Nasal High-Flow Therapy vs Standard Care During Neonatal Endotracheal Intubation

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SUMMARY

In this randomized controlled trial, nasal high-flow therapy was compared with standard care (no nasal high-flow therapy or supplemental oxygen) in neonates undergoing oral endotracheal intubation at two neonatal intensive care units. The primary outcome was successful intubation on the first attempt without physiological instability (defined as an absolute decrease in the peripheral oxygen saturation of >20% from the pre intubation, baseline level or bradycardia with a heart rate of <100 beats per minute) in the infant. At the time of intubation, infants had a median postmenstrual age of 27.9 weeks and a median weight of 920 g. The primary intention-to-treat analysis included the outcomes of 251 intubations in 202 infants; 124 intubations were assigned to the high-flow group and 127 to the standard-care group. A successful intubation on the first attempt without physiological instability was achieved in 62 of 124 intubations (50%) in the high-flow group and in 40 of 127 intubations (31.5%) in the standard-care group (adjusted risk difference, 17.6 percentage points; 95% CI, 6.0 to 29.2), for a number needed to treat of 6 (95% CI, 4 to 17) for 1 infant to benefit. Successful intubation on the first attempt regardless of physiological stability was accomplished in 68.5% of the intubations in the high-flow group and in 54.3% of the intubations in the standard-care group (adjusted risk difference, 15.8 percentage points; 95% CI, 4.3 to 27.3). The authors concluded that among infants undergoing endotracheal intubation at two Australian tertiary neo-natal intensive care units, nasal high-flow therapy during the procedure improved the likelihood of successful intubation on the first attempt without physiological instability in the infant.

COMMENTARIES

Evidence-based Medicine Viewpoint

A recent randomized controlled trial (RCT) compared the success of endotracheal intubation (*Outcome*) in preterm neonates requiring intubation (*Population/Problem*) using either high-flow oxygen delivered through the nose (*Intervention*), or usual care i.e., no high flow or supplemental oxygen (*Comparison*) [1]. The RCT was conducted in two tertiary-level neonatal intensive care units (NICU) in Australia, over a period of 30 months.

Briefly, neonates requiring oral endotracheal intubation were eligible for inclusion in the trial. Those with life-threatening situations (necessitating emergency intubation, or having bradycardia) were excluded, as were those requiring nasal endotracheal intubation, those having contraindications to nasal high-flow oxygen, cyanotic congenital cardiac defects, or maternal/neonatal COVID-19 infection. The informed consent procedure allowed prospective (even antenatal) consent where possible, although retrospective consent was also permitted. The precise method for screening potentially eligible participants was not described.

Following randomization, neonates allocated to high-flow oxygen underwent removal of any pre-existing respiratory support interface, and insertion of nasal cannulae. They received oxygen at 8 L/min, targeting the pre-procedure fractional oxygen concentration (FiO_2), with the provision to increase it to 100% if transcutaneous saturation fell below 90%. High flow oxygen was delivered throughout the intubation process and terminated when the 'intubation attempt' ceased. Neonates in the comparison group did not receive high-flow or supplemental oxygen. In both groups, transcutaneous oxygen saturation was monitored using a pulse oximeter set to its highest sensitivity.

The sample size was calculated to detect an increase in intubation success from the baseline 30% to 50%, with alpha error 0.05 and beta error 0.10. To achieve this, a total of 246 intubations were planned.

At randomization, the neonates were comparable with respect to post-menstrual age, gestational age, birth weight, mode of delivery, proportion with twin deliveries, gender ratio, place of delivery, and 5-minute Apgar score. Neonates in the intervention group had a median age of 7 hours at intubation, whereas it was 13 hours among those in the comparison group. However, the confidence intervals were wide and overlapping. The FiO_2, respiratory support,

oxygen saturation, and indication for intubation, were all comparable between the groups. About half the intubating personnel in each group had performed >20 similar procedures previously.

The primary outcome was 'intubation success,' defined as intubation at the first attempt without physiological destabilization. The definition included correct insertion of the endotracheal tube (confirmed by detecting exhaled CO_2 with a detector device), without fall in oxygen saturation >20% from the baseline, or heart rate <100/minute. The time interval between insertion of the laryngoscope beyond the lips, to its removal, was counted as the duration of the intubation attempt.

Secondary outcomes were oxygen saturation during intubation, time to desaturation, duration of desaturation, duration of intubation attempt, number of intubation attempts, serious adverse events (defined as need for chest compressions, epinephrine within an hour, pneumo-thorax, or mortality within 72 hours). The results of the RCT are summarized in **Table I**.

CRITICAL APPRAISAL

The trial randomized eligible neonates using a computer-generated, block randomization method (with variable block sizes), stratified by trial site, post-menstrual age, and pre-medication use for intubation. However, the unit of randomization was 'intubation episode' and not 'infant', in the sense that infants undergoing multiple intubations could be re-enrolled if the repeat episode was >7 days after the preceding attempt, or the use of premedication differed from the preceding attempt. Allocation concealment was achieved by randomizing at the bedside, using a secure, password-protected internet based system. These procedures and baseline similarity of the groups suggested a low risk of bias.

There was no blinding of those performing the intubations, or those recording the outcomes. This could be

Table I Summary of the Results

Intervention vs Comparison

Primary outcome

- Intubation success (without destabilization)[a]: 62/124 vs 40/127
  - Intubation success (irrespective of destabilization)[a]: 85/124 vs 69/127
  - Proportion without destabilization[a]: 79/124 vs 64/127
  - Proportion without desaturation >20% from baseline: 89/124 vs 77/127
  - Proportion without bradycardia (<100/min): 113/124 vs 111/127

  Subgroup analysis
  - Post-menstrual age: neonates ≤28wk[a]: 34/64 vs 23/66; >28 wk[a]: 28/60 vs 17/61
  - Use of premedication Yes[a]: 50/92 vs 30/93; No: 12/32 vs 10/34
  - Intubator's experience: <20 previous intubations[a]: 30/61 vs 8/51; ≥20 previous intubations: 32/63 vs 32/76

Secondary outcomes

- Median (IQR) oxygen saturation during intubation[a]: 94 (83,98), *n*=120 vs 89 (79,95), *n*=126
- Proportion with desaturation: 35/124 vs 50/127
- Mean (SD) time to desaturation (sec)[a]: 44.3 (19.5), *n*=34 vs 35.5 (19.5), *n*=50
- Mean (SD) duration of desaturation (sec): 65.0 (35.1), *n*=34 vs 63.6 (38.9), *n*=47
- Median (IQR) duration of intubation attempt (seconds):
  - First attempt: 50.5 (33.5, 69.0), *n*=124 vs 46.0 (33.0, 66.0), *n*=127
  - All attempts: 58.0 (36.0, 95.0), *n*=123 vs 68.0 (35.0, 125.0), *n*=127
- Median (IQR) number of intubation attempts: 1 (1,2), *n*=124 vs 1 (1,2), *n*=127
- Proportion with bradycardia: 11/124 vs 16/127
- Mean (SD) time to bradycardia (sec): 39.4 (22.9), *n*=11 vs 39.9 (19.9), *n*=15
- Mean (SD) duration of bradycardia (sec): 26.6 (20.7), *n*=11 vs 31.3 (23.3), *n*=15
- Serious adverse events
  - Need for chest compressions or epinephrine: 0/124 vs 2/125
  - Pneumothorax within 72 h: 2/124 vs 6/127
  - Mortality within 72 h: 1/124 vs 3/125

[a]*Statistically significant.*

a source of bias in this RCT, as the impact of foreknowledge of the allocation, on the measurement of the outcome cannot be judged. However, there were no major protocol deviations reported, and the investigators used intention-to-treat analysis. For most outcomes, almost all the randomized participants were included in the analysis, and the results do not appear to be biased by missing data. The methods used for measuring the outcomes appear to be appropriate, and ascertainment of outcomes did not differ in the two groups. The data were reported as specified a priori, and there is no suggestion that data presentation was influenced by the results obtained. Overall, the RCT may be classified as having low to moderate risk-of-bias, fostering reasonably high confidence in the reported results.

The RCT included several noteworthy methodological refinements. Strict definitions were used for the various outcomes recorded. Sensitive measurements such as oxygen saturation recording and confirmation of place-ment of the nasal cannulae, were done using sophisticated instruments. In addition to recording of outcomes by personnel present at the site, the entire procedure was videographed, and reviewed independently. Discrepancies between on-site versus observations based on video-recording were resolved by a different assessor. An independent data and safety monitoring board (DSMB) evaluated patient safety after each quartile of the population sample was enrolled, and an independent interim data analysis was planned midway through the trial.

Despite these, there are a few issues raising concern. It appears that the comparison group did not receive any oxygen during the intubation procedure. The rationale for this is unclear, especially because the indication for intubation itself was hypoxia in nearly 60% of the neonates, and apnea in another 20%. In such a population, omission of oxygen during intubation appears to put the com-parison group neonates at a disadvantage. As the study was designed to evaluate the efficacy of high-flow oxygen therapy, it would seem reasonable to provide the comparison group neonates at least (low-flow) blow-by oxygen delivered close to the nose.

The intervention group neonates required approximately 10 seconds for securing the high-flow nasal cannulae, during which time, they would have received high-flow oxygen for part or the entire duration. However, this duration of time was not factored into the total duration of delivering high-flow oxygen, which could tilt the results is favor of the intervention.

Further, 90% neonates in both groups were receiving continuous positive airway pressure (CPAP) at randomization. Presumably CPAP was delivered using oxygen; this is borne out by the high baseline FiO_2 in both groups. As supplemental oxygen was discontinued in the comparison group, most likely CPAP also had to be discontinued in them. In contrast, high-flow oxygen delivered at 8.0 L/min through nasal cannulae in the intervention group could have had some positive airway pressure effect, which was denied to the comparison group. These factors suggest that the comparison group neonates were at a disadvantage from the time of randomization to intubation. The influence of this on the overall results is unclear.

As in the real-word scenario, considerable leeway was provided to the intubating personnel with regards to pre-oxygenating the neonates, use of video laryngoscopy, and most important, the duration of each intubation attempt. This flexibility within a RCT is likely to have resulted in a scenario, wherein intubation attempts in individual neonates continued until desaturation occurred, rather than being ceased after a pre-specified time had elapsed. Thus, intubation time exceeded the suggested limit of 30 seconds [2] in both groups by more than 15 seconds. It can be argued that in a RCT, the duration of each intubation attempt should have been capped by a prespecified time limit. As statistically significant differences in successful intubation were observed only among less-experienced intubators, but not among more experienced personnel, this methodological aspect should not have been overlooked. However, to be fair, there was no difference in the actual duration of intubation (first attempt or overall) in the two groups.

In this RCT, although 462 neonates were eligible for inclusion, 161 (34.8%) were not enrolled because either the "researcher was unavailable" or "not notified." The reasons for (and impact of) these exclusions are unclear. If these occurred due to being out of routine working hours, it could have created a selection bias.

CONCLUSION

This well-designed RCT suggested that high-flow oxygen therapy delivered through nasal cannulae resulted in greater success in oral intubation, better oxygen saturation during the procedure, and longer time-to-desaturation, in preterm neonates requiring endotra-cheal intubation, compared to those who did not receive supplemental oxygen. However, some methodological issues, and the diversity of the study setting (compared to the usual settings in India) suggest that these apparently impressive results are insufficient for a blanket change in local clinical practice.

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REFERENCES

1. Hodgson KA, Owen LS, Kamlin COF, et al. Nasal high-flow

therapy during neonatal endotracheal intubation. N Engl J Med. 2022;386:1627-37.
2. Lane B, Finer N, Rich W. Duration of intubation attempts during neonatal resuscitation. J Pediatr. 2004;145:67-70.

Neonatologist's Viewpoint

Endotracheal intubation is one of the common procedures in neonatal intensive care units (NICUs) and is often realized as an emergency procedure. Hypoxemia, bradycardia, and cardiac arrest are serious adverse events, and the reported incidence in NICUs varies between 5-36% [1,2]. Neonates, especially preterms, are particularly predisposed due to their low functional residual capacity. Several strategies like use of video laryngoscope, premedication, selection of experienced operators, and use of checklists have been evaluated to ensure safe intubations [3-5]. Pre-oxygenation before intubation has been a standard of care in many adult ICUs [6], and in earlier recommendations of neonatal resuscitation.

High flow oxygen (HFO) is a device to provide heated and humidified high flow oxygen with very soft nasal cannula at titratable oxygen concentration (FiO2). In the current study done in Australia on preterm babies, the investigators report greater success in intubation rate in first intubation with the use of high flow oxygen (50%), using Vapotherm, immediately after removing the pre-exiting respiratory support (CPAP) interface, compared to standard intubation procedure with no supplemental oxygen (31.5%). The study describes outcomes from an innovative strategy to ensure successful intubation with-out any adverse outcomes. It was an unblinded randomized controlled trial, where video reviews of all the intubations were done, to assess the primary outcome. Per protocol analysis was not performed. The consent was taken antenatally; however, retrospective consent was also approved.

It was a well-planned and well executed study, and presents some thought provoking issues. Out of the 462 eligible neonates, nearly 50% (204) were not included in randomization, thus raising concerns of selection bias at enrolment. The characteristics and sickness scores of non-enrolled neonates would be interesting to look at. Use of video laryngoscopy is known to facilitate intubations and this factor in both groups was based on clinicians' discretion. It would be of interest to know the proportion of intubations that were performed using video laryngo-scope in the two groups.

Considering the current evidence, tight control of oxygenation for preterm neonates in the delivery room is prudent; the authors state that 25% of enrolled intubations were performed in delivery room, in the immediate period after birth. Use of high flow at 8L/min even for brief period during intubation, can be a potential source of harm due to hyperoxygenation, in the real world scenario of delivery room intubation. Of note, 90% of neonates before intubation were on CPAP in the study cohort, which raises a logistic concern of using or even just keeping both the high flow equipment as well as CPAP equipment and tubing in most of the resource-limited settings, like India.

Intubation by indication is one factor which can determine the success or failure of the procedure, and in this study 15% indications for intubations were non-specific. This may have implications on generalizability of this intervention in dissimilar settings. The authors state that mechanical failure of the nasal high flow device and dislodgment of nasal cannula were documented but not deemed to be protocol violation; however, such mecha-nical failures could be expected in settings where a skilled person may be the only person responsible for the management of the neonate. The use of premedication was 50.3% in high flow group compared to 34.8% in standard group; many neonatal units in developing world may still not be proficient with the use of premedication before intubation. The contribution of premedication to success of intubations remains to be explored in this context. Lastly, peripheral oxygen saturation can be sometimes misleading and use of EtO2 would be a better guide as a marker of saturation as outcome measure and efficacy of intubation [7,8].

HFO can also be delivered by use of the CPAP used for respiratory distress pre-intubation, but with increased FiO2 only for pre-oxygenation instead of removing CPAP and trying a new device like Vapotherm for pre-oxygenation for intubation. It would be worthwhile conducting another trial comparing successful intubation while continuing CPAP with higher FiO2 to HFO after removing CPAP interface and evaluate similar outcomes again. One should also be cognizant that Vapotherm, which is the device used in this study, is still not available universally in many neonatal care units. Other high flow oxygen devices that are very commonly used in India also need to be evaluated for aiding pre-oxygenation in success of intubation. We also need to evaluate how free flow oxygen with varying oxygen concentration through blender compares to Vapotherm or other HFO devices in reducing adverse events during neonatal intubations.

The study has raised the important question of devising a strategy for improving successful neonatal intubations. The external validity and generalizability of this intervention in other dissimilar settings remains to be evaluated. Whether improving the skills in existing standard operating procedure using simulators and/or video laryngoscopes for intu-bation is cost effective in resource limited settings is also to be deliberated upon. Till we have these questions answered, as

per results of this study, neonatal units may consider initiating Vapotherm as HFO for pre-oxygenation for successful intubation without physiological instability.

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REFERENCES

1. Dongara AR, Modi JJ, Nimbalkar SM, et al. Proficiency of residents and fellows in performing neonatal intubation. Indian Pediatr. 2014;51:561-64.
2. Saisamorn F, Sriwiset C, Sirisomboon R, et al. Indications and outcomes of neonatal intubation: A single-center, prospective study in a middle-income country. Pediatr Neonatol. 2022;63:125-30.
3. Jaber S, Amraoui J, Lefrant JY, et al. Clinical practice and risk factors for immediate complications of endotracheal intubation in the intensive care unit: a prospective, multiple-center study. Crit Care Med. 2006; 34:2355-61
4. Hatch LD, Grubb PH, Lea AS, et al. Interventions to improve patient safety during intubation in the neonatal intensive care unit. Pediatrics. 2016;138:e20160069.
5. Marx A, Arnemann C, Horton RL, et al. Decreasing neo-natal intubation rates: trends at a community hospital. J Neonatal Nursing. 2016; 22; 231-35.
6. Ricard JD. Hazards of intubation in the ICU: role of nasal high flow oxygen therapy for preoxygenation and apneic oxygenation to prevent desaturation. Minerva Anestesiol. 2016; 82:1098-106.
7. Farmery AD, Roe PG. A model to describe the rate of oxyhaemoglobin desaturation during apnoea. Br J Anaesth. 1996; 76:284-91.
8. Hanouz JL, Gérard JL, Fischer MO. Nasal high-flow preoxygenation for endotracheal intubation in the critically ill patient? Con. Intensive Care Med. 2019; 45:526-28.

Pediatrician's Viewpoint

Endotracheal intubation is a common procedure in a neonatal intensive care unit (NICU). Though, over the years, neonatal care has become more noninvasive and endotracheal intubations are more often preferred to be avoided. Nonetheless, intubations become essential when a sick neonate deteriorates on a noninvasive mode of ventilation or during delivery room care. This randomized control trial, which was conducted at two tertiary centers of Australia, compared the efficacy of nasal high flow therapy for successful attempts at oral intubation. The control group was given standard care during intubation without nasal high flow therapy. The randomization done in the study is robust and safety was monitored regularly during the trial. The trial results are encouraging as physiological instability (desaturation and/or bradycardia) during intubation is the major reason behind failed intubation attempts [1,2]. The intubations at delivery room were also included in the trial, which are done without premedication. The mean postmenstrual age of study population was 27.9 week and weight was 920 gram. The use of video recording during intubations has added to the objectivity of the outcomes studied.

The use of high flow therapy is common in Indian NICUs, nowadays. The neonates are primarily managed on noninvasive ventilation (nCPAP or High flow therapy). The need of intubation itself suggests that the neonate is critically sick and therefore successful intubation in a smaller number of attempts is what is aimed at by the treating pediatrician/neonatologist. This study is encouraging in Indian context as study population is relatively mature, which is the neonatal population mainly managed at district SNCUs (special care neonatal units). The availability of high flow nasal cannula may not be universal in district level SNCUs or government teaching institutes. The limitation of this study is treatment assigned was not concealed, and the number of intubations was taken into consideration and not individual neonates. Though this was minimized considering reintubations, which had an interval of one week.

Various studies have proven that experience of successful intubations further increases the confidence level of healthcare professional attempting intubation [3,4]. Thus, use of a simple equipment during intubation in order to improve efficacy should be attempted in Indian settings as well.

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REFERENCES

1. Foglia EE, Ades A, Napolitano N, et al. Factors associated with adverse events during tracheal intubation in the NICU. Neonatology. 2015;108:23-29.
2. Venkatesh V, Ponnusamy V, Anandaraj J, et al. Endotracheal intubation in a neonatal population remains associated with a high risk of adverse events. Eur J Pediatr. 2011;170:223-27.
3. Saisamorn F, Sriwiset C, Ratree Sirisomboon R, et al. Indications and outcomes of neonatal intubation: A single-center, prospective study in a middle-income country. Pediatr Neonatol. 2022;63:125-30.
4. Leone TA, Rich W, Finer NN. Neonatal intubation: Success of pediatric trainees. J Pediatr. 2005;146:638-41.