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Research article

The effect of shoulder muscle succinylcholine injection on the foreleg raising power: Sion's local paralysis☆

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ABSTRACT

Objective: We examined the change in foreleg raising power after Sion's local paralysis (SLP) with succinylcholine in the shoulder muscle.
Methods: A randomized, double blind, placebo-controlled, porcine study was designed and performed at a research institution. Ten male Korean native pigs were randomized into an intervention group (n = 5) and a control group (n = 5). The injection points were in the middle of the left trapezius muscle and the middle of the left deltoid muscle. The control group received 2 ml normal saline (NS), 1 ml injected in each point. The intervention group received 0.4 mg/kg succinylcholine diluted to 2 ml in NS, and 1 ml was injected in each point. To represent the foreleg raising power, the height of the left forelegs from baseline (experiment table) was measured. We measured the foreleg height and oxygen saturation at −4, −2, 0, +2, +4, +6, +8, +10, +20, +30, and +60 min.
Results: After SLP, foreleg height immediately declined in the intervention group. It recovered slightly for a few minutes and declined from 4 to 8 min. In the control group, foreleg height was relatively similar throughout the study period. A repeated-measure analysis of variance revealed a significant group × time interaction ($F_{10,80} = 2.37$, $P = 0.017$), a significant main effect for group ($F_{1,8} = 6.25$, $P = 0.037$), and a significant main effect for time ($F_{10,80} = 4.41$, $P < 0.001$). Post hoc analysis demonstrated that the intervention group showed significantly less foreleg raising power than the control group at 0, 4, 6, 8, 20, and 30 min ($P < 0.05$).
Conclusions: Compared with the control group, the foreleg raising power in the intervention group immediately decreased significantly and persisted for a period after SLP, without hypoxia, in a pig model.

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1. Introduction

Among neuromuscular blocking agents (NMBAs), succinylcholine can be administered via intramuscular (IM) injection [1]. To date, succinylcholine and other NMBAs such as vecuronium or rocuronium [2,3] have been used to induce whole body paralysis, via intravenous (IV) injection. However, the induction of a local paralysis with succinylcholine on the masseter muscle, termed Sion's masseter muscle paralysis (SMP) [4], conceptualized the idea that muscle paralysis can be accomplished as a form of local paralysis, unlike the general paralysis applied before. We called the concept of local paralysis Sion's local paralysis (SLP), coined after the first designer.

Previously, we tested the masseter muscle and reported changes in jaw occlusive power after SMP. This is based on the presumption that opening the patient's mouth with lesser power may facilitate endotracheal intubation. Likewise, it may be better to select potential muscle sites for SLP, considering its clinical applicability in practice.

Reduction of joint dislocation occasionally requires significant power to overcome the patient's periarticular muscle contraction, which is triggered by severe pain. Therefore, a procedure that facilitates a decrease in muscle power may be beneficial in clinical practice. Among various joint dislocations, shoulder dislocation is frequent [5], and the surrounding muscle is relatively strong. Thus, the muscle power decrement after SLP on the shoulder muscle would provide interesting preliminary information regarding the joint reduction procedure. Shoulder muscle power cannot be directly measured since the shoulder muscle is a complex of many muscles, including the rotator cuff, pectoralis major, pectoralis minor, deltoids, trapezius, and serratus anterior muscles [6]. In the present study, we aimed to investigate the change in muscle power after SLP on the shoulder muscle using a pig model. The deltoid and trapezius muscles were regarded as suitable injection points because they are relatively large and are more superficial than other shoulder muscles.

2. Methods

2.1. Study design and setting

We planned a randomized, double-blinded, placebo-controlled study design to evaluate shoulder muscle power after SLP in the shoulder muscle. This study was approved by the Institutional Animal Care and Use Committee at the study site (CRONEX-IACUC-170600). The experiments were performed in accordance with the guidelines for the care and use of laboratory animals by the Institutional Ethical Committee. The study adhered to the Animal Research: Reporting of In Vivo Experiments guidelines [7].

Because there is no established method for the direct measurement of shoulder muscle power in a pig model, we applied the following principle in the present study to develop a novel model for the measurement of shoulder muscle power. In the supine position, foreleg raising requires shoulder muscle power to flex the foreleg [8]. Thus, the height of the intervened foreleg can be used to reflect shoulder muscle power. We set the height of the intervened foreleg as the main parameter in the present study. To adjust for differences in baseline foreleg height between pigs, the height at −4 min was set as 100%, and the percentage of foreleg height at each time point was analyzed.

To achieve more rapid muscle power reduction [4], 0.4 mg/kg succinylcholine was chosen as the study drug for the intervention group, which was 10 times higher than that used in the high-dose group (0.04 mg/kg) in a previous study. For the intervention group, the study drug was diluted in normal saline (NS) to make up a final volume of 2 ml; in the control group, 2 ml of NS was used.

2.2. Animal preparation

Animals (M-Pig®) were purchased from Cronex (Cronex Co., Ltd., Hwaseong, Republic of Korea) and were housed in Cronex Animal SPF (specific pathogen free) facility for whole experimental period, where was environmentally controlled with temperature and relative humidity at 22 ± 2 °C and 50 ± 10%, respectively, under a 12-h light-dark cycle. Each cage (5 pigs per cage) has two self-feeders and two nipple drinkers.

Our previous study showed that the difference in jaw occlusive power at T-4 min and T+6 min was 4.67 ± 1.15 in the high dose group [4]. Based on these results, we used an effect size of 4.06. A sample size of 5 per each group was calculated to compare means between two time points using paired *t*-test based on two-tailed $\alpha = 0.005$, power = 90%, effect size = 4.06, and no dropout rate.

In the present study, 10 male Korean native black pigs from Jeju Island (age 10–12 months, weight 26–43 kg) were used. The diets for pig were fed twice daily (750 g/dose). The animals freely drank water through automatic water suppling system, the drinking water being supplied by filtering underground water with a reverse osmosis filter fluid sterilizer and by sterilizing it with ultraviolet ray. The pigs were fasted at midnight. There was no sedation or paralysis before study initiation.

2.3. Study protocol

The pigs were randomized into two groups: an intervention group (n = 5) and a control group (n = 5). Concealed random allocation to one of the two groups was performed in a 1:1 ratio. The researchers who performed injections were unaware which study drugs were prepared and to which group the study animals belonged.

The study animal was positioned supine on the study table, specifically designed for the present study. The study animal was fitted tight into the study table, thus there is no need for other restrain tools. The table allows exposure of the left shoulder. A pulse oximeter was attached to each pig's ear to evaluate the oxygen saturation (SpO_2).

The left middle deltoidus and trapezius muscles were injected with 1 ml each of the study drug solution (Fig. 1).

The heights of both forelegs from baseline (experiment table) were 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), 30 min after (T+30 min), and 60 min after (T = 60 min) (Fig. 1). Because the pig foreleg could sway, the highest height ± 10 s at each time point was measured. The SpO_2 at each time point was also checked. Overlying skin problems were also observed.

2.4. Statistical analysis

All measured variables are shown as raw data and given the small sample size, continuous data are presented as means with 95% confidence intervals (CIs). To adjust for differences in baseline foreleg height between pigs, the height at T-4 min was set as 100%, and the percentage of foreleg height at each time point was analyzed. Normality of data was tested using the Shapiro-Wilk test. If data were not normally distributed, the data were log-transformed. Repeated-measures analysis of variance (ANOVA) and post hoc tests using the Bonferroni correction were used to compare the log-transformed foreleg height and percent of foreleg height to T-4 min according to group, before and after the injection. The results were considered statistically significant at a threshold of $P < 0.05$ (two-tailed). All analyses were performed using the R software package (version 4.0.1; R Core Team, Vienna, Austria), Stata 11.1 (StataCorp LP, TX, USA), and Statistical Analysis System (SAS) 9.1 (SAS Institute Inc., Cary, NC, USA).

3. Results

Table 1 shows the mean foreleg height with 95% confidence interval (CI) at each time point. In the intervention group, foreleg height immediately declined after SLP [mean foreleg height 33.1 cm (95% CI 26.0–40.2)]. It recovered marginally for a few minutes and declined from 4 to 8 min. Thereafter, it recovered slightly. In the control group, foreleg height was relatively similar during the study period. The percentage of foreleg height was approximately 80% immediately after SLP, at T+8 min, and at T+10 min. No abnormalities in SpO_2 were detected. No overlying skin problems were visually noted.

A repeated-measures ANOVA performed on the log-transformed foreleg height revealed a significant group × time interaction ($F_{10,80} = 2.37$, $P = 0.017$), a significant main effect for group ($F_{1,8} = 6.25$, $P = 0.037$), and a significant main effect for time ($F_{10,80} = 4.41$, $P < 0.001$). Post hoc analysis demonstrated that the intervention group showed significantly less foreleg height than the control group at 0, 4, 6, 8, 20, and 30 min ($P < 0.05$). Compared with 4 min before the intervention, foreleg height was significantly decreased

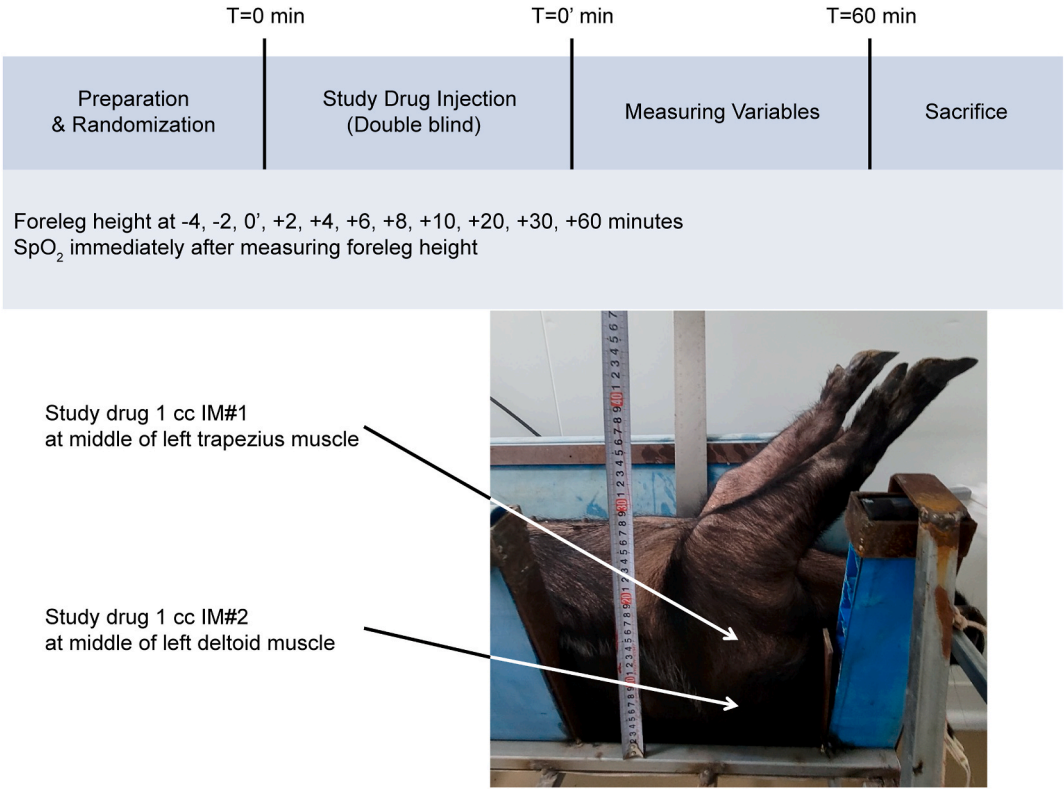

Fig. 1. Study protocol and injection points.

Table 1
Changes over time in the variables of the study in each study 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	T+60 min
Control group												
Animal #1	Foreleg height	43.2	43.3	42	41.2	42.3	43	43.3	43	41.5	41.8	46
(40 kg)	SpO2	100	100	100	100	100	100	100	100	100	100	100
	Skin problem	X	X	X	X	X	X	X	X	X	X	X
Animal #2	Foreleg height	54	53.8	52.7	48	46.5	48.7	49	48.7	47.3	50	37
(43 kg)	SpO2	100	100	100	100	100	100	100	100	100	100	100
	Skin problem	X	X	X	X	X	X	X	X	X	X	X
Animal #3	Foreleg height	42.7	41.7	41.5	42	42.5	42	42.8	42.6	48.2	42.8	31.5
(38 kg)	SpO2	100	100	100	100	100	100	100	100	100	100	100
	Skin problem	X	X	X	X	X	X	X	X	X	X	X
Animal #4	Foreleg height	42.2	42.3	40.3	38.6	45.4	44.5	43.5	44	40.5	43.6	41.4
(39 kg)	SpO2	100	100	100	100	100	100	100	100	100	100	100
	Skin problem	X	X	X	X	X	X	X	X	X	X	X
Animal #5	Foreleg height	39.3	40.4	37	36.4	37.5	37	36.2	33.6	42.6	41.6	34.5
(33 kg)	SpO2	100	100	100	100	100	100	100	100	100	100	100
	Skin problem	X	X	X	X	X	X	X	X	X	X	X
Intervention group												
Animal #1	Foreleg height	35	35.8	28	36.2	34.2	35	27	26	36	33.6	32
(26 kg)	SpO2	100	100	100	100	100	100	100	100	100	100	100
	Skin problem	X	X	X	X	X	X	X	X	X	X	X
Animal #2	foreleg height	33.5	43	35.2	36.4	36.5	38	36.5	36.5	33.5	35.7	41.5
(36 kg)	SpO2	100	100	100	100	100	100	100	100	100	100	100
	Skin problem	x	x	x	x	x	x	x	x	x	x	x
Animal #3	Foreleg height	42	47	35.7	38.2	37.4	35.5	38	35.5	35.8	34	34.6
(42 kg)	SpO2	100	100	100	100	100	100	100	100	100	100	100
	Skin problem	X	X	X	X	X	X	X	X	X	X	X
Animal #4	Foreleg height	46	42	32.4	31.8	41	34.4	33.4	33.4	32.8	29.5	28.7
(41 kg)	SpO2	100	100	100	100	100	100	100	100	100	100	100
	Skin problem	X	X	X	X	X	X	X	X	X	X	X
Animal #5	Foreleg height	50.5	48.4	41.5	41.5	41.6	40.6	40.3	49	39.5	39.8	46.5
(38 kg)	SpO2	100	100	100	100	100	100	100	100	100	100	100
	Skin problem	X	X	X	X	X	X	X	X	X	X	X
Control group	Foreleg height	44.3	44.3	42.7	41.2	42.8	43.0	43.0	42.4	44.0	44.0	38.1
	Mean (95% CI)	(37.3–51.3)	(37.6–51.0)	(35.3–50.1)	(35.8–46.7)	(38.5–47.2)	(37.8–48.3)	(37.3–48.6)	(35.6–49.2)	(39.7–48.4)	(39.7–48.3)	(31.0–45.2)
Intervention	Foreleg height	41.7	41.8	33.1	36.8	37.7	36.1	33.1	34.0	36.0	34.1	34.8
group	Mean (95% CI)	(33.2–50.2)	(34.4–49.2)	(26.0–40.2)	(32.4–41.2)	(33.3–42.1)	(32.9–39.3)	(25.5–40.8)	(22.3–45.7)	(33.1–39.0)	(29.5–38.7)	(26.2–43.3)
	Mean Difference (95% CI)	2.6 (−6.5–11.7)	2.5 (−5.8–10.8)	9.6* (1.1–18.1)	4.5 (−1.3–10.3)	5.2* (0.0–10.3)	6.9* (1.8–12.0)	9.8* (1.9–17.7)	8.4 (−2.8–19.6)	8.0* (3.6–12.4)	9.9* (4.6–15.1)	3.3 (−5.9–12.6)

Abbreviation SpO2, peripheral oxygen saturation; CI, confidence interval. * indicates the significant differences between the control and intervention groups.

at 0, 8, and 10 min in the intervention group ($P < 0.05$). Compared with 2 min before the intervention, foreleg height was significantly decreased at 0 and 8 min in the intervention group ($P < 0.05$). There were no significant changes over time in the control group (Fig. 2).

A repeated-measures ANOVA performed on the percentage of foreleg height at T-4 min revealed a significant group × time interaction ($F_{9,72} = 2.07$, $P = 0.044$), a significant main effect for group ($F_{1,8} = 6.32$, $P = 0.036$), and a significant main effect for time ($F_{9,72} = 3.40$, $P = 0.002$). Post hoc analysis demonstrated that the intervention group showed a significantly lower percentage of foreleg height than the control group at 0, 8, 10, and 30 min ($P < 0.05$). Compared with 2 min before the intervention, the percentage of foreleg height was significantly decreased at 0, 8, 10, and 30 min in the intervention group ($P < 0.05$). There were no significant changes over time in the control group (Fig. 3).

4. Discussion

After SLP on the shoulder muscle, foreleg height decreased rapidly by 20% in the intervention group in our pig model. There was a significant difference between the two groups in the foreleg height. Moreover, we detected no abnormalities in the SpO_2. This is the second study to demonstrate the potential of SLP, which induces local paralysis by succinylcholine IM at a target site.

Traditionally, NMBAs have been used to induce general paralysis during surgery [9,10], mechanical ventilation [11,12], or endotracheal intubation [13,14]. Most NMBAs are used intravenously. However, succinylcholine can be administered via the intramuscular route. The concept of selective use of succinylcholine to induce local paralysis in a target muscle was proposed and tested on a masseter muscle in our previous study [4] using a canine model. A concentration of 0.04 mg/kg of succinylcholine was used in the high-dose group. Jaw occlusive power decreased by approximately 50% at 6 and 8 min. There was no hypoxia or hypercapnia during the study period. Based on the rationale that higher doses of succinylcholine would result in greater and faster muscle power reduction, we tested SLP using 0.4 mg/kg of succinylcholine in the present porcine model, resulting in greater and faster muscle power reduction without hypoxia. The current dose (0.4 mg/kg) is approximately 1/10 of the recommended dose via the IM route (3–4 mg/kg).

Shoulder dislocation is the most common joint dislocation in the human body [5]. Shoulder joint dislocation frequently requires significant force to overcome the patient's periarticular muscle contraction, which is triggered by severe pain. Clinically, analgesia and sedative agents such as benzodiazepine and opiates have often been used to achieve sedation and muscle relaxation [15–17]. Alternatively, intra-articular injection of a local anesthetic has been used [18–20]. Therefore, the clinical potential of SLP on shoulder muscles alone or in combination with these drugs in eliciting sedation, as well as assessing the muscle power decrement after SLP on the shoulder muscle would be an interesting preliminary information with regard to a joint reduction procedure.

In the present study, we chose the deltoid and trapezius muscles among the shoulder muscles. The deltoid muscle flexes the shoulder joint and ducts the arm. The trapezius muscle elevates and protracts the limbs. Both the deltoideus and trapezius are relatively superficial and accessible. The other shoulder muscles are relatively small or lie deep inside. Thus, these two points were regarded as optimal for investigating the study object. In pigs, the trapezius muscle is larger than the deltoid muscle.

However, the potential SLP points for shoulder reduction in humans are somewhat different. The deltoid muscle would be appropriate considering that it is one of the important muscles to stabilize the shoulder joint. However, the trapezius muscle mainly stabilizes the scapula and is not directly involved in shoulder joint stability. Instead, the rotator cuff muscles (supraspinatus, subscapularis, infraspinatus, and teres minor) play an important role in shoulder stabilization [21]. Thus, the rotator cuff muscles can be a potential SLP point. Currently, among patients with rotator cuff tears, platelet-rich plasma is injected into the rotator cuff muscle [22,23]. Additionally, various shoulder muscles may be related to the reduction methods. Many techniques have been introduced in

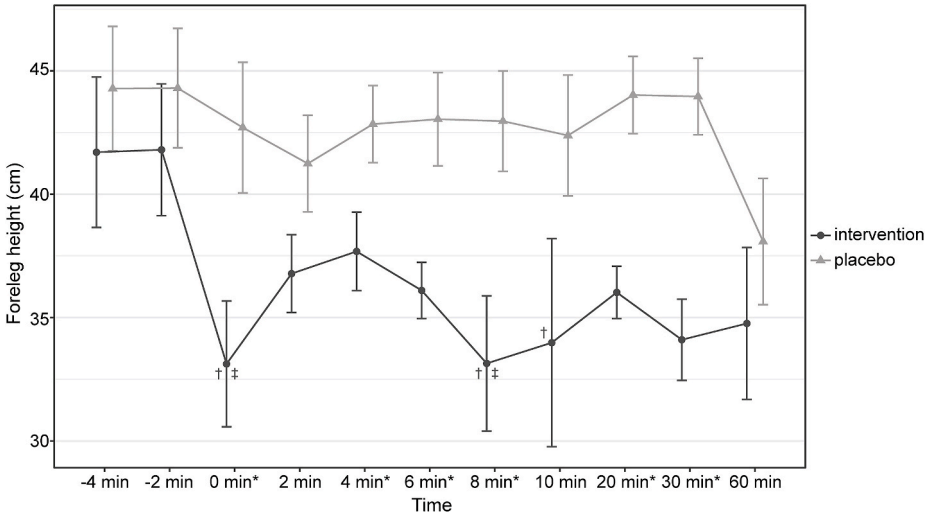

Fig. 2. Changes in foreleg height over time. Footnote: * indicates the significant differences between the control and intervention groups. † indicates the significant difference when compared to T-4 min.

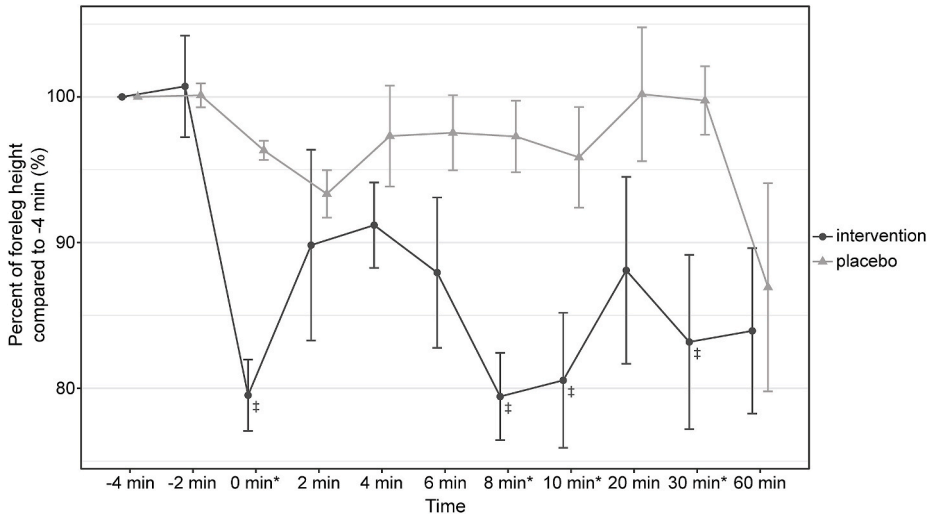

Fig. 3. Changes in percent of foreleg height over time. Footnote: * indicates the significant differences between the control and intervention groups.

practice [24–26], and target muscles other than the deltoid or rotator cuff muscle may be possible. Further evaluation of the target point is required.

Some points need to be addressed prior to strictly determining the target muscle. It is not clear whether the paralytic action of succinylcholine is limited to the injected muscle or spreads to the nearby muscle. The essential point of SLP is the administration of a low dose of succinylcholine into the target muscle. If the paralytic action of succinylcholine can spread to the nearby muscle, physicians do not need to target the deep or small muscle. Rather, nearby large or superficial muscles may be appropriate to achieve the desired paralytic effect. However, the possible dose of succinylcholine for SLP remains to be elucidated. In the present porcine study, a 1/10 dose of the recommended IM route did not result in hypoxia. Further studies are needed to determine the optimal succinylcholine dose for SLP.

The foreleg height difference at T 0 min would be noteworthy. Considering onset of action of succinylcholine is 2–3 min, difference at T 0 min may not be resulted by an intervention. However, because data regarding onset of action (2–3 min) is derived from systemic paralysis after systemic dose administration, onset of action by SLP may be shorten considering its local administration. Another explanation would be an avoidance reaction against drug-injection pain. Succinylcholine is known to cause post-operative myalgia [27,28]. Because succinylcholine is traditionally used systemically, immediate pain after succinylcholine injection is impossible to be identified to date. Whether SLP will cause substantial pain or not seems to be an interesting subject.

Some limitations of the present study should be noted. First, muscle power decrement occurred rapidly, as expected, but was less than that in a previous study. In our previous study, jaw occlusive power decreased 50% in maximal in the high-dose group [4]. In the present study, foreleg height decreased by 20% in maximal in the intervention group, although higher dose was injected (0.4 mg/kg of succinylcholine). However, direct comparison of the results of the two studies is impractical since the measurements are not equal. Second, the feature of height decrement was not similar to typical pharmacokinetics. The effect of succinylcholine is expected to show a U-shape but this was not observed in the present study, which showed a W shape. The passive manner of the measurement might result in these findings. Further study is needed to measure the actual height in an active manner, such as pain stimulation before each measurement. Third, the sample size is too small to draw finite conclusions. Data from only five animals in each group may be inadequate for generalization. Therefore, a larger sample size in future studies is required. Fourth, a more advanced and improved model should be designed to measure shoulder muscle power without causing fatigue during the study period. Fifth, the variables could not be measured in a continuous manner; therefore, we may have missed the maximal or minimal values. Sixth, SpO_2 measurements were recorded using non-invasive equipment. Although high correlations with invasive methods have been reported, precise values can only be recorded invasively. Last, we could not measure hypercarbia or hypocarbia. Usually, end-tidal carbon dioxide (ET CO2) is measured using a facemask application in animal studies. However, the pigs became uncooperative after facemask application; thus, we were unable to measure the ET CO2 level.

5. Conclusion

Compared with the control group, foreleg raising power in the intervention group immediately decreased significantly and persisted for a period following SLP, without inducing hypoxia in a pig model. Overall, this preliminary study supports our presumptive hypotheses. Nonetheless, further research is warranted to determine the clinical potential of SLP.

Author contribution statement

Sion Jo: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Yu Chan Kye, Jungyoup Lee, Euigi Jung, Minwoo Kang, Byunghyun Kim, Dongsung Kim, Boyoung Park: Analyzed and interpreted the data.

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Data availability statement

All data are showed in the present paper.

Declaration of interest's statement

The authors declare no conflict of interest.

Additional information

We have no repository because all data are presented in the manuscript.

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