A pilot study of limb stimulation for the treatment of neonatal apnea

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Abstract  
This study explored the feasibility effect and safety of the limb stimulation (LS) for the treatment of neonatal apnea (NAP). The cases of 30 eligible premature infants with NAP were included in this retrospective study. These cases were equally divided into an intervention group (n = 15) and a control group (n = 15). The infants in both groups received caffeine treatment. Moreover, cases in the intervention group also received LS for a total 30 hours, while the subjects in the control group did not receive LS during this period. The primary outcome included apnea frequency (number of episodes per 24 hours), and apnea rate. The secondary outcomes consisted of desaturation (number of episodes per 24 hours), and heart rate (beats per minute). Additionally, adverse events were also documented during the treatment period. After treatment, LS did not show better outcomes in apnea frequency (P = .48), apnea rate (P = .33), desaturation (P = .55), and heart rate (P = .41). Furthermore, no significant differences of all adverse events were found between 2 groups. The results of this pilot study demonstrated that LS might not be efficacious for premature infants with NAP.  
Abbreviations: LS = limb stimulation, NAP = neonatal apnea.  
Keywords: effect, limb stimulation, neonatal apnea, premature infants

1. Introduction  
Neonatal apnea (NAP) is a very common condition, which often affects most of premature infants of less than 34 weeks of gestational age.\textsuperscript{1--3} It has been reported that the incidence of NAP happens in almost all infants with gestational age of less than 29 weeks or the birth weight of less than 1000 g.\textsuperscript{4,5} Such condition is often accompanied by intermittent hypoxia, and is also associated with cardiovascular sequela as well as the retinopathy and neurodevelopmental diseases.\textsuperscript{6--9}  
The management for this condition involves pharmacologic therapy (most common drugs include caffeine and theophylline), continuous positive airway pressure, and intermittent mandatory ventilation.\textsuperscript{10--16} However, those therapies still have insufficient efficacy and do not work effectively and optimally for early development. Additionally, infants who received those interventions often accompanied with a variety of adverse events.\textsuperscript{17--19} Thus, alternative effective intervention with few adverse events is needed to be explored.

Presently, few similar studies try to explore the effect of limb stimulation (LS) for the treatment of NAP.\textsuperscript{20} Unfortunately, limit data is still available to support the evidence of such intervention. Therefore, in this study, we tried to investigate the feasibility effect and safety of LS for the treatment of NAP.

2. Methods/design  
2.1. Objective  
This pilot study tried to explore the feasible effect of LS for treating premature infants with NAP.

2.2. Ethical considerations  
This pilot study was performed based on the principles of the Declaration of Helsinki (version Seoul, 2008). It was approved by the Ethical Committee of Second Affiliated Hospital of Mudanjiang Medical University and was conducted at this hospital from June 2016 to December 2017. The guardians of all included infants provided written informed consent.

2.3. Design  
A total of 30 eligible infants with NAP were included and were equally allocated to an intervention group (n = 15) and a control group (n = 15). All subjects in both groups received caffeine treatment. In addition, the participants in the intervention group also received LS. All subjects were treated for a total of 7 days, and all outcomes were measured after 7-day treatment. Neither procedure of randomization, nor blinding (including patients and researchers) was applied to this study. However, data analyst was masked to this study.

2.4. Participants  
Preterm newborns were included with gestational age between 23 weeks to 34 completed weeks. Additionally, all subjects were
diagnosed with NAP.\textsuperscript{[3]} However, infants were excluded if they had major congenital anomalies/malformations, and respiratory depression from medications. Furthermore, subjects were also excluded if they had history of hypoxic-ischemic encephalopathy or intraventricular hemorrhage.

2.5. Treatment schedule

All patients in both groups received caffeine citrate (20 mg/kg) and then continued on maintenance with dose of 5 mg/kg/day every 24 hours for a total of 7 days. Additionally, subjects in the intervention group also received LS. Both hands and feet of infants received gently massage by an experienced trained massage practitioner for 10 minutes, a total of 40 minutes daily for 7 days.

2.6. Outcome measurements

The primary outcome was measured by apnea frequency (number of episodes per 24 hours), and apnea rate. The secondary outcomes included desaturation (number of episodes per 24 hours), and heart rate (beats per minute). In addition, adverse events were also recorded during the treatment period.

2.7. Statistical analysis

All characteristic values and outcome data were analyzed by SPSS Statistics 17.0 (IBM Corp., Armonk, NY). Due to the short duration of 7 days, the desired sample size for this pilot study is 30 patients, with 15 for each group.\textsuperscript{[21]} Mann–Whitney U test was employed to analyze the continuous outcome data, while chi-square or Fisher exact test was utilized to analyze the categorical outcome data. Statistical significance was set as $P < .05$.

### Table 1
Baseline characteristics.

| Characteristics                  | Intervention group (n=15) | Control group (n=15) | $P$ value |
|----------------------------------|--------------------------|----------------------|-----------|
| Gestational age, week            | 29.5 (1.7)               | 29.2 (2.1)           | .67       |
| Sex                              |                          |                      |           |
| Male                             | 6 (40.0)                 | 8 (53.3)             | .47       |
| Female                           | 9 (60.0)                 | 7 (46.7)             | —         |
| Race, Chinese Han                | 15 (100.0)               | 15 (100.0)           | —         |
| Birth weight, g                  | 1142.3 (340.1)           | 1151.7 (327.6)       | .94       |
| Both at study hospital           | 15 (100.0)               | 15 (100.0)           | —         |
| Small for Gestation Age          | 2 (13.3)                 | 3 (20.0)             | .63       |
| Delivery by caesarean section    | 9 (60.0)                 | 11 (73.3)            | .44       |
| Apgar score at 1 min<7           | 7 (46.7)                 | 6 (40.0)             | .71       |
| Apgar score at 5 min<7           | 3 (20.0)                 | 2 (13.3)             | .63       |
| Caffeine                         | 15 (100.0)               | 15 (100.0)           | —         |

Data are present as mean±standard deviation or number (%).

### Table 2
Comparison of apnea frequency between 2 groups (change from baseline).

| Apnea frequency       | Intervention group (n=15) | Control group (n=15) | Difference | $P$ value |
|-----------------------|---------------------------|----------------------|------------|-----------|
| Number of episodes per 24 hours | -0.7 (−1.1, −0.2)         | -0.6 (−1.0, −0.2)    | −0.1       | .48       |

Data are present as mean and range.

### Table 3
Comparison of apnea rate between 2 groups (change from baseline).

| Endpoint                  | Intervention group (n=15) | Control group (n=15) | Difference | $P$ value |
|---------------------------|---------------------------|----------------------|------------|-----------|
| Apnea rate                | −0.9 (−1.3, −0.5)         | −0.7 (−1.1, −0.3)    | −0.2       | .33       |

Data are present as mean and range.

### Table 4
Comparison of desaturation (number of episodes per 24 hours) between 2 groups (change from baseline).

| Desaturation              | Intervention group (n=15) | Control group (n=15) | Difference | $P$ value |
|---------------------------|---------------------------|----------------------|------------|-----------|
| Number of episodes per 24 hours | 1.1 (0.6, 1.5)            | 1.0 (0.7, 1.4)       | 0.1 (0.1, 0.3) | .55       |

Data are present as mean and range.

### Table 5
Comparison of heart rate (beats per minute) between 2 groups (change from baseline).

| Heart rate (beats per minute) | Intervention group (n=15) | Control group (n=15) | Difference | $P$ value |
|-------------------------------|---------------------------|----------------------|------------|-----------|
| Jitteriness                   | 6.8 (5.6, 7.7)            | 6.5 (5.4, 7.3)       | 0.3 (0.1, 0.5) | .41       |

Data are present as mean and range.

### Table 6
Comparison of adverse events between 2 groups.

| Adverse events              | Intervention group (n=15) | Control group (n=15) | $P$ value |
|-----------------------------|---------------------------|----------------------|-----------|
| Tachycardia                 | 2 (0.5)                   | 1 (0)                | .55       |
| Jitteriness                 | 1 (1.4)                   | 2 (4.8)              | .55       |
| Feed intolerance            | 4 (4.8)                   | 3 (0)                | .37       |
| Weight gain, g/m/kg/day     | 12.5 (6.2)                | 12.3 (6.4)           | .93       |

Data are present as mean±standard deviation or number (%).

3. Results

The characteristics of all include premature infants in both groups are summarized in Table 1. The comparison of all characteristics did not differ significantly between 2 groups.

After treatment, there were not significant differences in the primary outcomes of apnea frequency (number of episodes per 24 hours) ($P = .48$, Table 2), and apnea rate ($P = .33$, Table 3); and secondary outcomes of desaturation (number of episodes per 24 hours) ($P=.55$, Table 4), and heart rate (beats per minute) ($P=.41$, Table 5) between 2 groups.

Adverse events are also listed in Table 6. No significant differences of all adverse events were detected between 2 groups (Table 6). No death related to the treatment was recorded in either group.

4. Discussion

To our best knowledge, no study investigated the effect and safety of LS for treating premature infants with NAP. Thus, this pilot...
The present study first explored the effect and safety of LS for treating infants with NAP. Although its results did not show promising effect of LS in NAP in this study, it may help to provide evidence for the future studies.

The results of this pilot study showed that subjects in the intervention group did not show more promising outcomes in apnea frequency, apnea rate, desaturation, and heart rate, compared with participants in the control group. Moreover, no significant differences in adverse events were found between 2 groups. It indicated that LS might not help for premature infants with NAP after 7 days intervention.

The present study has several following limitations. First, the present study is a pilot study, which just explored the feasible effect and safety of LS for treating subjects with NAP. Then, the present study included a small sample size of 30 subjects only, which might also affect the results of this study. Thirdly, the effectiveness of the intervention was the combination of LS plus caffeine, but not the LS alone. Finally, the present study only had a short treatment period with only 7-day intervention, which might also impact the results of this study. Therefore, further studies should avoid all above limitations.

5. Conclusion
The results of the present pilot study showed that LS might not help to manage the NAP for premature infants.

Author contributions
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