Trial Protocol

1. **Title:** Apneic oxygenation with low-flow oxygen cannula for rapid sequence induction and intubation in pediatric patients: A randomized-controlled trial
2. **Principle Investigator:** Naiyana Aroonpruksakul, MD
3. **Co-Investigators:** Peerapong Sangsungnern, MD, Taniga Kiatchai, MD
4. **Affiliations:** Department of Anesthesiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand

   2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand

   Tel: (+66) 2-419-7990; Fax: (+66) 2-411-3256

   E-mail: naiyana.aro@mahidol.edu
5. **Trial Registration:** Thai Clinical Trials Registry TCTR20210802002
6. **Ethical Information:** The study protocol was approved by the Siriraj Institutional Review Board (Si 059/2020).
7. **Funding:** The Siriraj Research Development Fund of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand (grant number [IO] R016331029).
8. **Background**

Rapid sequence induction and intubation (RSII) is defined as endotracheal intubation that is performed as soon as possible without face mask ventilation to reduce the risk of pulmonary aspiration. The RSII protocol avoids positive pressure ventilation to prevent regurgitation of gastric contents; however, this puts the patient at risk for hypoxemia (1). The incidence of hypoxemia after classical RSII in the operating room (OR), emergency department (ED), and intensive care unit (ICU) was reported to range

from 7-25% in adults (2), from 14-33% in pediatric patients (3-6), and from 30-59% in pediatric patients aged <2 years (7, 8). The one exception was reported by Gencorell, *et al.* who found an incidence of hypoxemia of 3.6% in the pediatric OR (1).

Apneic oxygenation (ApOx) refers to the passive movement of oxygen to the alveoli in the absence of lung movement by patient effort or positive pressure ventilation (2, 9-11). This technique reduced desaturation during intubation in the ED and ICU, and in healthy patients undergoing elective surgery in adult studies (2, 12, 13). In a small number of pediatric studies in a non-RSII condition, ApOx could prolong safe apneic time and decrease the incidence of hypoxemia (14-17). ApOx using low-flow nasal cannula was preferable during RSII due to its wide availability, affordability, and ease of use.

9. **Objective:** To examine the effect of apneic oxygenation using low-flow nasal cannula during RSII. The primary outcome was the incidence of hypoxemia, defined as oxygen saturation (SpO_2) ≤92%. The secondary outcomes were the time to desaturation during RSII, the lowest SpO_2, and complications of RSII.
10. **Study design:** single center, single-blind, randomized controlled study
11. **Inclusion criteria**
    - Neonates, infants, and children aged up to 7 years
    - American Society of Anesthesiologists (ASA) physical status 1 to 3
    - Elective or emergency surgery under general anesthesia with RSII
12. **Exclusion criteria**
    - History of heart disease or respiratory disease
    - Expected difficult airway management
    - Fever (body temperature >37.5°C)

- Having received preoperative oxygen supplementation
- Allergy to any study drug

13. Withdrawal criteria

- Inadvertent mask ventilation
- Postinduction hypotension
- Unexpected difficult airway
- Gastric content regurgitation
- Critical cardiovascular disturbance
- Esophageal intubation

14. Randomization

Study subjects were randomized to either the ApOx group or the classical group (1:1 ratio allocation) using computer-generated block size of four randomization by an independent statistician. The random allocation sequence was kept separately in sealed opaque envelopes with sequential numbers. Co-investigator opened the envelope containing each patient group assignment before induction of anesthesia, then assigned participants to interventions. Anesthetic personnel in the OR could not be blinded because a nasal cannula was used for the intervention. As such, only the patients and parents were blinded to the group allocation.

15. Sample size calculation

The sample size was calculated using nQuery Advisor® version 6.0 (Statistical Solutions Limited; GraphPad Software, Inc., San Diego, CA, USA). Soneru, *et al*. applied ApOx with nasal cannula 5 LPM in children aged 0-8 years and reported an incidence of desaturation (SpO_2 <95%) in the ApOx and control groups of 9% and 43%, respectively

(14). Using this data, we estimated that the incidence of hypoxemia in the present study ($SpO_2 \leq 92\%$) would be 10% and 40% in the ApOx and classical groups, respectively. Using a type I error of 0.05 and a power of 80%, the calculated sample size was 32 participants in each arm.

16. Intervention

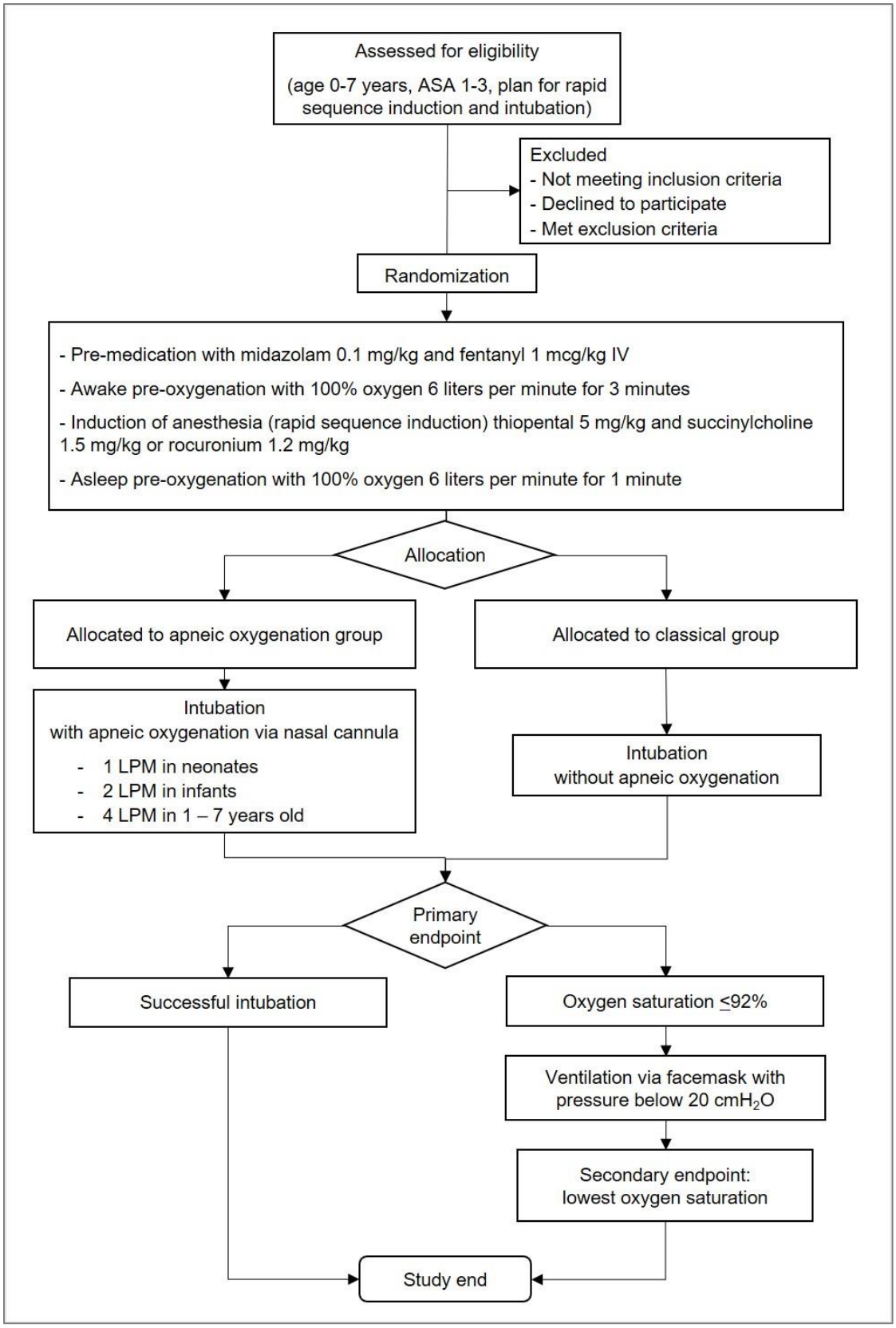
Upon arrival in the OR, standard monitoring was applied prior to induction. All participants were premedicated with midazolam 0.1 mg/kg and fentanyl 1 mcg/kg intravenously. When mask acceptance was expected, awake preoxygenation was administered with 100% oxygen 6 liters per minute (LPM) using a tight-fitting facemask connected to the circle circuit of the anesthetic machine for 3 minutes. Rapid sequence induction of anesthesia was conducted with thiopental 5 mg/kg followed by either succinylcholine 1.5 mg/kg or rocuronium 1.2 mg/kg. The choice of rapid-onset muscle relaxant was according to anesthesiologist discretion. After induction, asleep oxygenation was administered with jaw thrust maneuver and 100% oxygen 6 LPM via tight-fitting facemask for 1 minute, by which time muscle relaxation was expected to be fully achieved. No cricoid pressure was applied in this study.

16.1 Intervention group (ApOx): A nasal cannula with no oxygen flow was applied prior to awake preoxygenation with facemask. ApOx was initiated at the end of asleep oxygenation. The oxygen flow rate was administered according to World Health Organization (WHO) recommendation for maximum flow rate via nasal cannula, as follows: 1 LPM in age 0-1 month, 2 LPM in age 1-12 months, and 4 LPM in age 1-7 years (18).

16.2 Control group (classical): A nasal cannula was not applied, and intubation was performed without ApOx.

In both groups, SpO_2 was focused upon until reaching the primary endpoint. The primary endpoint was defined as hypoxemia (oxygen saturation decreased to 92%) or successful intubation. Study participants were intubated by pediatric anesthesia fellows or senior anesthesia residents.

In case of desaturation, the procedure was discontinued as soon as the oxygen saturation reached 92%. Rescue procedure comprised jaw thrust and positive pressure ventilation with pressure below 20 cmH_2O via facemask. Intubation was then reperformed after the SpO_2 increased to 100%. The lowest oxygen saturation was recorded as the secondary endpoint in patients with desaturation.


Assessed for eligibility
(age 0-7 years, ASA 1-3, plan for rapid sequence induction and intubation)
Excluded
- Not meeting inclusion criteria
- Declined to participate
- Met exclusion criteria
Randomization
- Pre-medication with midazolam 0.1 mg/kg and fentanyl 1 mcg/kg IV
- Awake pre-oxygenation with 100% oxygen 6 liters per minute for 3 minutes
- Induction of anesthesia (rapid sequence induction) thiopental 5 mg/kg and succinylcholine 1.5 mg/kg or rocuronium 1.2 mg/kg
- Asleep pre-oxygenation with 100% oxygen 6 liters per minute for 1 minute
Allocation
Allocated to apneic oxygenation group
Allocated to classical group
Intubation
with apneic oxygenation via nasal cannula
- 1 LPM in neonates
- 2 LPM in infants
- 4 LPM in 1 – 7 years old
Intubation
without apneic oxygenation
Primary endpoint
Successful intubation
Oxygen saturation ≤92%
Ventilation via facemask with pressure below 20 cmH2O
Secondary endpoint:
lowest oxygen saturation
Study end

17. Data collection

Demographic and clinical data that were collected included age, weight, height, gender, indication for RSII, and baseline oxygen saturation. Adequate preoxygenation was defined as patient cooperation with breathing via tight-fitting facemask for 3 minutes that facilitated successful capnographic monitoring. The primary outcome was the incidence of hypoxemia, defined as oxygen saturation (SpO_2) ≤92%. The secondary outcomes were the time to desaturation during RSII, the lowest SpO_2, and complications of RSII. Procedure time was defined as the duration from the end of asleep oxygenation until achievement of the primary endpoint. If primary endpoint was hypoxemia, procedure time was called time to desaturation. If primary endpoint was successful intubation, procedure time was called time to successful intubation. Complication was evaluated after successful intubation, including bradycardia, hypotension, airway injury, and pulmonary aspiration. Sign of regurgitation of gastric content was recorded.

18. Statistical analysis plan

Statistical analysis was performed using SPSS Statistics version 21 (SPSS, Inc.; IBM Corporation, Armonk, NY, USA). Demographic and clinical data are reported using descriptive statistics. Continuous variables are reported as mean plus/minus standard deviation for normally distributed data (Student's *t*-test), and as median and interquartile range for non-normally distributed data (Mann-Whitney U test). Categorical variables are reported as number and percentage (chi-square test or Fisher's exact test). Incidence of desaturation, time to primary endpoint, and lowest SpO_2 were compared between two groups. Survival analysis for time to the primary endpoint is described by Kaplan-Meier curve with log-rank test. *Post hoc* analysis was performed in patients considered to be at

high risk for desaturation. A *p*-value (2-sided) less than 0.05 was considered to be statistically significant.

19. **Recruitment of participants:** Written informed consent was taken from the parent(s) or legal guardian(s) of all included participants during February 2020 to March 2021. The families had the right to withdraw from the study at any time.
20. **Patient protection:** All the investigators involved in this study will conduct the study in compliance with the Declaration of Helsinki. Identification of participant is made by the registration number of the study.

21. References

1. Gencorelli FJ, Fields RG, Litman RS. Complications during rapid sequence induction of general anesthesia in children: a benchmark study. Paediatr Anaesth 2010;20(5):421-4.
2. Tan E, Loubani O, Kureshi N, et al. Does apneic oxygenation prevent desaturation during emergency airway management? A systematic review and meta-analysis. Can J Anaesth 2018;65(8):936-49.
3. Kemper ME, Buehler PK, Schmitz A, et al. Classical versus controlled rapid sequence induction and intubation in children with bleeding tonsils (a retrospective audit). Acta Anaesthesiol Scand 2020;64(1):41-7.
4. Sun J, Li XH, Zuo YX. Comparison of Incidence of hypoxia during modified rapid sequence induction and an alternative technique: a prospective randomized controlled trial. Int J Clin Exp Med 2015;8(9):16231-7.
5. Kerrey BT, Rinderknecht AS, Geis GL, et al. Rapid sequence intubation for pediatric emergency patients: higher frequency of failed attempts and adverse effects found by video review. Ann Emerg Med 2012;60(3):251-9.
6. Overmann KM, Boyd SD, Zhang Y, et al. Apneic oxygenation to prevent oxyhemoglobin desaturation during rapid sequence intubation in a pediatric emergency department. Am J Emerg Med 2019;37(8):1416-21.

7. Park RS, Rattana-Arpa S, Peyton JM, et al. Risk of Hypoxemia by Induction Technique Among Infants and Neonates Undergoing Pyloromyotomy. Anesth Analg 2021;132(2):367-73.
8. Rinderknecht AS, Mittiga MR, Meinzen-Derr J, et al. Factors associated with oxyhemoglobin desaturation during rapid sequence intubation in a pediatric emergency department: findings from multivariable analyses of video review data. Acad Emerg Med 2015;22(4):431-40.
9. Lyons C, Callaghan M. Uses and mechanisms of apnoeic oxygenation: a narrative review. Anaesthesia 2019;74(4):497-507.
10. Lyons C, Callaghan M. Apnoeic oxygenation in paediatric anaesthesia: a narrative review. Anaesthesia 2021;76(1):118-27.
11. Else SDN, Kovatsis PG. A Narrative Review of Oxygenation During Pediatric Intubation and Airway Procedures. Anesth Analg 2020;130(4):831-40.
12. Holyoak RS, Melhuish TM, Vlok R, et al. Intubation using apnoeic oxygenation to prevent desaturation: A systematic review and meta-analysis. J Crit Care 2017;41:42-8.
13. White LD, Melhuish TM, White LK, et al. Apnoeic oxygenation during intubation: a systematic review and meta-analysis. Anaesth Intensive Care 2017;45(1):21-7.
14. Soneru CN, Hurt HF, Petersen TR, et al. Apneic nasal oxygenation and safe apnea time during pediatric intubations by learners. Paediatr Anaesth 2019;29(6):628-34.
15. Napolitano N, Laverriere EK, Craig N, et al. Apneic Oxygenation As a Quality Improvement Intervention in an Academic PICU. Pediatr Crit Care Med 2019;20(12):e531-e7.
16. Humphreys S, Lee-Archer P, Reyne G, et al. Transnasal humidified rapid-insufflation ventilatory exchange (THRIVE) in children: a randomized controlled trial. Br J Anaesth 2017;118(2):232-8.
17. Riva T, Pedersen TH, Seiler S, et al. Transnasal humidified rapid insufflation ventilatory exchange for oxygenation of children during apnoea: a prospective randomised controlled trial. Br J Anaesth 2018;120(3):592-9.
18. World Health Organization. Oxygen therapy for children: a manual for health workers. Geneva: World Health Organization; 2016 2016.

Article information: https://dx.doi.org/10.21037/tp-21-484