Nasal high-flow therapy to Optimise Stability during Intubation: the NOSI pilot trial

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ABSTRACT

Objective In adult patients with acute respiratory failure, nasal high-flow (NHF) therapy at the time of intubation can decrease the duration of hypoxia. The objective of this pilot study was to calculate duration of peripheral oxygen saturation below 75% during single and multiple intubation attempts in order to inform development of a larger definitive trial.

Design and setting This double-blinded randomised controlled pilot trial was conducted at a single, tertiary neonatal centre from October 2020 to October 2021.

Participants Infants undergoing oral intubation in neonatal intensive care were included. Infants with upper airway anomalies were excluded.

Interventions Infants were randomly assigned (1:1) to have NHF 6 L/min, FiO_2 1.0 or NHF 0 L/min (control) applied during intubation, stratified by gestational age (<34 weeks vs ≥34 weeks).

Main outcome measures The primary outcome was duration of hypoxaemia of <75% up to the time of successful intubation,

Results 43 infants were enrolled (26 <34 weeks and 17 ≥34 weeks) with 50 intubation episodes. In infants <34 weeks' gestation, median duration of SpO_2 of <75% was 29 s (0–126 s) vs 43 s (0–132 s) (p=0.78, intervention vs control). Median duration of SpO_2 of <75% in babies ≥34 weeks' gestation was 0 (0–32 s) vs 0 (0–20 s) (p=0.9, intervention vs control).

Conclusion This pilot study showed that it is feasible to provide NHF during intubation attempts. No significant differences were noted in duration of oxygen saturation of <75% between groups; however, this trial was not powered to detect a difference. A larger, higher-powered blinded study is warranted.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The SHINE trial (Stabilisation with nasal High flow during Intubation of NEonates) has recently demonstrated that nasal high-flow (NHF) therapy during intubation increases the rate of intubation without physiological instability compared with standard care.

WHAT THIS STUDY ADDS

⇒ This is the first blinded study of NHF therapy in infants. This study measures cumulative hypoxia rather than a binary outcome of oxygen saturation and bradycardia. It includes all intubation attempts and provides baseline data for powering a future trial.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Cumulative hypoxia is of greater clinical significance than a potentially brief one-time reduction in oxygen saturation below a certain target. A blinded trial using cumulative hypoxia as a primary outcome could help neonatologists decide whether NHF therapy is warranted beyond the first intubation attempt.

INTRODUCTION

Nasal high-flow (NHF) oxygen therapy is a standard, evidence-based treatment as primary respiratory therapy and postextubation support in spontaneously breathing infants.[1 2] Among adults, NHF has also been shown to maintain blood oxygenation for a significant period of time during apnoeic conditions, including intubation.[3] Neonatal intubation is often associated with repeated attempts and is often associated with physiological instability.[4] Hypoxia (as defined by SpO_2 of <90%) has been reported in up to 94% of infants during intubation, particularly those who are preterm.[5] The recently completed SHINE trial has shown NHF was associated with increased success rates on first intubation attempt.[6] Our objective was to determine whether apnoeic oxygenation with NHF[7] would reduce the duration of hypoxia in neonates undergoing intubation.

METHODS

Study design

This was a single-centre, double-blinded, randomised controlled feasibility trial. It was conducted at the National Maternity Hospital, a tertiary perinatal centre with approximately 8000 deliveries and 1500 admissions per year, from October 2020 to October 2021.

Participants

Infants with respiratory failure undergoing oral endotracheal intubation in the neonatal intensive care unit (NICU) were eligible for inclusion. Our NICU performs oral intubation as standard. Hypoxaemic acute respiratory failure was defined as clinical signs (worsening tachypnoea and recession), acidosis pH of <7.2 on two gases of ≥30 min apart, oxygen: FiO_2 >0.4 to keep SpO_2 >90% for >30 min, carbon dioxide: $PaCO_2$ >9 kPa on two blood gases of ≥30 min apart, apnoea: recurrent apnoea treated with positive pressure ventilation. Infants were excluded if they had upper airway

anomalies contraindicating the use of NHF therapy. Infants were also excluded if the treating clinician deemed exclusion necessary. As this was a pragmatic study to establish cumulative duration of hypoxia, infants could be randomised more than once.

Randomisation

Infants were randomly assigned (1:1) to intervention or control groups, stratified by gestational age (<34 weeks vs ≥34 weeks). The group assignment schedule was generated using a random numbers table,[8] in blocks of 4. Group allocation was contained in sequentially numbered, opaque envelopes.

Intervention

Infants randomised to the intervention group had appropriately sized, NHF cannulae (Optiflow Junior, Fisher and Paykel, Auckland, New Zealand) placed in their nares for the duration of each intubation attempt. The NHF (Fabien Therapy Evolution; Acutronic Medical Systems AG, Hirzel, Switzerland) was set at a flow of 6 L/min and FiO_2 of 1.0 in keeping with local unit practice. The cannulae were temporarily secured to the baby's face using the inner half of the hydrocolloid adhesive pad supplied with the device to facilitate quick removal following intubation and in between attempts. A mannequin trial conducted prior to the pilot study demonstrated that an effective mask seal was not possible with NHF cannulae in situ. The NHF cannulae were removed after each attempt and reattached at the start of any subsequent attempts. Infants randomised to the control group had appropriately sized NHF cannulae (Optiflow Junior, Fisher and Paykel) placed, but no flow administered during laryngoscopy. All infants received premedication with fentanyl, atropine and suxamethonium as per standard unit practice. The size of the endotracheal tube, choice of direct or video laryngoscopy, and criteria for stopping each attempt were at the discretion of the attending consultant. Endotracheal tube placement was confirmed by a colorimetric exhaled carbon dioxide detector (Pedicap; Nellcor Puritan Bennett, Pleasanton, California, USA). A chest radiograph was performed to confirm tube position.

Blinding

Infants in both groups had nasal cannulae placed in their nares and a suction tube placed adjacent to their head to blind the noise of air flow. For the first 10 study participants, intubating clinicians were asked if they could identify which study arm the baby was randomised to, but they were unable to in all cases, indicating sufficient blinding. Additionally, the NHF device interface was covered by study personnel randomising the baby to conceal flow settings. Data were transferred using VSCaptureMP, a C# application designed to capture data from Phillips Intellivue monitors. Haemodynamic data were written on a second-by-second basis to a .csv file including a timestamp, heart rate as measured by pulse oximeter, heart rate as measured by ECG leads, oxygen saturations for each probe attached, perfusion index, invasive blood pressure and respiratory rate. The study was blinded for data analysis.

Outcome measures

The primary outcome was the length of time in seconds where infants had SpO_2 below 75% during laryngoscopy and attempted intubation. This was determined by allowing for a 20% drop in oxygen saturations from an expected preintubation oxygen saturation of 95%, the upper threshold of the unit preterm oxygen saturation target as informed by the SUPPORT (Surfactant, Positive Pressure, and Oxygenation Randomized Trial) trial.[9] If more than one intubation attempt was required, the cumulative time below 75% SpO_2 during laryngoscopy and attempted/successful intubation was recorded.

Secondary outcome variables included markers of oxygenation quality including duration (seconds) of SpO_2 of >85% and 65%, lowest oxygen saturation during procedure, bradycardia defined as heart rate of <80 beats/min, lowest heart rate, number of

Table 1 Primary and secondary outcomes by treatment group

Primary outcome	<34 weeks (n=33)			≥34 weeks (n=17)		
	NHF (n=15)	Standard care (n=18)	P value	NHF (n=7)	Standard care (n=10)	P value
Median (IQR) time peripheral oxygen saturation below 75% (s)	29 (0–126)	43 (0–132)	0.78	0 (0–32)	0 (0–32)	0.90
Secondary outcomes (haemodynamics)						
Lowest SpO_2 during procedure	58 (33–81)	52 (6–75)	0.47	80 (54–92)	89.5 (66-95)	0.65
Median time SpO_2 <85% (s)	70 (20–211)	66 (14–203)	0.82	18 (0–55)	0 (0–38)	0.74
Median time SpO_2 <65% (s)	22 (0–63)	21.5 (0–87)	0.89	0 (0–6)	0 (0–3)	0.42
Median SpO_2 during first intubation attempt	83 (68–90)	83 (71–91)	0.85	95 (84–98)	95 (79–98)	0.94
Median SpO_2 during second intubation attempt	87 (57–92)	84 (51–97)	0.70	91.5 (89.5–93.5)	89 (86–92)	0.67
Median SpO_2 during third and subsequent intubation attempts	80.75 (72–77.5)	75 (72–93)	0.22	NA	NA	
Median time to SpO_2 <75% (all attempts)	58 (48–69)	53 (37–72)	0.37	53 (52–54)	57 (54–65)	0.59
Lowest heart rate during procedure	141 (125–159)	149 (121–160)	0.17	144 (140–165)	120 (100–175)	0.71
Bradycardia defined as heart rate below 80 beats/min during procedure	1	1		0	0	
Successful intubation following first attempt without physiological instability as per SHINE trial, n (%)	4 (26)	3 (16)	0.48	3 (42)	4 (40)	0.9
Secondary outcomes (technical)						
Successful intubation on first attempt	8/15	9/18	0.84	5/7	8/10	0.68
Number of intubation attempts	1 (1–2)	1.5 (1–4)	0.60	1 (1–2)	1 (1–2)	1
Time to successful intubation (s)	93 (72–147)	85 (34–122)	0.43	86 (49–148)	60 (51–75)	0.40
Operator experience (defined by role) (n=57)						
Junior registrar (<1 year's clinical experience in NICU as a registrar)	14	15		7	7	
Subspecialty trainee in neonatology	1	3		0	3	
Consultant	3	4		0	0	

NA, not applicable; NHF, nasal high flow; NICU, neonatal intensive care unit.
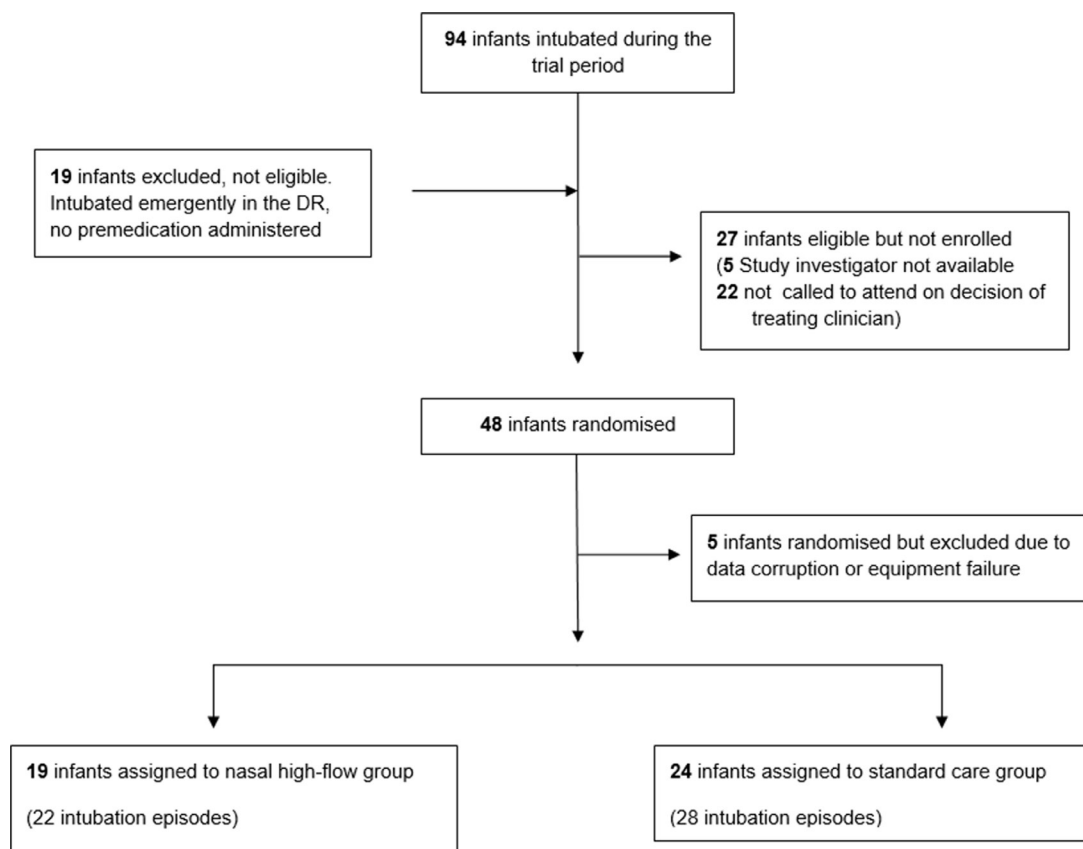
Figure 1 Flow diagram of recruitment. Numbers presented indicated first randomisation per infant. DR, delivery room.

intubation attempts, time to successful intubation (seconds) and mortality rate by day 28 following recruitment to study.

Sample size

At the time of study design, there were no published data available to determine cumulative length of hypoxia during intubation, and this pilot trial was designed to power a future multicentre study of NHF therapy. A pragmatic sample size of 50 intubation episodes was chosen to establish the total duration of hypoxia during intubation attempt(s).

Data collection and management

We collected demographic data including age, sex, weight, mode of delivery, antenatal corticosteroids and indication for intubation. Intubation factors such as operator experience and use of video or direct laryngoscopy were also recorded. Outcomes included duration of SpO_2 of <75%, as well as additional markers of oxygenation quality including duration of low oxygen saturation and bradycardia (table 1). We collected data on the number of intubation attempts and time to successful intubation (seconds).

Statistical methods

Data were formatted and aggregated using anonymised study IDs. Due to non-normality of the data, non-parametric Wilcoxon rank-sum tests were used to compare the control and intervention groups for the outcomes. We carried out a post hoc regression analysis to assess rates of desaturation between groups. Intention-to-treat analysis was used. Statistical analysis was performed before unblinding to allocation using Matlab V.2019a.

Analysis of secondary outcomes

The χ^2 test (or Fisher's exact test as appropriate) was used for secondary binary outcomes. Continuous variables were compared using the Mann-Whitney U test.

RESULTS

Forty-eight infants were recruited to the study from October 2020 to October 2021. In five instances, no data were available due to data corruption or equipment failure. Recruitment to the pilot study ceased once 50 intubation episodes (from 43 infants) with adequate data were obtained. There were 26 infants <34 weeks recruited (33 intubation episodes). No repeat intubations were required in the 17 infants ≥34 weeks. Data on enrolment are outlined in figure 1. Baseline characteristics are presented in table 2. Overall, there were 30 babies with SpO_2 of <75%, 35 with SpO_2 of <85% and 24 with SpO_2 of <65%. In infants <34 weeks' gestation, median duration of SpO_2 below 75% during intubation was 29 s (0–126 s) vs 43 s (0–132 s) (p=0.78) in the intervention group versus the control group. Median duration of SpO_2 below 75% in infants ≥34 weeks was 0 s (0–32 s) vs 0 s (0–20 s) (p=0.9). For secondary outcomes, see table 1. Both infants with bradycardia of <80 beats/min demonstrated significant hypoxia (SpO_2 of 25% and 32%) prior to onset of bradycardia. Median SpO_2 levels fell below 75% at approximately 1 min in infants <34 and ≥34 weeks who were not intubated in the first minute (see figure 2). Operator experience and use of video versus direct laryngoscopy are reported in table 1.

Figure 2 presents median SpO_2 for the intervention and control groups within each cohort over time. Estimated rate of desaturation in all attempts in the preterm intervention group was 3.9% vs 5.1% with the Chow test for structural stability

Table 2 Baseline demographic and clinical characteristics of study participants

|	Preterm (n=26 infants and 33 intubation episodes)		Term (n=17 infants 17 intubation episodes)	
	High flow 6 L/fraction of inspired oxygen 1.0 (n=12)	Standard care (n=14)	High flow 6 L/fraction of inspired oxygen 1.0 (n=7)	Standard care (n=10)
Median gestational age at birth (weeks)	26.3 (24.3–29.4)	26.9 (24.3–30.6)	38.9 (35.6–41.0)	38.8 (37.0–41.0)
Corrected gestational age at intubation (weeks)	26.9 (25.6–28.6)	28.6 (25.1–30.7)	38.9 (35.6–41.0)	38.8 (37.0–41.0)
Median birth weight (g)	805 (690–1130)	878 (730–1310)	3090 (2965–4155)	3728 (2975–3950)
Median weight at intubation (g)	870 (690–1130)	875 (660–1310)	3090 (2965–4155)	3728 (2975–3950)
Delivery by caesarean section, n (%)	10 (83)	12 (85)	5 (71)	6 (60)
Antenatal steroids given, n (%)	8 (75)	10 (72)	1 (14)	0 (0)
Full course (≥2 doses), n (%)	5 (42)	7 (50)	1 (14)	0 (0)
Female, n (%)	6 (50)	8 (57)	3 (42)	3 (30)
Respiratory support before procedure (n=50)				
CPAP (Continuous Positive Airway Pressure)	14	13	6	8
BiPAP (Bi-level Positive Airway Pressure)	1	5	0	0
Intermittent PPV for apnoea	0	0	1	2
Mortality by day 28 following randomisation, n (%)	3 (25)	4 (28.5)	0 (0)	1 (10)
Fraction of inspired oxygen before randomisation	0.4 (0.4–0.7)	0.4 (0.32–0.55)	0.40 (0.38–0.66)	0.5 (0.3–0.6)
Peripheral oxygen saturation immediately before procedure	97% (94–99)	97% (94–99)	97% (93.5–98.0)	100% (95.5–100)
Laryngoscope used video/direct	3/12	6/12	2/5	3/7

showing a significant difference (p<0.01). Rate of desaturation for the intervention arm was 3.4% every 10 s compared with 4.6% per 10 s for the control arm (p<0.001) for infants <34+0 weeks. We also carried out a post hoc analysis to replicate the primary outcome used in the SHINE trial[6] (20% reduction in SpO_2 from baseline and/or heart rate of <100 beats/min; see table 1.)

DISCUSSION

Neonatal intubation is an essential procedure that all neonatologists need to be competent and proficient in performing. The procedure in this population is complicated not just by the small size of the baby but also by the unique physiology of the newb,orn which leads to decreased reserve and less apnoeic tolerance during laryngoscopy.[10–16] As infants are surviving at lower gestational ages and birth weights than before, the procedure is only likely to become more challenging. As the difficulty increases, procedural experience is decreasing due to greater use of non-invasive ventilation, a reduction in working hours and significantly increased numbers of not just trainees but also consultants.[17–20] In response to this, many strategies have been employed to try and either reduce the need for intubation,[21–23] provide greater stability medically during the procedure[24 25] or improve education and therefore proficiency of the intubator.[26–36] Despite these strategies, intubation remains a problem and by comparison to adult studies our population show high rates of physiological instability and adverse events.[5 37–40]

Our challenge is to keep infants stable during an apnoeic procedure of variable length, difficulty and operator experience. In designing our study, we hypothesised that duration rather than incidence of hypoxia would be of greater clinical significance for the baby and chose this as our primary outcome. Our study
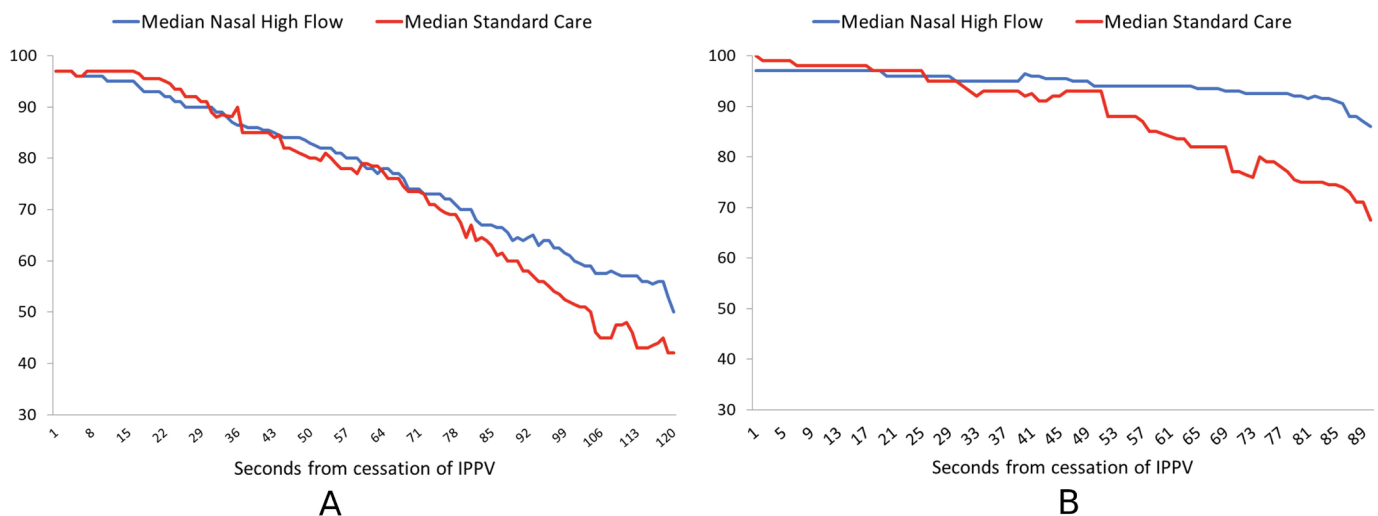
Figure 2 Median SpO_2 from cessation of IPPV for (A) Intubation events for babies <34+0 weeks and (B) intubation events for babies ≥34 weeks. IPPV, intermittent positive pressure ventilation.

was designed as a feasibility study and to provide a measure of cumulative hypoxia in both groups to allow for powering of a larger study, while this study was underpowered it allowed us to calculate background duration of hypoxia in each arm in order to inform a proposed larger study. When we also apply a post hoc analysis using the primary outcome as defined by SHINE[6] (reduction of 20% in SpO_2 and/or bradycardia OF <100 beats/min), our study showed results in the same direction while statistically insignificant.

As described in our methodology, we modified the standard (lengthier) technique for application of the NHF cannulae reducing time taken to secure/remove the cannulae to 2–3 s. This allowed us to carry out a sham procedure, placing the nasal cannulae in the nares without flow in an effort to blind the intubating clinicians (without causing nasal obstruction) before laryngoscopy was commenced.

Our trial aimed to decrease duration of hypoxia; to facilitate this analysis, we chose to include infants who were genuinely apnoeic, following premedication with a muscle relaxant, and did not include intubations in the delivery unit. We also did not include bradycardia in addition to hypoxia in the primary outcome as the incidence of bradycardia following atropine is low. The recently published SHINE trial[6] has demonstrated that using NHF therapy improves the likelihood of successful intubation in the first attempt without physiological instability. The SHINE trial was not designed to evaluate NHF therapy beyond the first intubation attempt, however, or the duration rather than incidence of physiological instability. Many infants will not be intubated on first attempt, and these infants are at higher risk of hypoxia. We used NHF therapy in all intubation attempts rather than just on first attempt. We noted that physiological instability appeared to increase with increasing number of intubation attempts particularly when inexperienced operators were involved, although our numbers are too small to draw definitive conclusions.

In terms of likely mechanisms, we noted that the rate of desaturation appeared to decrease with use of NHF therapy in the preterm infant and postulated that greater success may be related to the increased time allowed for intubation.

Strengths and weaknesses

Our study is the first study of NHF therapy to attempt blinding of NHF during laryngoscopy and intubation. We were able to collect second-by-second physiological data on all intubation attempts, but we did not monitor transcutaneous pO_2, which could provide additional information on hyperoxia. We included both term and preterm infants in our study. Although we did not show a difference in duration of hypoxia across all attempts, the rate of decline in oxygen saturation appeared to be faster in the control group and may be of clinical significance. Variables such as operator experience and use of direct compared with videolaryngoscopy could not be controlled for in this small pilot study. We used an FiO_2 of 1.0 for the intervention, but as the median FiO_2 before intubation was 0.4 in our cohort, it may be more appropriate to follow the guideline as per the SHINE trial (starting at current FiO_2 requirement and increasing as required) for future use of high flow in this setting.

CONCLUSION

In conclusion, we believe this study adds to a growing body of work designed to inform practice in this high-risk procedure in a vulnerable cohort. We have demonstrated that it is feasible to provide NHF therapy to infants during intubation attempts and describe how we adapted the current fixation device in order to quickly transition between attempts. A larger, appropriately powered, blinded trial of NHF therapy beyond the first intubation attempt is warranted as while the SHINE trial has demonstrated efficacy in the first intubation attempt, those infants requiring subsequent attempts represent a subpopulation who warrant further analysis.

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