

The Optimal Predictors of Readiness for Extubation in Low Birth Weight Infants

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Background: Reintubation, following an unsuccessful extubation from mechanical ventilation is traumatic to the infant and the family. However, 20 to 40% of infants fail extubation and reintubation.

Objective: Determine the optimal predictors of readiness for extubation in low birth weight infants during endotracheal tube-continuous positive airway pressure (ET CPAP) for three minutes. The primary outcome was reintubation within 72 hours of extubation and the secondary outcomes were the causes and risk factors of reintubation.

Material and Method: A prospective cohort study was undertaken in 51 mechanically ventilated infants who were considered to be ready for extubation. The infants were changed to ET CPAP for a 3-minute spontaneous breathing test (SBT) before extubated. Infants were divided into two groups based upon whether they failed or passed the extubation attempt. Extubation failure was defined as reintubation within 72 hours of extubation.

Results: Forty-five of 51 infants (88%) were successfully extubated. Out of the 51 infants only one infant failed the SBT. The three predictors of extubation success that included the SBT, ratio of minute ventilation during ET CPAP to mechanical ventilation and ratio of respiratory frequency during ET CPAP to mechanical ventilation were not significantly different. Using synchronized nasal intermittent positive pressure ventilation after extubation in the failed extubation group was significantly higher than the successful extubation group (66.7% vs. 15.7%, $p = 0.02$).

Conclusion: The SBT and minute ventilation ratio in low birth weight infants were not optimal predictors of readiness for extubation. However, a further prospective study in this field with a larger number of subjects and a proper indication for extubation should be considered.

Keywords: Extubation, Low birth weight infant, Predictor, Preterm infant

J Med Assoc Thai 2017; 100 (4): 427-34

Full text. e-Journal: <http://www.jmatonline.com>

Mechanical ventilation is a common therapy in the neonatal intensive care unit (NICU), especially in low birth weight (LBW) infants, even in the current era of noninvasive respiratory support. Invasive respiratory support is associated with risk and complications including mortality and neurological impairments. Consequently, extubation of a ventilated infant should be as early as possible⁽¹⁾.

Recently, in the absence of good data, the decision to extubate is usually based on a clinical subjective assessment, which takes into account personal experience, analysis of blood gas, and ventilator settings. However, 20 to 40% of infants failed extubation and had to be reintubated⁽²⁾. The adverse

effects of reintubation such as trauma, bradycardia, hypercapnia, alteration of cerebral blood flow, ventilator associated pneumonia, and sepsis are common⁽¹⁾. Therefore, a predictor to assess extubation readiness in LBW infants may reduce the morbidity. Several studies have investigated prediction tools that could determine extubation readiness in neonates. Some studies used physiologic measurements, such as dynamic compliance, respiratory system resistance, breathing work, tidal volume, and minute ventilation⁽³⁻⁶⁾. Some studies used a spontaneous breathing test (SBT) and respiratory variability^(2,7-12). Moreover, spontaneous expiratory minute ventilation (MV) of intubated infants provides an assessment of respiratory drive. Most modern ventilators measure MV continuously and allow measurement during endotracheal continuous positive airway pressure (ET CPAP). Therefore, physicians must determine the optimal time for extubation that minimizes the duration of ETT and maximizes the chances of success. However,

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there is no consensus on the predictors of readiness for extubation in neonates.

The objective of the study was to evaluate the optimal predictors of readiness for extubation in LBW infants during ET CPAP for three minutes and to test the hypothesis that a combination of the SBT (passed if there was no hypoxia or bradycardia during ET CPAP) and MV ratio (ratio of mean minute ventilation between breathing on ET CPAP and mechanical ventilation) is the optimal predictor of readiness for extubation in LBW infants. The primary outcome was reintubation within 72 hours of extubation and the secondary outcomes were the causes and risk factors of reintubation.

Material and Method

This was a cohort prospective study. The study was conducted at the NICU of Songklanagarind Hospital in Songkhla, Thailand. The patients were enrolled from 1 October 2013 to 28 February 2014. The NICU is a level III, single 15-bed room in a university-affiliated teaching hospital at Prince of Songkla University in southern Thailand. Patient selection was based upon an infant birth weight less than 2,500 g, ventilated using the Puritan Bennett™ 840 NeoMode® (Covidien, USA) for at least 24 hours, infants who were assessed by the clinical team to be ready for extubation and were weaned by using a synchronized intermittent mandatory ventilator with pressure support (SIMV/PS) or an assist/control ventilator (A/C) with reducing ventilator rates to 20 to 30 breaths/minute, positive end expiratory pressure (PEEP) of 3 to 4 cm H₂O, and an inspiratory time of 0.3 second with inspired oxygen concentration (FiO₂) less than 40%. The endotracheal tube was suctioned two hours before the study. Infants who had major congenital malformation or extubated accidentally were excluded from the study. The study was approved by the Ethics Committee Board of Faculty of Medicine, Prince of Songkla University and informed consent was obtained from the parent or legal guardian before the study.

Data collection

When the clinical team decided that an infant was ready for extubation, the ventilator was switched to ET CPAP at the same pressure as the PEEP setting. The ventilator data were downloaded from the port of the ventilator every one minute for analysis during the two minutes of mechanical ventilator support before ET CPAP (expiratory tidal volume [V_{TE}], expiratory minute ventilation [V_{E TOT}], frequency [f_{TOT}], compliance

[C_{STAT}], peak pressure plateau at 1 minute before extubation [P_{PL}], peak airway pressure [P_{PEAK}], and oxygen saturation [SpO₂]) until three minutes of ET CPAP (CPAP level, V_{TE}, V_{E TOT}, f_{TOT}, P_{PEAK}, and SpO₂). The vital signs (heart rate, respiratory rate, and mean arterial pressure) were recorded after extubation using the IntelliVue MP40 (Covidien, USA). Arterial blood gas test results were obtained at one hour before extubation. The ratio of the mean respiratory frequency (ratio fr) was calculated from breathing on ET CPAP and mechanical ventilation.

A failed SBT was defined as the infant who had bradycardia (defined as heart rates less than 100 beats/minutes) for more than 15 seconds or a fall in SpO₂ below 85% despite a 15% increase in FiO₂. If the SBT failed, the test was discontinued and the patient was returned to the pre-test ventilation mode until the normal parameters were restored and the newborn was extubated. The clinical teams who cared for the infants were not present during the tests and were blinded to the results. All of the studies were performed by the researchers. Post-extubation respiratory support determined by the clinical team ranged from room air, nasal cannula, CPAP (4 to 6 cmH₂O), or nasal intermittent positive pressure ventilation (SNIPPV) or oxygen hood regardless of the results of the SBT. Extubation failure was defined as reintubation required within 72 hours of extubation. Reintubation was indicated when the infant had one of the following three criteria: (a) At least 6 episodes of apnea requiring stimulation in 6 hours; (b) One or more episodes of apnea requiring bag and mask ventilation; (c) Respiratory acidosis (PaCO₂ more than 65 mmHg and pH less than 7.25) or hypoxemia (needed FiO₂ more than 0.6 to maintain SpO₂ 90 to 95%). If the infants had to be reintubated, the causes of failed extubation were investigated and recorded.

Death or bronchopulmonary dysplasia (BPD) was taken as a composite morbidity to account for death before 36 weeks postmenstrual age. The definition of BPD was defined as a need for supplemental oxygen for at least 28 days and times of point assessment were at 36 weeks' postmenstrual age for babies born before 32 weeks' gestational age or at 56 days of life for babies born at or beyond 32 weeks' gestational age or discharged home, whichever came first⁽¹³⁾. Other outcomes included necrotizing enterocolitis (NEC) stage II or more of modified Bell's criteria⁽¹⁴⁾, patent ductus arteriosus (PDA) diagnosed by echocardiogram considered hemodynamically significant and requiring medical or surgical treatment, and intraventricular

hemorrhage (IVH) diagnosed by a pediatric radiologist.

Statistical analysis

The data and clinical parameters were expressed as mean (SD) or median (IQR). The Shapiro-Wilk normality test was used to determine if the sample values suited to a normal distribution. Since the data were non-normal distribution, the Wilcoxon signed-rank test was applied. The Chi-square test was used to find associations between extubation success and failure. A difference was considered significant for p -values <0.05 . A sample size of 10 and 40 were planned to detect a difference of one standard deviation in the mean ratio of $V_{E\text{TOT}}$ in the failed extubation group and successful extubation group, respectively, to achieve an 80% power and a two tailed p -value less than 0.5. Standard formulas were used to calculate sensitivity, specificity, and positive and negative predictive values (PPV and NPV) respectively. The R program and epicalc package (version 2.15.1.0; Free Software Foundation, Songkhla, Thailand) was used for the statistical analysis.

Results

Of the 51 infants studied, 45 (88%) infants were extubated successfully and 6 infants (12%) required reintubation and mechanical ventilation within 72 hours of extubation. Mean (SD) gestational age was 30.4 (3.5) weeks. Mean (SD) birth weight, and current weight at study were, 1,363 (505) and 1,525 (475) g, respectively. Birth weight, gestational age, mode of delivery, use of antenatal steroid and surfactant use after birth, use of xanthine derivatives, incidence of PDA, NEC, and grade III/IV IVH were not different between the groups (Table 1). The majority of the intubated infants were respiratory distress syndrome (20/51, 39.2%) and pneumonia (14/51, 27.5%). The main causes of reintubation were lung atelectasis (4/6, 66.7%), aspiration (1/6, 16.7%), and pneumothorax (1/6, 16.7%). Seven (7/45, 15.6%) infants in the successful group were weaned by using nasal synchronized intermittent mandatory ventilation compared to 4 (4/6, 66.7%) infants in the failed group ($p = 0.02$). All of the infants in the failed extubation group required noninvasive respiratory support (SNIPPV or CPAP) after extubation

Table 1. Clinical characteristic of the infants

Clinical characteristic	Failed extubation n = 6, n (%)	Successful extubation n = 45, n (%)	p -value
Gestational age, week*	29.0 (2.4)	30.5 (3.6)	0.31
Birth weight, g**	1,222.5 (1,146, 1,269)	1,205.0 (1,020, 1,775)	0.59
Current weight at study, g*	1,345 (220)	1,549 (496)	0.99
Male	3 (50)	22 (49)	1.00
Vaginal delivery	1 (16.7)	20 (44.4)	0.38
Apgar score at 5 min**	8 (5, 8)	8 (6, 8)	0.48
Cause			0.88
Respiratory distress syndrome	3 (50.0)	17 (37.8)	
Pneumonia	2 (33.3)	12 (26.7)	
Transient tachypnea of newborn	0 (0)	3 (6.7)	
Sepsis	1 (16.7)	5 (11.1)	
Meconium aspiration syndrome	0 (0)	1 (2.2)	
Other	0 (0)	7 (15.6)	
Patent ductus arteriosus	4 (66.7)	19 (42.2)	0.39
Necrotizing enterocolitis \geq stage 2	0 (0)	12 (26.7)	0.32
Duration of ventilation, day**	22 (12, 47)	12 (5, 21)	0.08
Methylxanthine used	4 (66.7)	22 (48.9)	0.67
Noninvasive respiratory support			
SNIPPV	4 (66.7)	7 (15.6)	0.02***
NCPAP	2 (33.3)	23 (51.1)	0.67
Oxygen box	0 (0)	12 (26.7)	0.32
Oxygen cannula	0 (0)	3 (6.6)	1.00

* mean (SD); ** median (IQR), *** $p < 0.05$

NCPAP = nasal continuous positive airway pressure; SNIPPV = synchronized nasal intermittent positive pressure ventilation

whereas only 30 infants (30/45, 66.7%) of the successful group required noninvasive respiratory support ($p = 0.02$). The mean (SD) current weight at extubation of the 6 infants in the failed extubation group was 1,345 (220) g. All of them needed reintubation within 24 hours that resulted in lung atelectasis in 50% of the infants.

Pulmonary function testing was performed for 3 minutes during ET CPAP and up to 2 minutes prior to extubation. There was no statistically significant difference between both groups in pre-extubation ventilator support, pulmonary function, ratio $V_{E\text{TOT}} \geq 0.8$, ratio $V_{E\text{TOT}} \geq 0.5$, and ratio $fr \geq 1.5$ during the ET CPAP prior to extubation and combination between the SBT, ratio $V_{E\text{TOT}} \geq 0.8$, ratio $V_{E\text{TOT}} \geq 0.5$, and ratio $fr \geq 1.5$ (Table 2). The SBT, ratio $V_{E\text{TOT}} \geq 0.5$, and ratio $fr \geq 1.5$ were

highly sensitivity and PPV but low specificity and NPV. However, there was no statistically significant difference between both groups. Forty-four infants (44/45, 97.8%) in the successful extubation passed the SBT and all 6 infants (6/6, 100%) in the failed extubated group passed the SBT ($p = 1.00$) (Table 3). No statistically significant changes were seen on mean arterial pressure, heart rate, respiratory rate, or SpO_2 before and after extubation. Table 4 compares the outcomes at hospital discharge between the infant groups. Infants who failed extubation had no difference in incidence of BPD, apnea, length of hospital stay, and duration on oxygen after extubation compared to infants who were successfully extubated. There were no mortality cases in either group.

Table 2. Pulmonary mechanics, pulmonary function test, and predictive values during continuous positive airway pressure (ET CPAP)

Indicators	Failed extubation n = 6	Successful extubation n = 45	p-value
Weaning ventilator**			
Positive inspiratory pressure (cmH ₂ O)	14 (14, 14)	14 (13, 14)	0.32
Ventilator rate (/min)	22 (20, 25)	25 (20, 25)	0.87
Mean airway pressure (cmH ₂ O)	5.4 (5.0, 5.7)	5.2 (5.0, 5.5)	0.64
FiO ₂	0.30 (0.21, 0.30)	0.30 (0.21, 0.30)	0.59
Expiratory tidal volume (mL/kg)**	5.1 (3.3, 6.7)	6.2 (4.6, 7.3)	0.36
Expiratory minute ventilation (L/min/kg)*	0.3 (0.2)	0.4 (0.1)	0.51
Frequency (/min)**	81 (76, 83)	68 (60, 81)	0.23
Pass SBT, n (%)	6 (100.0)	44 (97.8)	1.00
Ratio $V_{E\text{TOT}} \geq 0.8$, n (%)	4 (66.7)	41 (91.1)	0.14
Ratio $V_{E\text{TOT}} \geq 0.5$, n (%)	2 (33.3)	25 (55.6)	0.40
Ratio $fr \geq 1.5$, n (%)	1 (16.7)	2 (4.4)	0.32
Combination, n (%)			
Pass SBT + ratio $V_{E\text{TOT}} \geq 0.8$	2 (33.3)	25 (55.6)	0.44
Pass SBT + ratio $V_{E\text{TOT}} \geq 0.5$	4 (66.7)	41 (91.1)	0.21

* mean (SD), ** median (IQR)

SBT = spontaneous breathing test; ratio $V_{E\text{TOT}}$ = ratio of mean minute ventilation; ratio fr = ratio of mean respiratory rate

Table 3. Predictive values for successful extubation

Indicators	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
SBT	98	0	88	0
Ratio $V_{E\text{TOT}} \geq 0.8$	56	67	93	17
Ratio $V_{E\text{TOT}} \geq 0.5$	91	33	91	33
Ratio $fr \leq 1.5$	96	17	90	33

SBT = spontaneous breathing test; ratio $V_{E\text{TOT}}$ = ratio of mean minute ventilation; ratio fr = ratio of mean respiratory rate; PPV = positive predictive value; NPV = negative predictive value

Table 4. Outcomes of patients

Discharge outcomes of patients	Failed extubation n = 6, n (%)	Successful extubation n = 45, n (%)	p-value
Bronchopulmonary dysplasia			0.06
Mild	2 (40.0)	4 (9.8)	
Moderate	1 (20.0)	13 (31.7)	
Severe	2 (40.0)	4 (9.8)	
Apnea	3 (50.0)	5 (11.1)	0.06
Duration of oxygen after extubation, day*	27.5 (21.5, 31.8)	7 (3.0, 19.2)	0.06
Home oxygen therapy**	1/4 (25)	8/41 (19.5)	1.00
Length of hospital stay, day*	56 (46.5, 82.8)	37 (16, 64)	0.11

* median (IQR); ** some infants were transferred

Discussion

Early successful extubation in LBW infants reduces the morbidity and mortality rates in caring for LBW infants especially with the current use of noninvasive respiratory support. If the best optimal predictor of readiness for extubation could be used, not only would the quality of life of LBW infants improve but also a savings of resources in respiratory support would be realized. The present study was designed to determine the best optimal predictor for the successful extubation of the tests (the SBT, ratio $V_{E\text{TOT}} \geq 0.8$, ratio $V_{E\text{TOT}} \geq 0.5$, and ratio $fr \geq 1.5$ during ET CPAP) in preterm infants judged ready for extubation on clinical criteria which are simple methods for mechanical ventilation discontinuation. Unfortunately, there were no statistically significant differences in any of the tests between the successful and failed extubation groups. The SBT and measurements of the dynamic lung volumes after extubation had limited clinical utility. The minute ventilation and lung volumes did not provide clear threshold values for reliable discrimination between extubation success and failure^(6,15,16).

The results of the study revealed that using the 3-minute SBT and the MV ratio as the predictors could not significantly predict successful extubation in LBW infants with a PPV and NPV of 88% and 0%, respectively. The optimal duration of the SBT before extubation to determine an infant's independent breathing ability is uncertain. In previous studies, the ranges of SBT were from 3 minutes to 2 hours⁽⁹⁻¹¹⁾. The 3-minute SBT was conducted in the present study; however, ET CPAP adds to the resistance of the respiratory system⁽¹⁷⁾ leading to increased breathing work which jeopardizes successful extubation⁽¹⁸⁾. There is evidence that extubation after several hours of ET

CPAP is less successful than extubation from low rate ventilation due to the longer duration of ET CPAP and the increased airway resistance that increased breathing work⁽¹⁸⁾.

The predictor tests in previous studies varied, such as the SBT, spontaneous MV and respiratory variability^(4,12-17). Kamlin CO et al⁽²⁾ performed a 3-minute ET CPAP trial in very low birth weight infants before extubation to predict successful extubation. The PPV and NPV of successful SBT for extubation were 93% and 89%, respectively. Chawla S et al⁽⁸⁾ performed a 5-minute ET CPAP. The PPV and NPV of a successful SBT for extubation were 88% and 63%, respectively. Chavez A et al⁽⁹⁾ performed a 15-minute SBT connected to a flow-inflating bag set to provide 5 cmH₂O CPAP. The PPV and NPV for successful extubation were 92% and 50%, respectively. Vento G et al⁽¹¹⁾ evaluated the percentage of time spent at a spontaneous expiratory MV of less than 125 mL/kg/min during a 2-hour ET CPAP trial. The result was more than 8.1% and a sensitivity of 100% and specificity of 90% were obtained to predict failed extubation. Kaczmark J et al⁽⁷⁾ combined the SBT and variability index of either the inspiratory time or the tidal volume to predict a successful extubation with a PPV and NPV of 95% and 100%, respectively.

Alternatively, the PPV of the SBT, the MV ratio, and ratios fr were high while the NPV was very low compared to previous studies. However, when the data were reevaluated the reproducibility showed that the power of the test was only 30%.

The rate of reintubation in this study was 12%, compared to 20 to 40% in other studies^(3,7,8,10,12). This might be from differences in the criteria of extubation with a lower rate and lower pressure compared to other

studies. Also, all the preceding studies were conducted in infants with a greater weight range and difference in current weight at study time. The authors limited the present study to infants <2,500 g because they represent a variety of respiratory problems.

Apnea is a common cause of the extubation failure, which was found in 50% of the infants in the failed extubation group. In the present study, all of the infants who failed extubation required reintubation within 24 hours after extubation and the cause of apnea was lung atelectasis which was consistent with previous reports in other studies⁽¹⁹⁾. There may also be several other factors responsible for extubation failure that the SBT and pulmonary mechanics such as the MV may fail to recognize, for example, postextubation laryngeal edema, apnea, or thick secretions. As the present study was not powered to look at these secondary outcomes, the results should be interpreted with caution. This study has some limitations such as a small sample size and the indication for extubation with a lower rate and lower pressure.

In summary, the SBT and the MV ratio produced perfect sensitivity and PPV but limited specificity and NPV in low birth weight infants; therefore, there were no optimal predictors of readiness for extubation. However, a further prospective study in this field with a larger number of subjects and a proper indication for extubation should be considered.

What is already known on this topic?

Both prolonged endotracheal intubation and re-intubation of low birth weight infants are associated with increases in short- and long-term morbidity. Approximately one-third of ventilated infants fail extubation. Currently, no consensus on the predictors of readiness for extubation in neonates.

What this study adds?

A stable breathing test and minute ventilation (MV) ratio are not the optimal predictors in low birth weight infants. Future research should focus in better identifying the best predictive tools for a successful weaning.

Acknowledgements

The authors thank Nannapat Pruphetkaew (Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Thailand) for the statistical analysis and Glenn Shingledecker (Office of International Affairs, Faculty of Medicine, Prince of Songkla University, Thailand) for editing the manuscript.

Funding

Faculty of Medicine, Prince of Songkla University, Thailand.

Potential conflict of interest

None.

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ตัวชี้วัดที่เหมาะสมสำหรับความพร้อมของการถอดท่อหลอดลมคอในทารกแรกเกิดน้ำหนักตัวน้อย

วาริชา เจนจินดาชัย, สิตาภา ภาณี, อนุชา ธาตรีมนตรีชัย

ภูมิหลัง: การใส่ท่อหลอดลมคอซ้ำในทารกที่ไม่ประสบความสำเร็จในการถอดท่อหลอดลมคอ ส่งผลให้เกิดการบาดเจ็บต่อทารกและส่งผลกระทบต่อครอบครัว พบอัตราการล้มเหลวจากการถอดท่อหลอดลมคอถึงร้อยละ 20-40

วัตถุประสงค์: เพื่อศึกษาตัวชี้วัดที่เหมาะสมสำหรับความพร้อมของการถอดท่อหลอดลมคอในทารกแรกเกิดน้ำหนักน้อย ขณะใส่ท่อหลอดลมคอด้วยการหายใจแบบ continuous positive airway pressure (ETT CPAP) นาน 3 นาที

วัสดุและวิธีการ: การศึกษาแบบไปข้างหน้า ทารกแรกเกิดน้ำหนักน้อยที่ใช้เครื่องช่วยหายใจ และพร้อมในการถอดท่อหลอดลมคอจำนวน 51 ราย ได้รับการทดสอบการหายใจด้วยตนเองผ่าน ETT CPAP เป็นเวลา 3 นาที (spontaneous breathing test, SBT) โดยจะเก็บข้อมูลพื้นฐาน ข้อมูลเครื่องช่วยหายใจ และนำข้อมูลมาเปรียบเทียบระหว่างกลุ่มที่ประสบความสำเร็จ และไม่ประสบความสำเร็จในการถอดท่อหลอดลมคอ (กลุ่มที่ไม่ประสบความสำเร็จคือกลุ่มที่ต้องได้รับการใส่ท่อหลอดลมคอใหม่ภายใน 72 ชั่วโมง) โดยทีมการรักษายะทำการถอดท่อหลอดลมคอผู้เข้าร่วมการศึกษาทุกรายโดยไม่ขึ้นกับผลการทดสอบ

ผลการศึกษา: ทารกได้เข้าร่วมการศึกษทั้งหมด 51 ราย พบ 45 ราย (ร้อยละ 88) ประสบความสำเร็จในการถอดท่อหลอดลมคอ มีทารก 1 ราย ใน 51 ราย ไม่ผ่าน SBT ไม่พบมีความแตกต่างอย่างมีนัยสำคัญทางสถิติระหว่างกลุ่มในการทดสอบ SBT, อัตราส่วน minute ventilation และอัตราหายใจระหว่างหายใจด้วย ETT CPAP กับเครื่องช่วยหายใจ แต่พบกลุ่มที่ไม่ประสบความสำเร็จในการถอดท่อหลอดลมคอจำเป็นต้องใส่ synchronized nasal intermittent positive pressure ventilation มากกว่าอย่างมีนัยสำคัญทางสถิติ (ร้อยละ 66.7 เปรียบเทียบกับร้อยละ 15.7, $p = 0.02$)

สรุป: การทดสอบด้วย SBT หรือการดูอัตราส่วน minute ventilation ก่อนถอดท่อหลอดลมคอในทารกน้ำหนักน้อยไม่ได้เป็นตัวชี้วัดถึง การประสบความสำเร็จในการถอดท่อหลอดลมคอ ควรมีการศึกษาเพิ่มเติมโดยเพิ่มประชากรในการศึกษา และปรับปรุงข้อบ่งชี้ในการถอดท่อหลอดลมคอให้เร็วขึ้น
