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Clinical paper

Repetitive versus standard tactile stimulation of preterm infants at birth – A randomized controlled trial☆

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ABSTRACT

Aim: To evaluate the direct effect of repetitive tactile stimulation on breathing effort of preterm infants at birth.
Methods: This randomized controlled trial compared the effect of repetitive stimulation on respiratory effort during the first 4 min after birth with standard stimulation based on clinical indication in preterm infants with a gestational age of 27–32 weeks. All details of the stimulation performed were noted. The main study parameter measured was respiratory minute volume, other study parameters assessed measures of respiratory effort; tidal volumes, rate of rise to maximum tidal volumes, percentage of recruitment breaths, and oxygenation of the infant.
Results: There was no significant difference in respiratory minute volume in the repetitive stimulation group when compared to the standard group. Oxygen saturation was significantly higher (87.6 ± 3.3% vs 81.7 ± 8.7%, p = .01) while the amount of FiO_2 given during transport to the NICU was lower (28.2 (22.8–35.0)% vs 33.6 (29.4–44.1)%, p = .04). There was no significant difference in administration of positive pressure ventilation (52% vs 78%, p = .13), or the duration of ventilation (median (IQR) time 8 (0–118)s vs 35 (13–131)s, p = .23). Caregivers decided less often to administer caffeine in the delivery room to stimulate breathing in the repetitive stimulation group (10% vs 39%, p = .036).
Conclusion: Although the increase in respiratory effort during repetitive stimulation did not reach significance, oxygenation significantly improved with a lower level of FiO_2 at transport to the NICU. Repetitive tactile stimulation could be of added value to improve breathing effort at birth.

Introduction

Most preterm infants need respiratory support for lung aeration during transition at birth [1–3]. In order to avoid injury to the still developing lungs and brain, the focus of respiratory support at birth has shifted from intubation and mechanical ventilation towards non-invasive ventilation [4–7]. However, there is still a high failure rate of Continuous Positive Airway Pressure (CPAP) in preterm infants after birth [4], which requires the infant to breath effectively. Studies have shown that most preterm infants breathe at birth [3], even during and in between Positive Pressure Ventilation (PPV) [1,2], but in the majority of infants their respiratory drive is weak and insufficient to aerate their lungs. Little attention has focussed on strategies that stimulate breathing during the immediate new-born period. Stimulating preterm infants to increase their respiratory effort could enhance the efficacy of CPAP support and might reduce the risk of CPAP-failure. Thereby, it has been shown that preterm infants in whom mechanical ventilation is avoided after birth have better lung mechanics and decreased work of breathing at 8 weeks post-term [8].

Currently, tactile manoeuvres (warming, drying and rubbing the back or the soles of the feet) to stimulate breathing are recommended during the initial assessment of the infant at birth [9,10]. This recommendation is largely based on many years of experience and expert opinion as at the time the recommendation was published, there were

Abbreviations: CPAP, Continuous Positive Airway Pressure; FiO_2, fraction of inspired oxygen; IVH, intraventricular haemorrhage; LUMC, Leiden University Medical Center; MV, minute volume; NICU, neonatal intensive care unit; PPV, positive pressure ventilation; RFM, respiratory function monitor

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no studies available that specifically examined the effect of tactile stimulation of infants at birth. Only experimental studies, in apnoeic lambs and new-born rats after birth, have demonstrated increased spontaneous breathing after tactile stimulation [11,12].

We recently reported our current practice in tactile stimulation by reviewing previously recorded video and physiological parameters made in the delivery room. In this study we observed that duration and method of stimulation in preterm infants was variable and often not performed despite being clearly indicated [13]. Frequent omission of stimulation of infants at birth was also found by Gaertner et al. [14] Omitting stimulation could be related to the use of polyethylene wraps and the use of more extensive respiratory support [14–16]. The observed variation could be explained by the fact that the guidelines are not clear on how the stimulation should be used, possibly due to scarcity of data on this topic.

Our aim was to test the effect of systematically applied tactile stimulation at birth in a randomized controlled trial. We demonstrated in a recent observational study [13] that only 67% of preterm infants were stimulated and an effect could be observed in 18% of stimulation episodes. However, it is difficult to interpret this result as we also observed that in 1/3 of episodes stimulation was given while there was no indication and in 1/3 of infants stimulation was not given while this was indicated. Colleagues of the neonatal team were still very reluctant to not stimulate infants as tactile stimulation is one of the most basic interventions during neonatal resuscitation. It would be therefore difficult to achieve clinical equipoise for a study in which tactile stimulation was compared to the omission of stimulation. In this recent observational study, we determined that stimulation could be applied either repetitively or when needed based on clinical indication [13]. It is possible that repetitive stimulation could improve the infant's breathing effort, as continuous stimulation might result in habituation [17]. We aimed to evaluate the direct effect of a standardized repetitive tactile stimulation on breathing effort of preterm infants at birth compared to standard stimulation based on clinical indication.

Methods

A single blinded randomized controlled trial was conducted at the Leiden University Medical Center. Preterm infants with a gestational age between 27 and 32 weeks were included. Infants with congenital abnormalities or conditions that might have an adverse effect on breathing effort or ventilation were excluded. Infants were randomized using sequentially numbered opaque sealed envelopes to either be stimulated repetitively or to receive standard stimulation after birth. Allocation was stratified by gestational age (27^{+0}–28^{+6} week vs 29^{+0}–31^{+6} week), using variable block (4–6) sizes.

The intervention consisted of repetitive stimulation in the first 4 min after birth, defined as gently rubbing the back or the soles of the feet during 10 s, alternated with 10 s of rest. We have demonstrated in an observational study that stimulation was applied either repetitively or based on clinical indication [13]. For this reason we compared repetitive stimulation with standard stimulation, in conformation with the World Health Organization guidelines: gently rubbing the back or the soles of the feet when clinicians considered the breathing to be insufficient or absent [7]. After 4 min after birth, both groups received similar treatment, and stimulation was performed on discretion of the caregiver. The intervention was performed solely in the first 4 min after birth, as most preterm infants have a stable breathing pattern after this time interval [18].

In both groups standard care was provided in the delivery room. Local resuscitation guidelines were followed using a Neopuff™ T-Piece Resuscitator, including delayed cord clamping of 30 s, oxygen administration to target oxygen saturations based on the international normograms [19], and caffeine administration in the delivery room based on the discretion of the caregiver, as previously described in the study of Dekker et al. [20]. In both groups, physiological parameters, including respiratory function monitoring (RFM) were recorded during stabilization in the first 10 min of life. This RFM uses a small (dead space 1 ml) variable orifice anemometer to measure gas flow in and out of a facemask, thereby calculating inflation pressures, flow and tidal volumes. The difference between inspired and expired tidal volume equals the leak from the facemask. The minute volume (MV), rate of rise to maximum tidal volumes (RoR) and time of PPV given were calculated. Oxygenation and heart rate were measured with the Masimo SET pulse oximeter. A pulse oximetry probe was placed around the ulnar aspect of the infant's right wrist. Fraction of inspired oxygen (FiO_2) was measured with a Teledyne oxygen analyser inserted into the inspiratory limb of the Neopuff circuit. All signals measured were recorded at 200 Hz using the New Life Box physiological recording system with Polybench software (Advanced Life Diagnostics, Weener, Germany). Pulmochart software (Advanced Life Diagnostics, Weener, Germany) was used for analysing recorded data.

The main study parameter was the average MV at 1–4 min after birth. Other respiratory effort parameters which were blindly assessed, were: MV in the first 7 min after birth, tidal volumes, RoR, respiratory rate, percentage of tidal volumes > 4 ml/kg or 8 ml/kg (recruitment breaths), respiratory support given after birth (CPAP vs PPV) and caffeine administration in the delivery room. Time of PPV, oxygen delivery, oxygen saturation and heart rate were also compared between groups. The following demographic data were collected: gestational age, birth weight, gender, Apgar score, antenatal use of corticosteroids, mode of delivery. Short-term clinical outcomes were noted: intraventricular haemorrhage, intubation during resuscitation or within the first 24 h after birth and need for surfactant.

Mian et al. measured an average MV of 150 ± 70 ml/kg/min over the first 100 breaths in preterm infants < 33 weeks GA [21]. The study of Huberts et al. shows that MV in spontaneous breathing preterm infants increases with 60% from minute 2 to minute 5, but this increase was lower in infants receiving PPV [18]. We therefore considered an increase of 40% in average MV at 1–4 min clinically relevant, for this a sample size of 44 infants would be needed (α of 0.05 and power (1-β) of 0.8, 2-sided *t*-test).

The ethical committee of the LUMC approved the study protocol. Informed parental consent was obtained antenatally when possible. In case of an emergency situation (e.g. mother in full labour or when immediate delivery was necessary) or when obtaining antenatal consent was inappropriate (e.g. if the condition of the mother did not allow for proper consideration on participation), consent was asked retrospectively. This study was registered in www.trialregister.nl, with registration number NTR6021.

Statistical analysis was performed with SPSS software version 23.0 (SPSS, Chicago, Illinois). The parameters of both groups were assessed for normality using the Kolmogorov-Smirnov and Shapiro-Wilkinson test. Demographics of the repetitive and standard stimulation groups were compared by χ^2 test for categorical variables, Student's *t*-test for normally distributed data, or Mann-Whitney *U* test for non-normally distributed data. Parameters of respiratory effort were compared between the groups over time using a linear mixed-effect regression model after appropriate transformation to meet the normality assumption, in which the time after birth, stratification group and randomisation group were entered. We allowed for interaction between time and randomisation group. Study parameters that were only assessed once over time were compared by a two-way factorial ANOVA, including both the randomisation and stratification group. Categorical outcomes were assessed by Fisher's exact test.

For the calculation of parameters of respiratory effort, tidal volumes during inspiration were used, as this is the active part of a breath and represents effort, expired tidal volumes represent expiration and are passive, which does not completely represent respiratory effort. However, when there is mask leak, inspired tidal volumes cannot be used, the best approximation to measure effort is then only expired tidal volume. Whenever there was a mask leakage of 100%, MV was

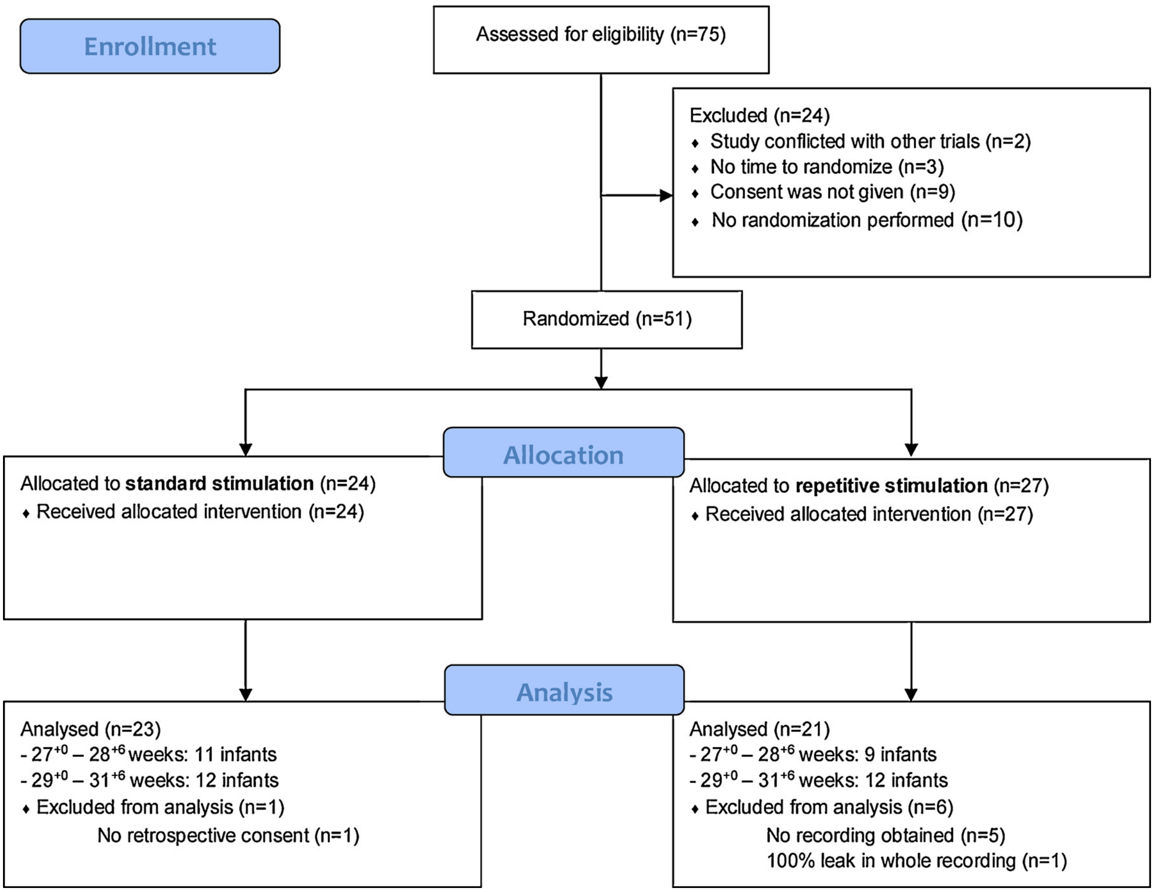

Fig. 1. CONSORT flow diagram.

calculated for that minute using only tidal volumes recorded without 100% mask leakage, and dividing it by the number of seconds for which data was present. Calculations of the other variables were made based on available data. Two-sided p-values < 0.05 were considered statistically significant.

Results

A total of 75 eligible infants were born in the LUMC between September 2016 and April 2017. During this period 24 infants could not be included due to inclusion in other studies, antenatal consent was refused or due to logistical reasons. Thus, 51 infants were randomized to receive either repetitive or standard stimulation, but 7 infants were excluded from the analysis because there was no retrospective consent, there was no recording obtained or the recording could not be analysed because of persistent 100% leak (Fig. 1).

There were no significant differences between the repetitive and standard stimulation groups with regard to gestational age, birth weight, gender, Apgar score at 1, 5 and 10 min, mode of delivery, and full dose of antenatal steroids (Table 1).

Stimulation performed

At least one tactile stimulation episode was performed in all infants in the repetitive stimulation group and in 22/23 (96%) infants in the standard stimulation group. Infants in the repetitive stimulation group were stimulated significantly more often (8 (7–10) vs 3 (3–6) episodes, p < .001), although there were no significant differences in starting time, episode duration, or total stimulation time (Table 2). According to the study protocol, the standard stimulation group received significantly more episodes of stimulation based on clinical indication

Table 1
Demographical data.

	Standard stimulation (n = 23)	Repetitive stimulation (n = 21)	P-value
Gestational age (weeks) [b]	29^{+0} (27^{+5}–31^{+0})	29^{+5} (28^{+1}–30^{+6})	0.487
Birth weight (grams) [b]	1252 (1050–1388)	1350 (1073–1580)	0.597
Gender (% male) [c]	14/23 (61%)	11/21 (52%)	0.570
Apgar score at 1 min [a]	6 ± 3	6 ± 2	0.897
Apgar score at 5 min [b]	8 (7–9)	8 (7–9)	0.655
Apgar score at 10 min [b]	9 (8–9)	9 (9–9)	0.492
Mode of Delivery (% caesarean section) [c]	17/23 (74%)	12/21 (57%)	0.241
Antenatal steroids (% full dose) [c]	14/23 (61%)	13/21 (62%)	0.944

Data is presented as mean ± SD for normally distributed data (a), median (IQR) for data that were not normally distributed (b), and n (%) for categorical data (c).

(46% vs 63%, p = .009) (Table 2).

Effect of tactile stimulation on breathing effort

There was no significant difference in the median (IQR) MV at minutes 1–4 and 1–7 (1–4 min: 51.5 (5.3–114.2) vs 69.2 (11.5–153.9) ml/kg, p = .439, 1–7 min: 89.6 (21.4–141.7) vs 110.5 (42.3–166.8) ml/kg, p = .324). In addition, there were no significant differences in respiratory rate, tidal volume and RoR of spontaneous breaths on CPAP in the repetitive stimulation group when compared to the standard stimulation group during the intervention (1–4 min) and during the total period (1–7 min) (Table 3, Fig. 2). The period of mask ventilation did not significantly differ between the groups as well (median (IQR) time 8

Table 2
Stimulation performed.

	Standard stimulation (n = 23)	Repetitive stimulation (n = 21)	P-value
Stimulation performed (%)[c]	22/23 (96%)	21/21 (100%)	1.000
Time stimulation started (s after birth)[a]	74.5 ± 42.9	71.3 ± 34.1	0.794
Duration of stimulation episodes (s)[a]	12 (4–24)	10 (9–11)	0.076
Total stimulation time (s)[a]	59 (24–120)	86 (63–105)	0.388
Number of stimulation episodes[b]	3 (3–6)	8 (7–10)	< 0.001
Type of stimulation[c]			0.271
- Rubbing the back	4/92 (4%)	2/168 (1%)	
- Rubbing soles of the feet	84/92 (91%)	160/168 (95%)	
- Both	4/92 (4%)	6/168 (4%)	
Clinical indication for stimulation[c]	57/91 (63%)	76/166 (46%)	0.009
Type of indication[c]			0.048
- Bradycardia	3/57 (5%)	4/76 (5%)	
- Apnea	14/57 (25%)	36/76 (47%)	
- Hypoxia	15/57 (26%)	11/76 (15%)	
- Combination	25/57 (44%)	25/76 (33%)	

Data is presented as mean ± SD for normally distributed data (a), median (IQR) for data that were not normally distributed (b), and n (%) for categorical data (c).

(0–118) sec vs 35 (13–131) sec, p = .231). There were no differences in percentage of tidal volumes > 4 ml/kg or > 8 ml/kg (Table 3).

There were no significant differences between the groups in pulse rate but the average oxygen saturation was significantly higher in the repetitive stimulation group (87.6 ± 3.3% vs 81.7 ± 8.7%, p = .007), while there was no significant difference in the FiO_2 given at each minute (p = .121) (Fig. 3). While the maximum FiO_2 during stabilisation was not different, the requirement for a lower FiO_2 extended well beyond the 7-min stabilisation period. This was reflected by a significantly lower FiO_2 requirement at the time of transport to the NICU in the repetitive stimulation group (28.2 (22.8–35.0)% vs 33.6 (29.4–44.1)%; p = .036), while there was no difference in the time at which infants were transported (Table 3). None of the infants were intubated in the delivery room. There was no significant difference in administration of PPV (48% vs 22%, p = .130) or the duration of PPV administered (16 (0–118) sec vs 35 (13–131) sec, p = .231). Caregivers decided less often to administer caffeine in the delivery room to stimulate breathing in the repetitive stimulation group (10% vs 39%, p = .036) (Table 3). Caffeine was administered at a mean ± SD time point of 6:25 ± 1:13 min after birth.

Effect of tactile stimulation on clinical outcomes

There were no significant differences in incidence of intraventricular haemorrhage (IVH) or administration of surfactant during NICU admission (Table 3).

Discussion

This randomized trial is the first study quantifying the respiratory minute volume as a direct effect of tactile stimulation. Tactile stimulation to stimulate breathing of infants at birth has been common practice before living memory and has been recommended even before the first version of the resuscitation guidelines [22]. Sharing the observations of the retrospective study and the lack of clinical equipoise in the neonatal team in “not to stimulate” could have resulted in bias prior to the start of the trial. For this reason we tested the effect of tactile stimulation by comparing standard stimulation, which is dependent upon the discretion of the caregiver, with an unambiguous protocol of repetitive stimulation. Performing a trial of this nature could have influenced the caregiver’s performance in all patients (Hawthorne effect). We considered this to be unavoidable and for this reason we noted all details of the tactile stimulation performed.

While there was no significant difference in MVs, tidal volumes and RoR, all respiratory effort values were increased in the repetitive stimulation group and thus all point to the same direction. Therefore, although no significant statistical differences were observed, the findings might be clinically relevant. This is also expressed by a significant increase in oxygen saturations. Also, fewer infants in the repetitive stimulation group received caffeine at birth when compared to the standard stimulation group. As caffeine was administered at the discretion of the caregiver, this indicates that infants in the repetitive

Table 3
Effect of tactile stimulation on breathing effort.

	Standard stimulation (n = 23)	Repetitive stimulation (n = 21)	P-value
Minute volume at 1–4 min after birth (ml/kg)[a]	51.5 (5.3–114.2)	69.2 (11.5–153.9)	0.439
Minute volume at 1–7 min after birth (ml/kg)[a]	89.6 (21.4–141.7)	110.5 (42.3–166.8)	0.324
Tidal volume at 1–4 min after birth (ml/kg)[a]	2.7 (1.0–5.7)	3.6 (1.7–6.3)	0.131
Tidal volume at 1–7 min after birth (ml/kg)[a]	2.9 (1.3–5.4)	3.7 (2.1–5.9)	0.134
Rate of rise to maximum tidal volumes at 1–4 min after birth (ml/kg/sec)[a]	7.4 (3.7–13.6)	10.3 (4.5–19.3)	0.213
Rate of rise to maximum tidal volumes at 1–7 min after birth (ml/kg/sec)[a]	8.4 (4.5–14.1)	10.8 (6.0–17.5)	0.219
Respiratory rate/min at 1–4 min after birth[a]	23 (7–36)	24 (8–45)	0.795
Respiratory rate/min at 1–7 min after birth[a]	32 ± 19	35 ± 19	0.627
Oxygen saturation (%)[b]	81.7 ± 8.7	87.6 ± 3.3	0.007
Pulse rate [b]	143 (133–150)	138 (133–151)	0.581
Percentage of tidal volumes > 4 ml/kg (%)[b]	39.7 ± 21.2	47.1 ± 25.0	0.315
Percentage of tidal volumes > 8 ml/kg (%)[b]	5.0 (2.0–14.0)	6.0 (1.5–22.5)	0.673
Time of mask ventilation (sec)[b]	35 (13–131)	16 (0–118)	0.231
Maximum FiO_2 during resuscitation (%)[b]	93.4 (48.9–99.9)	62.0 (35.3–99.3)	0.110
Time at which infant is transported to NICU (min:sec)[b]	15:06 (10:34–19:09)	12:32 (9:24–16:21)	0.258
FiO_2 at start of transport to the NICU (%)[b]	33.6 (29.4–44.1)	28.2 (22.8–35)	0.036
Caffeine administered during stabilization at birth (%)[d]	9/23 (39.1)	2/21 (9.5)	0.036
Time after birth of caffeine administration (minutes)[b]	6:32 (5:25–7:46)	6:00 (4:10–6:00)	0.661
Respiratory support after birth (% CPAP only)[d]	5/23 (21.7)	10/21 (47.6)	0.112
Intraventricular haemorrhage ≥ grade 3[d]	0/23 (0%)	1/21 (5%)	0.477
Surfactant administration at NICU[d]	4/23 (17%)	5/21 (24%)	0.716

Data is presented as median (IQR) or mean ± SD of the raw data; *p*-values are presented of the linear mixed model (a). Data is presented as median (IQR) or mean ± SD of the raw data; *p*-values are presented of the two-way factorial ANOVA (b). Data is presented as n (%) of the raw data, *p*-values are presented of the two-way factorial ANOVA (c). Data is presented as n (%) of categorical data, *p*-values are presented of the Fisher’s exact test (d).

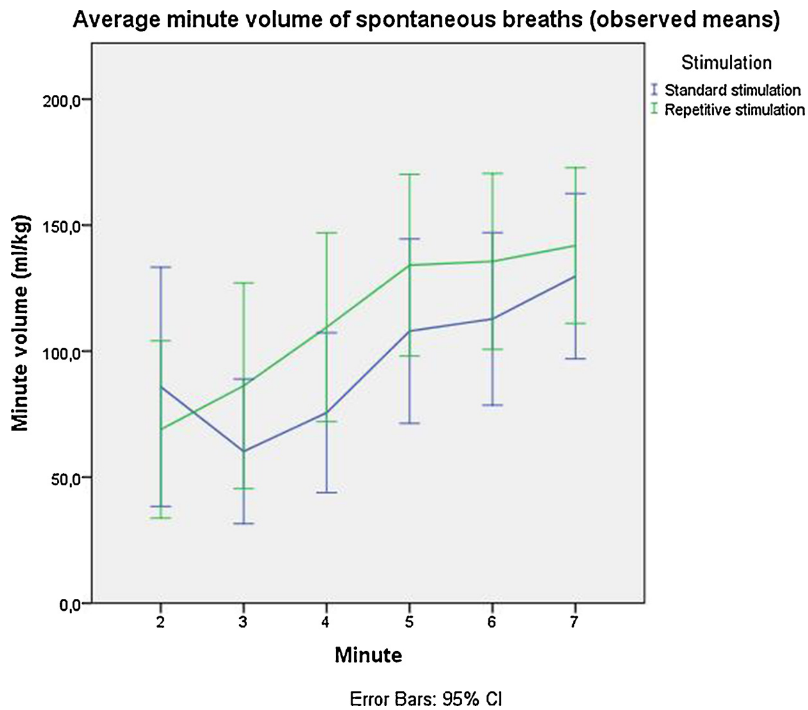

Fig. 2. Average minute volume of spontaneous breaths (observed means) (ml/kg).

stimulation group were assessed to have a better respiratory effort. These results indicate that repetitive tactile stimulation at birth has value in improving breathing efforts in preterm infants at birth and should not be overlooked as an important contributor to the provision of respiratory support in the delivery room.

Respiratory care at birth has shifted towards non-invasive ventilation and the need to avoid intubation and mechanical ventilation [2,5,23,24]. However, it has become clear that mask ventilation is often inadequate and ineffective[1] and that the larynx is mostly closed at birth in apnoeic new-borns and only opens during a spontaneous breath, which is demonstrated in new-born sheep [25]. The larynx must be open to ventilate the lung non-invasively, and the best way to do so is to stimulate breathing. We recently demonstrated that caffeine at birth increases respiratory effort [20] and we now observed similar positive effects with tactile stimulation. While we were unable to achieve statistical significance in the respiratory parameters examined, the higher oxygenation state, indicates that respiratory function was substantially better in the repetitive stimulation group.

Although the effect of tactile stimulation has been described previously in animal models [11,12], the effect in human preterm infants has only just recently gained attention [13,14]. In these studies [13,14] the incidence of stimulation was much lower than the high incidence of stimulation we observed in both stimulation groups in this trial. Initiating this trial therefore substantially increased awareness on and the

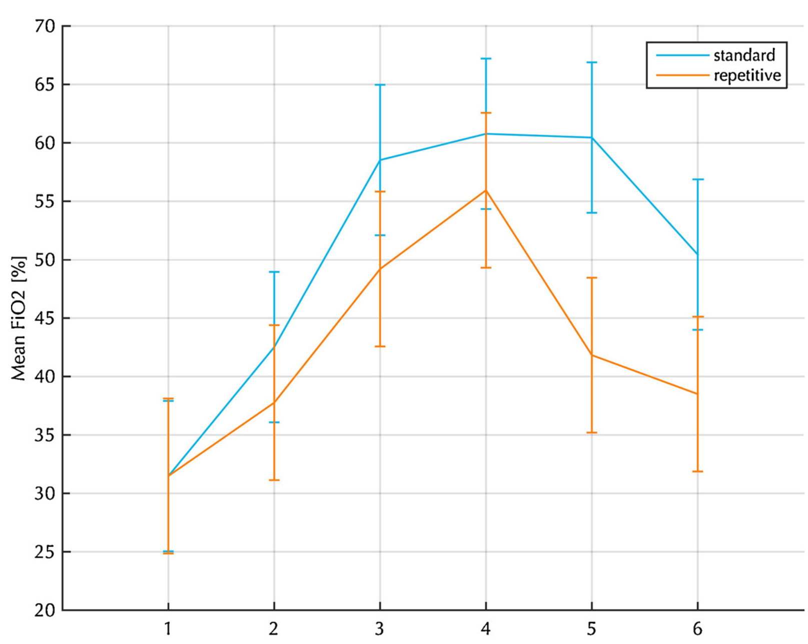

Fig. 3. Average FiO_2 over time during resuscitation (%).

incidence of tactile stimulation. Indeed, while infants in the standard stimulation group would normally only be stimulated when there was a clinical indication, we found that only 63% of stimulations were clinically indicated. This could have resulted in reducing the difference in primary outcome between the two groups. As a result, together with a higher than expected between patient variability in the primary outcome, a larger sample size would be needed to demonstrate statistical differences between the groups. Nevertheless, we demonstrated significant differences in oxygenation between the groups, indicating that the non-statistical significant differences in respiratory function between the two groups were biologically significant.

The most frequently used method of stimulation in this randomized trial was rubbing the soles of the feet, thereby activating proprioceptors which are known to reduce breathing pauses in preterm infants with apnoea of prematurity [26] and increase the frequency of breathing [27]. In contrast, in the study of Gaertner et al. [14], infants were more often stimulated by chest or back rub, and they noted a larger increase in crying, compared to stimulation by rubbing the soles of the feet [14]. Stimulation by chest or back rub might affect the respiratory center via somatic or visceral mechanoreceptors in the thorax region [28,29]. However, Binks et al. showed that this could also inhibit inspiration, as vibration of the thoracic surface could also excite intrapulmonary receptors and suggesting that the lung volume is already increased [30]. More data is needed on the effect of different stimulation locations to inform caregivers in what is the best and most effective way of stimulating preterm infants to enhance respiratory efforts. Although we do not introduce a new intervention, merely a repetition, caution should be taken to ensure the stimulation is performed gently and with care.

Conclusions

In this randomized trial, there were no differences in respiratory parameters between the repetitive tactile stimulation and standard tactile stimulation groups. Nevertheless, tactile stimulation overall improved oxygenation with a lower maximum FiO2 level, lower level of FiO2 at transport to the NICU and the need for less post transport caffeine administration. This suggests tactile stimulation improves respiration function. Future larger studies are required to confirm this finding and identify the best method for tactile stimulation.

Conflicts of interest

The authors have no conflicts of interest relevant to this article to disclose.

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Financial disclosure

The authors have no financial relationships relevant to this article to disclose.

Clinical trial registry

This study was registered in www.trialregister.nl, with registration number NTR6021.

Table of contents summary

Application of repetitive tactile stimulation to preterm infants in the delivery room improves oxygenation at birth.

What is known on this subject?

Tactile manoeuvres to stimulate breathing are recommended during the initial assessment of the infant at birth. There is however very little data on the effect of tactile stimulation of infants at birth.

What this study adds?

We observed a positive effect of the use of repetitive tactile stimulation on respiratory effort and oxygenation of preterm infants at birth. These results indicate that tactile stimulation at birth could be of added value to improve breathing effort at birth.

Acknowledgement

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