Intensive Care Med (2014) 40:592–599
DOI 10.1007/s00134-014-3226-7

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High-flow nasal cannula (HFNC) support in interhospital transport of critically ill children

Received: 11 December 2013
Accepted: 20 January 2014
Published online: 15 February 2014

Take home message: This study reports on the use of HFNC therapy in interhospital transport of critically ill children. The increasing use of HFNC was paralleled by a decrease in invasive ventilation initiated by the retrieval team.

Electronic supplementary material
The online version of this article (doi:10.1007/s00134-014-3226-7) contains supplementary material, which is available to authorized users.

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Abstract *Purpose:* Optimal respiratory support for interhospital transport of critically ill children is challenging and has been scarcely investigated. High-flow nasal cannula (HFNC) therapy has emerged as a promising support mode in the paediatric intensive care unit (PICU), but no data are available on HFNC used during interhospital transport. We aimed to assess the safety of HFNC during retrievals of critically ill children and its impact on the need for invasive ventilation (IV). *Methods:* This was a retrospective, single-centre study of children under 2 years old transported by a specialized paediatric retrieval team to PICU. We compared IV rates before (2005–2008) and after introduction of HFNC therapy (2009–2012). *Results:* A total of 793 infants were transported. The mean transport duration was 1.4 h (range 0.25–8), with a mean distance of 205 km (2–2,856). Before introduction of HFNC, 7 % ($n = 23$) were retrieved on non-invasive ventilation (NIV) and 49 % ($n = 163$) on IV. After introduction of HFNC, 33 % ($n = 150$) were retrieved on HFNC, 2 % ($n = 10$) on NIV, whereas IV decreased to 35 % ($n = 162$, $p < 0.001$). No patients retrieved on HFNC required intubation during retrieval, or developed pneumothorax or cardiac arrest. Using HFNC was associated with a significant reduction in IV initiated by the retrieval team (multivariate OR 0.51; 95 % CI 0.27–0.95; $p = 0.032$). *Conclusions:* We report on a major change of practice in transport of critically ill children in our retrieval system. HFNC therapy was increasingly used and was not inferior to low-flow oxygen or NIV. Randomized trials are needed to assess whether HFNC can reduce the need for IV in interhospital transport of critically ill children.

Keywords Transport · Critically ill · Child · Ventilation · High-flow nasal cannulae

Introduction

Respiratory diseases in childhood represent one of the main reasons requiring transfer to a paediatric intensive care unit (PICU) [1]. Traditionally, interhospital transport teams tended to have a very low threshold for intubation and invasive ventilation (IV), given the inherent difficulties of escalating respiratory support whilst being on road or air transport [2]. Intubation and ventilation are associated with intrinsic risks, such as pneumothorax, and endotracheal tube dislocation and obstruction. Patients will require sedation and neuromuscular paralysis for transport, and mechanical ventilation exposes the child to ventilator-induced lung injury (VILI) [3], taking into account that most transport ventilators are not as sophisticated as modern PICU ventilators.

Over the past decade, the increasing use of non-invasive ventilation (NIV) and, more recently, high-flow nasal cannula (HFNC) therapy has led to a reduced need for IV in intensive care units [4]. Given the side effects associated with IV, this approach is promising but the impact on outcome still needs further evaluation [5]. HFNC therapy is a non-invasive supportive air/oxygen therapy that has been used with success in critically ill neonates, children and adults [4, 6]. HFNC can provide a degree of continuous positive airway pressure (CPAP), reduces the work of breathing, and may have additional flow-related benefits such as a reduction in anatomical dead space [7, 8]. In our PICU, HFNC therapy was shown to reduce intubation rates from 37 to 7 % in infants with bronchiolitis, which has been supported by other studies [9–12].

There is little evidence to guide strategies for optimal respiratory management during interhospital transfer [13]. Previous small studies in neonates and children suggest that the use of NIV is safe [14, 15]. To date, there are no data on the use of HFNC therapy during transport of paediatric patients. We present our experience of HFNC therapy used for transporting critically ill children aged below 2 years and report safety and outcome data, as well as the impact of HFNC therapy on successive PICU management of these patients.

Patients and methods

Study design

This was a single-centre, retrospective, observational study investigating critically ill children under 2 years of age who required interhospital transport by our specialized tertiary paediatric retrieval team and who were consecutively admitted to our PICU (Mater Children's Hospital Brisbane, Australia) between 1 January 2005 and 31 December 2012. Children transported by other retrieval teams or children not requiring PICU admission were excluded. The study was approved by the institutional ethical review board (Mater Health Services Human Research Ethics Committee) including waiver of informed consent.

Data extraction

Data on the interhospital transfers were extracted from the institutional retrieval system database, which prospectively records demographic data, physiologic parameters, medications, interventions, respiratory support, complications, and mode and timing of transport. Data were verified by manually checking individual charts. Data on the management and course in the PICU were extracted from the PICU clinical information system (CIS). Diagnostic codes, Paediatric Index of Mortality 2 (PIM2) scores [16] and severity indicators were extracted from the Australian and New Zealand Paediatric Intensive Care registry (ANZPIC) [17].

Paediatric retrieval system characteristics

The Mater Children's PICU is the largest PICU in Queensland, Australia, with ca. 1,300 admissions per year, and covers an area extending from northern New South Wales up to Cairns, with a population of approximately 4.5 million inhabitants. Each year, on average 400 critically ill children are retrieved by the Mater Children's PICU Retrieval Team. Until 2008, children requiring respiratory support other than oxygen were treated with IV or NIV (including CPAP and biphasic positive airway pressure modes (BiPAP), delivered via mask or nasopharyngeal tube). In late 2008, given the positive experience and safety profile of HFNC therapy used at our PICU [9], it was decided to include HFNC therapy as a ventilatory support technique for interhospital transfers. Test runs confirmed the feasibility of its use during transport. After 1 January 2009, HFNC therapy was available as a standard treatment option in addition to IV and NIV.

Definitions and outcomes

The modes of respiratory support during transport were defined as (i) low flow oxygen/room air, (ii) HFNC (defined as 2 L/kg/min flow with the use of nasal cannula), (iii) non-invasive ventilation (NIV, defined as CPAP or BiPAP) and (iv) invasive ventilation (IV). Heart rate, respiratory rate, oxygen saturation, FiO_2 and the level of respiratory support were extracted from the database at four time points: first contact of the transport team with the patient in the referring hospital; immediately prior to leaving the referring hospital; at arrival to

PICU; and 24 h after admission to PICU. We compared the use of the respiratory support modes and the complication rates in a 48-month period pre-HFNC introduction (1 January 2005–31 December 2008) versus a 48-month period post-HFNC introduction (1 January 2009–31 December 2012). Adverse events during transport were defined as need for intubation, pneumothorax, cardiac arrest requiring cardiopulmonary resuscitation (CPR), and death. A secondary outcome was the need for IV during the first 24 h after PICU admission. The principal diagnosis requiring interhospital transfer was extracted from the ANZPIC registry, and was classified into respiratory conditions (bronchiolitis, pneumonia, apnoea, upper airway obstruction and other lung diseases), neurologic conditions (including seizures, encephalopathy and neuromuscular disorders), cardiac conditions, trauma, sepsis and other causes.

HFNC set-up

HFNC was delivered through paediatric specific nasal cannulae (neonatal, infant, paediatric size; Fisher & Paykel Healthcare Ltd., Auckland, New Zealand) which were connected to a heated humidifier (Fisher & Paykel Healthcare Ltd., Auckland, New Zealand) through a paediatric circuit kit (Fisher & Paykel Healthcare Ltd., Auckland, New Zealand) (see figure in Electronic Supplementary Material).

Statistics

Means and 95 % confidence intervals are reported. Independent *t* test and Chi-squared test were used to assess differences between the two periods. For small samples and non-parametric distributed data, the Mann–Whitney *U* test was used. Logistic regression was used to model the need for IV and IV/NIV. For multivariate models, covariates that had shown a trendwise association with the need for IV were selected. In the final models, the period pre/post-HFNC, age, transport distance, mode of transport (ground, rotary wing, fixed wing), disease group and PIM2 scores were used as covariates. SPSS 18.0 software was used. *P* values less than 0.05 were considered significant.

Results

Comparison of pre-HFNC versus post-HFNC period

In total, 793 children below 2 years of age were retrieved to PICU, 331 in the pre-HFNC period and 462 in the post-HFNC period (40 % increase, Table 1). During the same period, the total number of PICU admissions had increased by 55 %. The mean duration of transport was 1.4 h (range 0.25–8), with a distance of 205 km (2–2,856). Before introduction of HFNC therapy, 7 % ($n = 23$) were transported on NIV and 49 % ($n = 163$) on IV (Figs. 1, 2). A total of 119 (36 %) children had been intubated prior to arrival of the PICU retrieval team, and 44 (13 %) were intubated in the referring hospital by the retrieval team. After introduction of HFNC therapy, 33 % ($n = 150$) were transported on HFNC and 2 % ($n = 10$) on NIV, whereas IV decreased to 35 % ($n = 162$, $p < 0.001$). During this period, 128 (28 %) children were already intubated at baseline, whereas 34 (7 %) were intubated in the referring hospital by the PICU retrieval team. When restricting analyses to patients with bronchiolitis, both the absolute and relative number of infants requiring IV initiated by the retrieval team decreased between the two periods (34/102 (33 %) versus 26/169 (15 %), $p = 0.001$). Similarly, the rate of infants with bronchiolitis requiring IV/NIV decreased significantly (50/102 (49 %) versus 31/169 (18 %), $p < 0.001$).

Adverse effects during interhospital transport and safety of HFNC

In the pre-HFNC period, two children required CPR during transport. In the post-HFNC period, no patient required intubation during retrieval, and one already intubated child with septic shock required CPR. No patient developed a pneumothorax or died during transport during the entire study period.

In total, 150 children were retrieved on HFNC therapy post-HFNC introduction, covering distances of 25–744 km (mean 96 km) with transport duration of up to 4 h. Bronchiolitis (77 %) was the predominant condition requiring transport, and 144/150 (94 %) children retrieved on HFNC suffered from a respiratory condition (Table 2). Two patients retrieved on HFNC were escalated to NIV during the retrieval. Sedation was given to 1 % ($n = 2$) of children retrieved on HFNC; in contrast 97 % of infants on NIV or IV were given sedation.

Escalation of respiratory support after admission to PICU

The rate of retrieved children requiring intubation for respiratory reasons during the first 24 h after PICU admission did not change significantly between the two periods (pre-HFNC 5/331 (2 %) versus post-HFNC 12/462 (3 %), $p = 0.30$). The rate of retrieved children requiring initiation of NIV during the first 24 h after admission was reduced from 20/331 (6 %) to 14/462

Table 1 Baseline and demographic data comparing infants retrieved prior to introduction of high-flow nasal cannulae (HFNC) versus infants retrieved after HFNC introduction

	Pre HFNC ($n = 331$)	Post HFNC ($n = 462$)	p value*
Weight (kg)	6.4 (1.9–15.0)	6.6 (2.1–16.0)	0.46
Age (months)	6.2 (0.0–24)	6.5 (0.0–24)	0.47
Transport duration (h)	1.4 (0.1–8.8)	1.4 (0.1–5.0)	0.72
Transport distance (km)	191 (2–2,856)	214 (6–1,819)	0.41
Mode of transport			0.97
Road	217 (66 %)	300 (65 %)	
Helicopter	67 (20 %)	94 (20 %)	
Fixed wing	47 (14 %)	68 (15 %)	
Main cause requiring retrieval			0.037
Respiratory	170 (51 %)	262 (57 %)	0.14
Neuromuscular	54 (16 %)	49 (11 %)	
Cardiac	25 (8 %)	41 (9 %)	
Trauma	15 (5 %)	11 (2 %)	
Sepsis	6 (2 %)	18 (4 %)	
Others	61 (18 %)	81 (18 %)	
Patient severity			
PIM2 score	5.9 % (0.16–94.6 %)	5.3 % (0.07–99.3)	0.55
PICU LOS (days)	4.4 (0.1–135)	4.3 (0.1–215)	0.87
Hospital LOS (days)	12.6 (0.1–263)	11.6 (0.1–308)	0.52

Data are reported as *N* (%) or mean (range)
PIM2 Paediatric Index of Mortality 2, *LOS* length of stay
* p value of Chi-squared test (for ratios) and p value of Student's t test (for linear variables)

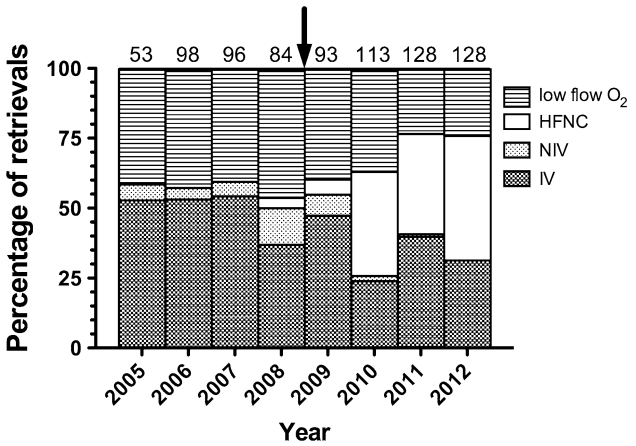

Fig. 1 Mode of respiratory support during the study period 2005–2012. The percentual use of each mode of transport is shown. The *arrow* indicates the introduction of high-flow nasal cannulae (HFNC) as a standard respiratory support option into the retrieval team. *NIV* non-invasive ventilation, *IV* invasive ventilation

(3 %) after introduction of HFNC ($p = 0.039$). Three of 150 (2 %) infants retrieved on HFNC therapy required intubation during the first 24 h after PICU admission due to respiratory reasons, and 9 (6 %) were escalated to NIV.

Multivariate models

The need for IV initiated by the retrieval team was significantly reduced post-HFNC therapy introduction even after adjusting for age, transport distance, transport modality, disease group and PIM2 score (odds ratio, OR 0.51, 95 % CI 0.27–0.95, $p = 0.032$, Table 3). Similarly, the rate of NIV or IV initiated by the retrieval team was significantly lower in the period 2009–2012 compared to the period prior to HFNC (OR 0.36, 95 % CI 0.22–0.60, $p < 0.001$). Sensitivity analyses restricted to infants with respiratory disease gave similar results (data not shown).

Discussion

We observed an important change in practice in respiratory support in critically ill infants under 2 years of age transferred by a specialized paediatric retrieval team. This finding parallels the general trend observed in paediatric critical care settings to early use of NIV in children with severe respiratory disease [11]. To the best of our knowledge, this is the first study reporting the use of HFNC therapy in transport medicine. Our data based on a single-centre, retrospective study indicate that the increasing use of HFNC therapy during transport in selected critically ill infants did not lead to an increased rate of complications. Further studies are needed to confirm our observation of a decrease in IV after the introduction of HFNC.

Safety of HFNC therapy during transport

There is a lack of studies describing the safety and quality of respiratory support in critically ill paediatric patients requiring interhospital transport [1, 18, 19]. Our

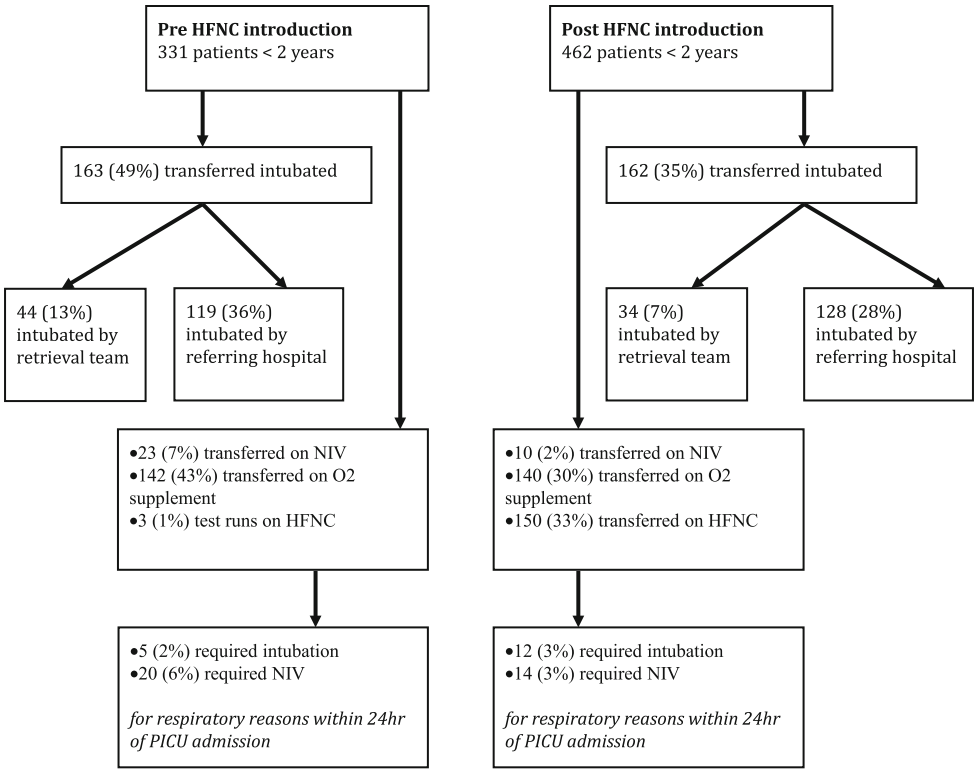

Fig. 2 Flow chart comparing respiratory support between the two study periods. *HFNC* high-flow nasal cannulae, *NIV* non-invasive ventilation

Table 2 Characteristics of infants retrieved on high-flow nasal cannula (HFNC) during the study period

	HFNC ($n = 150$)
Weight (kg)	6.7 (2.3–13.5)
Age (months)	6.2 (0.3–23)
Transport duration (h)	1.2 (0.1–3.8)
Transport distance (km)	96 (25–744)
Mode of transport	
Road	117 (78 %)
Helicopter	25 (17 %)
Fixed wing	8 (5 %)
Main cause requiring retrieval	
Bronchiolitis	115 (77 %)
Respiratory non-bronchiolitis	25 (17 %)
Neuromuscular	3 (2 %)
Cardiac	1 (1 %)
Trauma	0 (0 %)
Sepsis	4 (3 %)
Others	2 (1 %)
Patient severity	
PIM2 score	0.4 % (0.16–4.0 %)
PICU LOS (days)	2.4 (0.2–10)
Hospital LOS (days)	8.0 (1.6–150)

Data are reported as *N* (%) or mean (range)
PIM2 Paediatric Index of Mortality 2, *LOS* length of stay

retrospective study showed that, in general, complications during transport of children under 2 years of age are very rare: out of 793 children transported over 8 years only three needed a major intervention such as intubation or CPR during transport. This is a surprisingly low number considering that the geographic area covered by our retrieval system is likely among the largest in the world. We have not observed any increase in complications since the regular use of HFNC therapy during retrievals was initiated. Importantly, the safety profile of HFNC was excellent and we did not observe any major side effects [20]. In addition, the rate of children requiring intubation for respiratory reasons after being admitted to PICU did not increase after the introduction of HFNC therapy. Our data thus do not support the concern that children who are transported on HFNC therapy receive delayed definitive care such as IV.

Impact of HFNC therapy on intubation rates

We observed a twofold reduction in intubations performed by the retrieval team when comparing a 4-year period prior to use of HFNC therapy in retrievals versus a 4-year period after HFNC therapy became available. Since the proportion of infants that were already intubated by the referring hospital prior to arrival of the retrieval team had dropped from 36 to 28 %, it is unlikely that a change in intubation practice in the referring hospitals would account for reduced intubations by the retrieval team. We cannot exclude that changes in

Table 3 Uni- and multivariate logistic regression models analysing risk factors associated with intubation, and with intubation/non-invasive ventilation initiated by the retrieval team

Variable	Univariate OR [95 % CI]	*p* value	Multivariate OR [95 % CI]	*p* value
Intubation by retrieval team				
Distance (100 km)	1.05 [0.99–1.12]	0.11	1.02 [0.90–1.17]	0.80
Respiratory disease	0.75 [0.46–1.21]	0.24	3.76 [1.89–7.49]	<0.001
PIM 2 (tercile)	9.32 [5.82–14.91]	<0.001	14.44 [8.19–25.47]	<0.001
Rotary wing	3.02 [1.75–5.22]	<0.001	3.51 [1.72–7.16]	0.001
Fixed wing	2.18 [1.10–4.29]	0.025	1.26 [0.40–4.03]	0.69
Age (month)	0.95 [0.91–1.00]	0.04	0.95 [0.90–1.01]	0.074
HFNC period 2009–2012	0.43 [0.27–0.70]	0.001	0.51 [0.27–0.95]	0.032
Intubation or non-invasive ventilation by retrieval team				
Distance (100 km)	1.03 [0.97–1.10]	0.32	1.03 [0.92–1.15]	0.63
Respiratory disease	1.14 [0.74–1.76]	0.56	3.82 [2.12–6.85]	<0.001
PIM 2 (tercile)	3.81 [2.72–5.33]	<0.001	5.67 [3.75–8.57]	<0.001
Rotary wing	2.38 [1.47–3.84]	<0.001	2.49 [1.40–4.45]	0.002
Fixed wing	1.44 [0.77–2.69]	0.25	0.90 [0.33–2.51]	0.84
Age (month)	0.94 [0.91–0.98]	0.003	0.95 [0.91–0.99]	0.02
HFNC period 2009–2012	0.33 [0.21–0.50]	<0.001	0.36 [0.22–0.60]	<0.001

Infants already intubated prior to arrival of the retrieval team were excluded
OR odds ratio, *95 % CI* 95 % confidence interval, *PIM* Paediatric Index of Mortality 2, *HFNC* high-flow nasal cannula

patient mix may have affected the observed reduction in intubations. However, not only the relative but as well the absolute number of IV/NIV initiated by the retrieval team decreased after introduction of HFNC, and the same finding was observed in subgroup analyses restricted to infants with respiratory diseases and with bronchiolitis. In addition, the mean patient age, transport characteristics and severity indicators such as PIM2 scores and length of stay did not significantly change between the periods. The rate of infants failing HFNC therapy was low and only 2 % required intubation for respiratory reasons after admission. Most infants managed on HFNC therapy did not require any sedation, suggesting HFNC was well tolerated. These findings are supported by previous studies reporting on the use of HFNC therapy in PICU patients [9, 10, 21, 22]. While randomized controlled studies on HFNC in infants are lacking, a recent randomized controlled trial in very preterm neonates reported non-inferiority of HFNC to CPAP [23].

It is known that children admitted to PICU have a higher mortality if they have been retrieved [24], which may be related to a variety of factors such as selection bias, delays in presentation and in initiation of appropriate treatment, and diagnostic challenges under remote healthcare conditions. Furthermore, the low threshold for IV that many retrieval teams apply may expose children to the risks of IV, and potential impacts of sedation on the developing brain. It is therefore important to evaluate whether initiation of intensive care treatment at an early stage may potentially succeed in limiting disease progression. Owing to the inherent properties of the infant respiratory system with small airways and high chest compliance, the risk of developing atelectasis is high in bronchiolitis [25]. HFNC therapy applied early in the disease process may prevent progression of the disease and maintain normal lung volumes, thereby preventing atelectasis [26]. As a result, the functional residual capacity can be maintained and work of breathing reduced, which may stabilize the patient sufficiently to avoid the need for intubation. For this purpose we used flow rates of 2 L/kg/min which have been shown to result in a positive end-expiratory pressure of 4–5 cmH_2O [8, 25].

Limitations

Firstly, since this is not a randomized controlled trial, we cannot rule out that differences in the patient population accounted for the observed decrease in intubations. However, multivariate analyses adjusted for important potential confounders, including patient severity as measured by PIM2 score, confirmed the main results, as did subgroup analyses limited to infants with bronchiolitis. Secondly, the experience in our unit that HFNC is well tolerated and has an excellent safety profile [9] provided the basis for the early use of HFNC by our retrieval team. It is thus possible that the increase in infants retrieved on HFNC may partially represent overtreatment of some patients that hypothetically would have done well on low-flow oxygen. Yet, the increase of interhospital transfers observed in this study mirrors the growth of our PICU in the past decade which is attributable to populational growth and to the expansion of tertiary paediatric services including cardiac surgery and extracorporeal membrane oxygenation (ECMO). Thirdly, the study was not

powered to detect significant differences in major adverse events occurring at a low rate. Fourthly, it is important to mention that unique features of the Queensland Paediatric Retrieval Service need to be considered which may impact on the generalizability of our findings to other services: Our service is run by a fully dedicated specialized paediatric intensive care retrieval team and often performs retrievals over long distances. In addition, our PICU has acquired several years of experience with HFNC therapy prior to implementing this support mode in transport medicine.

Strengths of this study include the relatively large sample size and the adjustment of analyses for potential confounders. This study is the first to assess the safety and efficacy of HFNC therapy in retrievals. Transport medicine, particularly in the field of paediatric critical care, is often treated as an orphan discipline [27], and clinical practice and technological developments often lag considerably behind innovations that have already been implemented in the PICU. Only recently, a large study from the UK demonstrated that increased professionalism in paediatric retrieval teams was associated with improved survival [1]. Our study demonstrates that the application of a simple method of respiratory support is safe and may potentially lead to improved outcomes.

On the basis of this experience, our paediatric retrieval coordinators now recommend referring centres to initiate HFNC therapy early in infants with moderate work of breathing. Patient response to HFNC therapy can be assessed upon arrival of the retrieval team in the referring hospital which allows for stratification of patients into responders/non-responders [9].

Conclusion

We report on a major change of practice observed in respiratory support in interhospital transport of critically ill children in our retrieval system. HFNC therapy was increasingly used and was well tolerated, easy to perform and showed a good safety profile. Our observation of a reduction in intubation rates demonstrates that HFNC therapy is not inferior to the practice of using low-flow oxygen or NIV. Randomized controlled trials are urgently needed to assess whether HFNC therapy may indeed reduce the need for IV in interhospital transport of critically ill children.

Acknowledgments JS received a scholarship from University of Queensland, School of Nursing and Midwifery.

Conflicts of interest None declared.

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