 kgw. When a weight was added and the animal could not maintain the jaw occlusion, the total weight just before this was defined as the jaw occlusive power. A pulse oximeter was attached to each animal’s ear and a specifically designed mask was put over each animal to check oxygen saturation (SpO2) and end-tidal carbon dioxide (ETCO2), respectively.

The volume and weight of the masseter muscle are approximately 1/1000 of total body muscle in adult humans,\[3\] but there is no known reference for canine models. Therefore, given an appropriate succinylcholine dosage of 3–4 mg/kg for IM use in adult humans, we estimated that an appropriate dosage would be 0.003–0.004 mg/kg. In the present study, succinylcholine 0.004 mg/kg was chosen for the CD group, and succinylcholine 0.04 mg/kg was chosen for the HD group (10 times that of the CD group).

**Study protocol**

In the CD group, succinylcholine 0.004 mg/kg was diluted into normal saline (NS), to make a final volume of 4 ml. In the HD group, succinylcholine 0.04 mg/kg was diluted into NS to make up a final volume of 4 ml. In the placebo group, we simply prepared 4 ml of NS. Concealed random allocation to one of the four treatment groups was done in a 1:1:1:1 ratio, and the researchers performing injections did not know which study drugs were prepared and to which group the study animal belonged. We then injected 1 ml of the solutions into the masseter muscle, as follows: upper portion (#1) and lower portion (#2) of one side and upper portion (#3) and lower portion (#4) of contralateral side [Figure 1]. There was no intervention for NI group.

The jaw occlusive power was measured 4 min before injection of the study drug (T − 4 min), 2 min before (T − 2 min), just after (T + 0' min), 2 min after (T + 2 min), 4 min after (T + 4 min), 6 min after (T + 6 min), 8 min after (T + 8 min), 10 min after (T + 10 min), 20 min after (T + 20 min), and 30 min after (T + 30 min). SpO2
and ETCO₂ level were also measured just after the measurement of the occlusive power [Figure 1].

**Outcome measures**
The main outcome was jaw occlusive power at each time. The secondary outcomes were the SpO₂ and ETCO₂ value at each time. Normal ranges were ≥95% for SpO₂ and 35–45 mmHg for ETCO₂.

**Statistical analysis**
Because of a lack of reference values, we calculated the sample size based on the arbitrary assumption that SMP would decrease the jaw occlusive power by 75%. For an alpha of 0.05 and a beta of 0.2, the sample size needed to be three. All study analyses were conducted using STATA 11.1 (StataCorp LP, TX, USA), SAS 9.1 (SAS Institute Inc., Cary, NC, USA), and R statistics. All the measured variables are shown as raw data, and given the extremely small sample, continuous data are presented as arithmetic means. Considering the number of animals in each group, the nonparametric statistical analysis was considered. To compare whether there was a statistical difference in the jaw occlusive power before and after injection of the study drug (no control group, placebo control, CD, and HD), Wilcoxon signed-rank test was performed in each group. Friedman test with post hoc analysis was used for the comparison of the jaw occlusive power before and after the injection of the study drug at each time between groups. The results were considered significant at a threshold of \( P < 0.05 \) (one-tailed).

**Results**
The mean jaw occlusive powers at −4, −2, 0, +2, +4, +6, +8, +10, +20, and +30 min in the CD, HD, NI, and placebo groups are shown in Table 1 as raw data. Jaw occlusive power decreased slightly in the NI and placebo groups, but this appeared to be a result of the fatigue associated with repetitive measurement. In the CD group, jaw occlusive power started to decrease at 2 min and was at its lowest value at 10 min. In the HD group, jaw occlusive power started to decrease at 2 min and was at its lowest value at 6 min. Figure 2 shows, graphically, the change in jaw occlusive power (%) for each group. Jaw occlusive power decreased by approximately 30% at 8 min in the CD group and 50% at 6 min in the HD group. No abnormalities in SpO₂ or ETCO₂ were detected [as summarized in Figure 3]. Moreover, no overlying skin problem was visually noted.

Subsequently, we tested statistical significance for two hypotheses. First, for hypothesis 1, we stated that there would be significant difference before and after the injection of the study drug in each group (in-group difference). In all four groups (NI group, placebo, CD, and HD), there were no statistically significant differences before and after the injection. Second, for hypothesis 2, we stated that there would be significant differences between the groups before and after injection of the study drug at each time between groups (between-group difference). There were significant differences between \( T - 4 \) min and \( T + 6 \) min with \( P = 0.038 \). Panel B showed the percent of jaw occlusive power compared to the value at −4 min of each group.

**Discussion**
After SMP with succinylcholine, jaw occlusive power in our canine model decreased by approximately 30% in the CD group and 50% in the HD group. The reduction in power was more marked and appeared faster in the HD group compared with the CD group, and there was a significant difference in power between the NI group at \( T - 4 \) min and the HD group at \( T + 6 \) min. Moreover, we detected no abnormalities in either the SpO₂ or ETCO₂. This is a first study which demonstrated the potential...
of selective NMBA administration to induce muscle paralysis at a target site, in this case by IM injection of succinylcholine through the SMP method.

RSI is the standard treatment for endotracheal intubation, having been proven to improve success and decrease complication rates during emergencies. In fact, RSI comprises several steps, known as the seven Ps (preparation, preoxygenation, pretreatment, paralysis with induction, protection and positioning, placement with proof, and postintubation management). Among these, the pretreatment and paralysis with induction steps involve drug administration to mitigate against the adverse effects of endotracheal intubation. Although the drugs used for pretreatment vary significantly between clinicians, paralysis is imperative to successful RSI because simultaneous administration of a rapid-acting induction agent and an NMBA renders a patient rapidly unconscious and paralyzed. It is this combination of effects that facilitates endotracheal intubation and minimizes the risk of aspiration. The use of NMABs with induction agents has also been proven to produce better outcomes than intubation with induction agents alone. Bozeman et al. reported that etomidate plus succinylcholine was better than etomidate alone. Bozeman et al. reported that etomidate plus succinylcholine was better than etomidate alone on

### Table 1: Changes over time in the variables of interest in each study group

| Group                        | Variables                  | T−4 (min) | T−2 (min) | T0 (min) | T+2 (min) | T+4 (min) | T+6 (min) | T+8 (min) | T+10 (min) | T+20 (min) | T+30 (min) |
|------------------------------|----------------------------|-----------|-----------|----------|-----------|-----------|-----------|-----------|------------|------------|------------|
| No intervention group        | Jaw occlusive power (kgw)  | 8         | 8         | 8        | 8         | 8         | 8         | 8         | 7          | 7          | 7          |
| Animal #1 (bwt 30 kg)        |                            | 34        | 34        | 34       | 33        | 34        | 40        | 34        | 32         | 32         | 33         |
| Animal #2 (bwt 30 kg)        |                            | 99        | 96        | 96       | 95        | 96        | 99        | 98        | 99         | 97         | 95         |
| Animal #3 (bwt 31 kg)        |                            | 8         | 8         | 8        | 8         | 8         | 7         | 8         | 8          | 8          | 8          |
| Placebo group                | Jaw occlusive power (kgw)  | 8         | 8         | 8        | 8         | 8         | 8         | 8         | 8          | 8          | 8          |
| Animal #1 (bwt 32 kg)        |                            | 95        | 96        | 96       | 96        | 96        | 97        | 99        | 98         | 99         | 95         |
| Animal #2 (bwt 32 kg)        |                            | 33        | 35        | 35       | 36        | 35        | 35        | 35        | 31         | 30         | 31         |
| Animal #3 (bwt 30 kg)        |                            | 100       | 100       | 99       | 100       | 99        | 98        | 100       | 98         | 98         | 98         |
| Conventional dose group      | Jaw occlusive power (kgw)  | 10        | 10        | 10       | 7         | 7         | 7         | 5         | 5          | 6          | 5          |
| Animal #1 (bwt 35 kg)        |                            | 100       | 100       | 99       | 98        | 98        | 99        | 98        | 99         | 99         | 99         |
| Animal #2 (bwt 32 kg)        |                            | 30        | 33        | 32       | 28        | 28        | 28        | 28        | 28         | 28         | 28         |
| Animal #3 (bwt 35 kg)        |                            | 98        | 98        | 99       | 99        | 99        | 98        | 97        | 99         | 97         | 99         |
| High dose group              | Jaw occlusive power (kgw)  | 27        | 28        | 28       | 28        | 28        | 28        | 28        | 28         | 28         | 27         |
| Animal #1 (bwt 34 kg)        |                            | 10        | 10        | 10       | 10        | 10        | 8         | 8         | 7          | 7          | 6          |
| Animal #2 (bwt 34 kg)        |                            | 100       | 100       | 95       | 95        | 95        | 94        | 99        | 99         | 99         | 99         |
| Animal #3 (bwt 33 kg)        |                            | 51        | 49        | 51       | 48        | 47        | 46        | 40        | 38         | 38         | 40         |

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they will success in endotracheal intubation every time, because it is not a simple, easy, and well-controlled procedure. Every emergency physician knows well that failure of endotracheal intubation can be associated with multiple attempts and airway trauma. Further, restricting ventilation during attempts can lead to hypoxia, hypercapnia, and ultimately, can increase mortality. These concerns have led to many physicians avoiding NMBA use during RSI. For example, among noncardiac arrest patients who underwent intubation in Japan, 68% did not receive RSI between April 2010 and August 2012[19]. Furthermore, 628 of 3738 intubations (17%) in an urban emergency department in Scotland were performed without any drugs[20]. This reflects a kind of phobia of RSI among physicians, or more specifically, an NMBA-phobia. NMBA-free intubation which mainly studied in the operating room, not in the emergency field is said to be basically same with this[21].

To improve the current situation, we designed a method of selective low-dose NMBA administration into target sites, which we named SMP after the first designer. Because the masseter muscle contraction force is the main determinant of jaw occlusive power, selective paralysis of that muscle was expected to be beneficial for endotracheal intubation. Furthermore, systemic complications of NMBAs may be avoidable because only a low dose would be needed to achieve paralysis. As expected, SMP decreased the jaw occlusive power without inducing respiratory depression. In the CD group, jaw occlusive power decreased by as much as 30% at 8 min, and in the HD group, it decreased to nearly half at 6 min. These results provide the first step for future advances in RSI, based on the SMP method with succinylcholine as an attractive alternative to systemic NMBA.

It was noteworthy that not only did jaw occlusive power decrease faster and to a greater extent in the HD group compared with the CD group, but that there was also no deterioration in the SpO₂ or ETCO₂ level. Given that the succinylcholine dose for systemic IM use is 4 mg/kg, it may be worth investigating the efficacy and safety of SMP using higher doses of succinylcholine than were used in the current HD group (i.e., >0.04 mg/kg) because higher doses may result in earlier onset and greater effectiveness. Previous studies have already shown that a dose-dependent effect on time to onset when using succinylcholine. In the study by Walts and Dillon, the mean time to onset was 1.8 min for adults given 4 mg/kg of succinylcholine IM, but the mean time was 2.7 min at a dose of 1 mg/kg[22]. In the HD group of the present study, the percentage changes in jaw occlusive power from T − 4 min were 82.5% at T + 2 min and 69.1% T + 4 min. Because the rapid onset is desirable for RSI,
we believe that using a higher dose of succinylcholine for SMP would be most practical. Selective NMBA administration was expected to decrease the jaw occlusive power without deterioration in the SpO2 or ETCO2 level. Therefore, in a specific situation such as awake intubation, selective NMBA administration rather than systemic administration might have a practical role to achieve successful endotracheal intubation.

There are some limitations in the current study. First, the number of animals was too small to give a comprehensive analysis. Data from only three animals are inadequate for generalization, meaning that larger animal-based studies are needed. Second, a more advanced model should be designed that can measure jaw occlusive power in animals without causing fatigue as the measurements continue. Based on measurements of occlusive power in the NI group, we discovered that approximately 10% of the occlusive power appeared to be accounted for by repeat measurements. In the CD and HD groups, however, the effect of fatigue was probably quite small compared with the overall decrease in the jaw occlusive power. Third, we could not measure the variables in a continuous manner, so we may have missed the minimal or maximal values. Fourth, the SpO2 and ETCO2 measurements were recorded with noninvasive equipment. Although high correlations have been reported with invasive methods, precise hypoxia and hypercarbia values can only be recorded invasively. Fifth, we injected two sites in each masseter muscle (four in total per animal), but it is conceivable that injection in more sites would further decrease the jaw occlusive power.

**Conclusion**

Jaw occlusive power decreased after using IM succinylcholine for the SMP method, without causing respiratory depression. Overall, this preliminary study supports our postulated hypotheses and indicates that further research is warranted to determine the clinical potential of SMP, particularly with higher doses of succinylcholine.

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**Conflicts of interest**

There are no conflicts of interest.

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