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Elective use of nasal continuous positive airways pressure following extubation of preterm infants

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Abstract The aim of this study was to determine whether elective use of nasal continuous positive airways pressure (CPAP) following extubation of preterm infants was well tolerated and improved short- and long-term outcomes. A randomized comparison of nasal CPAP to headbox oxygen was undertaken and a meta-analysis performed including similar randomized trials involving premature infants less than 28 days of age. A total of 150 infants (median gestational age 30 weeks, range 24–34 weeks) were randomized in two centres. Fifteen nasal CPAP infants and 25 headbox infants required increased respiratory support post-extubation and 15 nasal CPAP infants and nine headbox infants required re-intubation (non significant). Eight infants became intolerant of CPAP and were changed to headbox oxygen within 48 h of extubation; 19 headbox infants developed apnoeas and respiratory acidosis requiring rescue nasal CPAP, 3 ultimately were re-intubated. Seven other trials were identified, giving a total number of 569 infants. Overall, nasal CPAP significantly reduced the need for increased respiratory support (relative risk, 0.57, 95% CI 0.43–0.73), but not for re-intubation (relative risk 0.89, 95% CI 0.68–1.17). Nasal CPAP neither influenced significantly the intraventricular haemorrhage rate reported in four studies (relative risk 1.0, 95% CI 0.55, 1.82) nor that of oxygen dependency at 28 days reported in six studies (relative risk 1.0, 95% CI 0.8, 1.25). In two studies nasal CPAP had to be discontinued in 10% of infants either because of intolerance or hyperoxia.

Conclusion Elective use of nasal continuous positive airways pressure post-extubation is not universally tolerated, but does reduce the need for additional support.

Key words Preterm infants · Extubation · Nasal continuous positive airways pressure

Abbreviations *IFD* infant flow driver · *IVH* intraventricular haemorrhage · *nCPAP* nasal continuous positive airways pressure · *PDA* patent ductus arteriosus · *RR* relative risk

Introduction

Randomized trials assessing the elective use of nasal continuous positive airways presure (nCPAP) post-extubation in preterm infants have yielded conflicting results regarding its influence on extubation success and have been of insufficient sample size to give meaningful data on long-term outcome [2, 3, 6, 7, 11, 12]. A further factor which may have influenced its application is that sustained use of nCPAP may not be practical in all infants because they became extremely agitated [3] or hyperoxic. Further data are required, however, to assess if such complications impact on the efficacy of nCPAP post-extubation. We, therefore, embarked on a ran-

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domized trial which we now report. It was performed in two centres and assessed whether elective nCPAP post-extubation was well tolerated and if it improved short- and long-term outcomes. The trial, however, was terminated prematurely after recruitment of 150 infants, following publication of a meta-analysis of the results of approximately 300 infants [5]. The meta-analysis demonstrated that nCPAP was associated with a reduction in extubation failure and chronic oxygen dependency [5]. Subsequently a further randomized trial assessing nCPAP has been reported [4]. This publication [4] meant that, including our own data, at least 569 preterm infants have been recruited into relevant randomized trials. We, therefore, felt a further systematic review of the literature and meta-analysis was timely, not only to assess whether elective use of nCPAP post-extubation influenced outcome, but also to determine if its use was limited by adverse effects.

Subjects and methods

All babies (inborn and outborn) admitted to the Neonatal Intensive Care Units at King's College Hospital, London and the University Hospital, Patras over a 3-year period were considered for this study. Eligibility criteria were that the infants were considered by the clinician in charge ready to be extubated, had a gestational age of ≤34 weeks and a postnatal age of ≤14 days. Infants < 28 weeks of gestational age, unless very vigorous at birth, were electively intubated in the delivery suite, more mature infants were intubated and ventilated if they had signs of respiratory distress. Infants were randomized immediately prior to extubation by opening sequentially numbered, sealed opaque envelopes to either nCPAP (via a single or binasal prong) or headbox oxygen. Infants were stratified according to centre. The study was approved by the local Hospitals' Research Ethics Committees.

All infants followed the routine policies of the neonatal intensive care units which were similar in the two centres. As the infant's respiratory illness recovered such that their requirement for ventilatory support was reduced, ventilator pressure and then rate was decreased. At a ventilator rate of 40 bpm theophylline/caffeine or aminophylline was started and the infant changed to patient triggered ventilation. When the clinician in charge thought the ventilator pressures had been reduced sufficiently, then the infant was changed to endotracheal CPAP. The minimum peak pressure used before transfer to endotracheal CPAP was lower in very immature infants. If this was tolerated for a maximum of 1 h, that is the infant had regular respiratory efforts and did not develop a respiratory acidosis (pH < 7.25), the infant was extubated on to the randomized form of support.

Infants were considered to have failed extubation if they required re-intubation within 48 h. The criteria for re-intubation were an increasing supplementary oxygen requirement (>60%), the development of a respiratory acidosis (pH < 7.25), and one major apnoea or frequent minor apnoeas. Infants receiving supplementary oxygen in a headbox who developed minor apnoeas or a respiratory acidosis were first tried on nCPAP. If this failed to improve their status, they were then re-intubated. Infants were designated to have required increased respiratory support post-extubation if they required higher supplementary oxygen levels than when immediately extubated and, in addition, if the headbox oxygen infants required rescue CPAP. Infants' results were analysed according to their original randomization category. Differences were assessed for statistical significance using the Chi squared or Mann Whitney test as appropriate.

The literature was reviewed to identify randomized or quasi randomized trials comparing the use of nCPAP to headbox oxygen post-extubation in preterm infants of < 28 days of age. For the purposes of this review, infants randomized to CPAP had to have been intended to receive this form of respiratory support for at least 48 h. Searches were made of the Oxford Database of Perinatal Trials, the Cochrane Database and Medline (mesh terms: CPAP; extubation; weaning; newborn infant; preterm). In addition, previous reviews, abstracts, published symposia proceedings, hand searching of journals in the english language and contacting expert informants was employed. Two reviewers (AG and GD) identified trials that might be included. Each trial was then assessed independently by each reviewer completing data collection forms that they had both previously agreed. The following information was collected on the data forms: the method of randomization, trial inclusion and exclusion criteria, sample size and clinical outcomes: intraventricular haemorrhage (IVH), patent ductus arteriosus (PDA), oxygen dependency at 28 days, increased requirements for respiratory support post-extubation, extubation failure (requirement for re-intubation within 48 h of extubation), CPAP intolerance (agitation sufficient to necessitate CPAP withdrawal) and hyperoxia (PaO_2 > 10kPa in air). Meta-analysis of the results of the trials identified from the literature and the currently presented study were expressed as the relative risk (RR) for positive or adverse effects (95% CI). Two subgroup analyses for requirement for increased respiratory support or re-intubation were identified a priori which included the results of infants who were planned to be extubated prior to 14 days of age and those of birth weight < 1.0 kg. In response to a referee's comments we also provide similar results for infants of birth weight < 1.5 kg.

Results

The 150 infants studied at King's College Hospital and Patras had a median gestational age of 30 weeks (range 24–34 weeks) and birth weight of 1.212 kg (range 0.610–2.450 kg). Their median postnatal age at randomization was 4 days (range 0.5–14 days). The two groups were well matched (Table 1). No statistically significant differences were noted between either the re-intubation rate or requirement for increased respiratory support between the groups (Table 1). The reasons for re-intubation did not differ significantly between the two groups (Table 2). Nineteen headbox infants developed apnoeas and respiratory acidosis and were tried on nCPAP, three

Table 1 Comparison of infants randomized at King's College Hospital and the University Hospital, Patras to nCPAP or headbox. Data are given as median (range) or *N* (%)

N	nCPAP 75	Headbox 75
Gestational age (weeks)	29 (24–33)	30 (26–34)
Birth weight (g)	1.140 (0.610–2.400)	1.280 (0.674–2.450)
Post-natal age (days)	3 (0.5–14)	4 (0.5–14)
Male	31 (41)	34 (45)
Antenatal steroids	51 (68)	52 (69)
Post-natal surfactant	46 (61)	53 (71)
Extubation failure	15 (20)	9 (12)
Increased respiratory support	15 (20)	25 (33)
Oxygen dependency (days)	17 (0.5–365)	11 (1–90)
At 28 days	32 (43)	22 (30)
At 36 weeks post-conceptional age	11 (15)	8 (11)
Mortality	2 (2.6)	1 (1.3)

Table 2 Causes of extubation failure. Data are given as the number of infants with a particular diagnosis. Some infants had more than one cause of extubation failure

	nCPAP	Headbox
Increased supplementary oxygen requirement	2	2
Development of respiratory acidosis	8	5
Apnoeas	11	4

ultimately required re-intubation. Eight nCPAP infants became extremely agitated and intolerant of the CPAP within 48 h of extubation and required transfer to headbox oxygen; none required re-intubation. No infant became hyperoxic.

Seven studies (Table 3) from the literature were selected for inclusion in the review, in addition to the presently reported study. Overall elective use of nCPAP was associated with a significant reduction in the need for increased respiratory support (Fig. 1), but not for re-intubation (Fig. 2). Similar rates were demonstrated in infants on the two methods of respiratory support for IVH (four trials), PDA (four trials) and oxygen dependency at 28 days (six trials) (Fig. 3) (Table 4).

Data were available from seven trials for the first subgroup analysis. This demonstrated nCPAP was associated with a lower requirement for increased respiratory support (RR 0.63, 95% CI 0.49, 0.82), but no significant reduction in the extubation failure rate (RR 0.93, 95% CI 0.70, 1.24). Data were available exclusively on infants of birth weight <1.0 kg from five trials; nCPAP was associated with a trend for a lower requirement for an increase in respiratory support (RR 0.76, 95% CI 0.57, 1.02), but no significant reduction in the extubation failure rate (RR 1.19, 95% CI 0.85, 1.66). Amongst infants of birth weight <1.5 kg, nCPAP was again associated with no significant reduction in the extubation failure rate (RR 1.00, 95% CI 0.74, 1.34); but a significant reduction in the need for increased respiratory support (RR 0.62, 95% CI 0.48, 0.80).

Adverse effects were commented on in very few of the trials. Sepsis rates were only given in two trials and affected 26 infants supported by CPAP and 21 nursed in a headbox (Table 4). Feeding intolerance was only commented on in one study (Table 3). The need to discontinue CPAP because of agitation or hyperoxia was only commented on in one study other than the currently reported trial, this meant in total 10% of infants were affected.

Discussion

In a randomized study, we were unable to demonstrate that elective use of nCPAP post-extubation improved outcome. Our trial was terminated prematurely, but involved 150 infants which allowed us to confidently (80% power) detect a reduction in the overall re-intubation rate from 35% [2, 3, 6, 7, 11, 12] to 15%. Our trial included infants of 34 weeks gestational age, but the numbers of mature infants was very small, as they had to have required intubation and ventilation to be included in the study. Thus we do not feel this biased our results. In addition, the meta-analysis now presented of eight trials confirms nCPAP does not reduce the re-intubation rate. Our randomized study was carried out in two centres, but the policies regarding weaning and extubation were very similar. Although in one institution theophylline or caffeine was used and in the other aminophylline, the two medications have been shown to have similar efficacy, at least in treating infants with apnoea [9]. Two different forms of CPAP were used, but although it has been claimed that the binasal system has superior function [8], this has been disputed [10]. Our trial was a pragmatic one and the use of different CPAP delivery modes reflects current clinical practice.

In the randomized trial there was no significant difference between the groups in the proportions who required re-intubation, but nCPAP was used to rescue headbox infants who developed a respiratory acidosis

Table 3 Characteristics of trials included in the meta-analysis. (*BW* birth weight, *GA* gestational age, *IPPV* intermittent positive pressure ventilation)

Reference	Total sample size	Period defining extubation failure	Method of randomization	Participants	Mode of nCPAP delivery
[4]	90	7 days	Sealed envelopes	BW 0.600–1.250 g; IPPV >12 h	Single prong
[6]	18	Not stated	Sealed envelopes	All >1.0 kg intubated for <72 h <14 days	Not reported
[11]	50	72 h	Not stated	BW <1500 g, GA <34 weeks; weaning started within 7 days of life	Single prong
[3][a]	60	48 h	Sealed envelopes	BW <1500 g; <14 days	Single prong
[12]	59	72 h	Assigned by alternative use	BW <1500 g; IPPV >48 h	Naso-pharyngeal (i.e. a long single prong)
[2]	82	7 days	Sealed envelopes using number table	BW 0.600–1500 g; <14 days	Naso-pharyngeal
[7]	58	5 days	Sealed envelopes	Weight <1 kg at time of extubation; Weight $>80\%$ of BW	Binasal prongs
Present study	150	48 h	Sealed envelopes	GA <34 weeks; <14 days	Single or binasal prongs

[a] 60 infants planned to be extubated after 28 days were excluded from the analysis

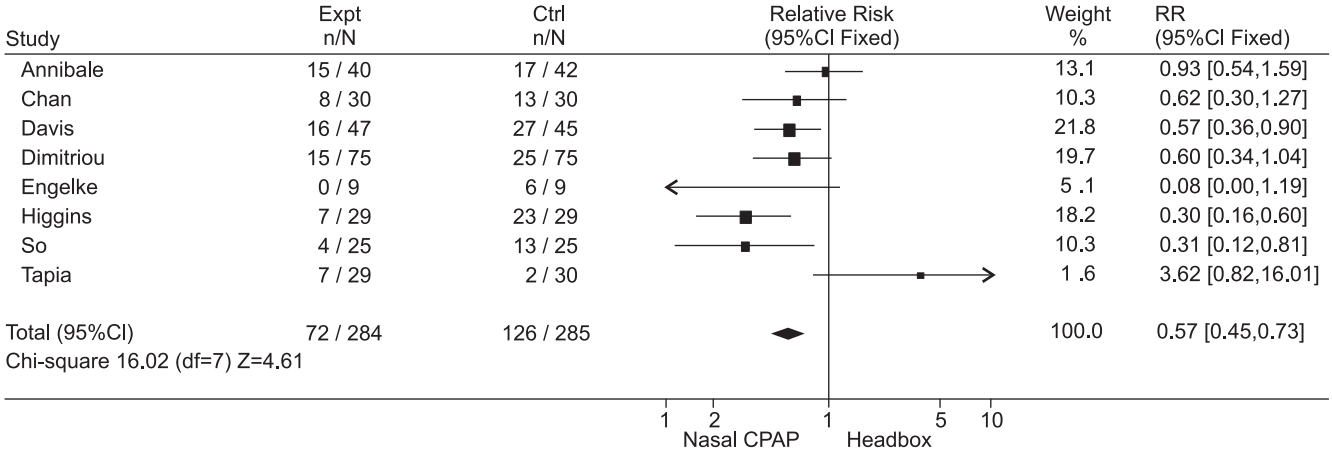

Fig. 1 Results from randomized studies comparing requirement for increased respiratory support between nCPAP and headbox oxygen. The results are given as the relative risk (95% CI). The definitions differed between the studies, but in all included a requirement for increased supplementary oxygen

and/or apnoeas and only 3 of the 19 infants so affected subsequently required re-intubation. Although it is thus tempting to speculate that use of rescue nCPAP biased our results, our meta-analysis confirmed that use of elective nCPAP did not significantly reduce the requirement for re-intubation. Indeed, in only one trial [11] included in the meta-analysis, was the re-intubation rate significantly lower than in the headbox group. Infants extubated within 14 days of birth or of birth weight <1.0 kg might be predicted to have residual respiratory problems, less able to maintain their lung volumes and hence benefit more from elective use of nCPAP. Our subanalyses do not support that hypothesis in that elective use of nCPAP did not significantly influence re-intubation requirement in infants of birth weight <1.5 kg or even if only those of birth weight <1.0 kg are considered.

Although meta-analysis allows examination of the results on a large number of infants, there are potential sources of bias. Although an extensive search of the literature was undertaken to identify appropriate trials, negative results are less likely to be published. As no long-term positive benefits of the elective use of nCPAP were highlighted by the meta-analysis, this is of less concern. The time periods in which an increased requirement for respiratory support was noted varied between the trials and, although usually being between 48 and 72 h post-extubation, in one trial it was 5 days and in two 7 days [2, 4]. No trend, however, was noted between the excess failure rate in the headbox group and the length of the time period after extubation in which the babies were examined. The mode of delivery of nCPAP varied between the studies; this may reflect the lack of randomized studies comparing their relative efficacy of CPAP delivery modes. Unless such a comparison does show superior results for one system, it is likely that neonatal intensive care units will continue to use a

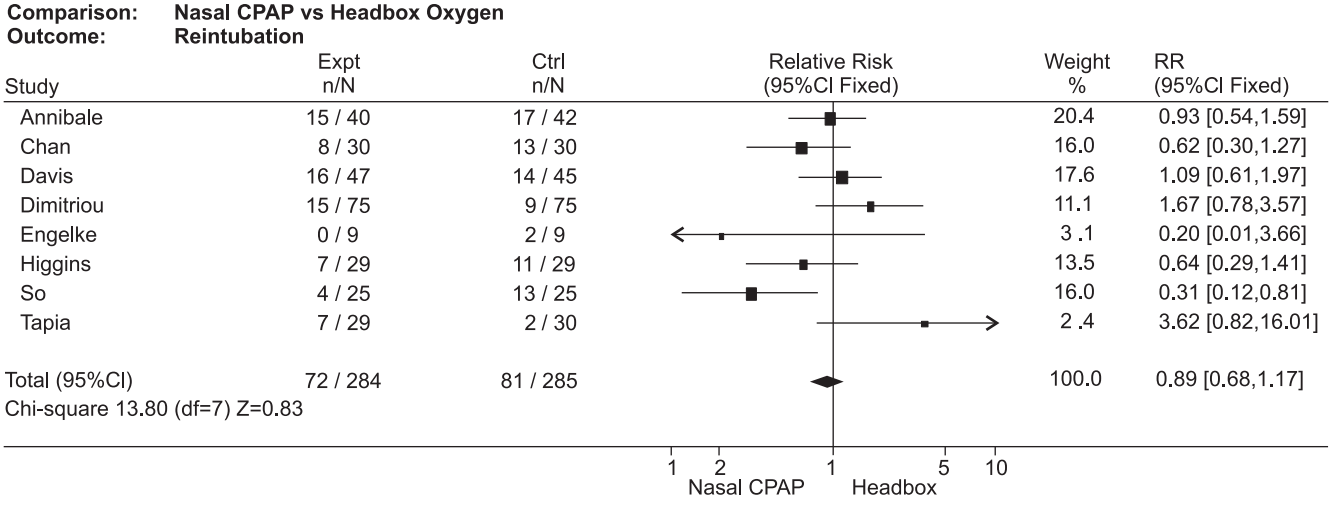

Fig. 2 Results from randomized studies comparing the re-intubation rate following extubation to nCPAP or headbox oxygen. The results are given as the relative risk (95% CI)

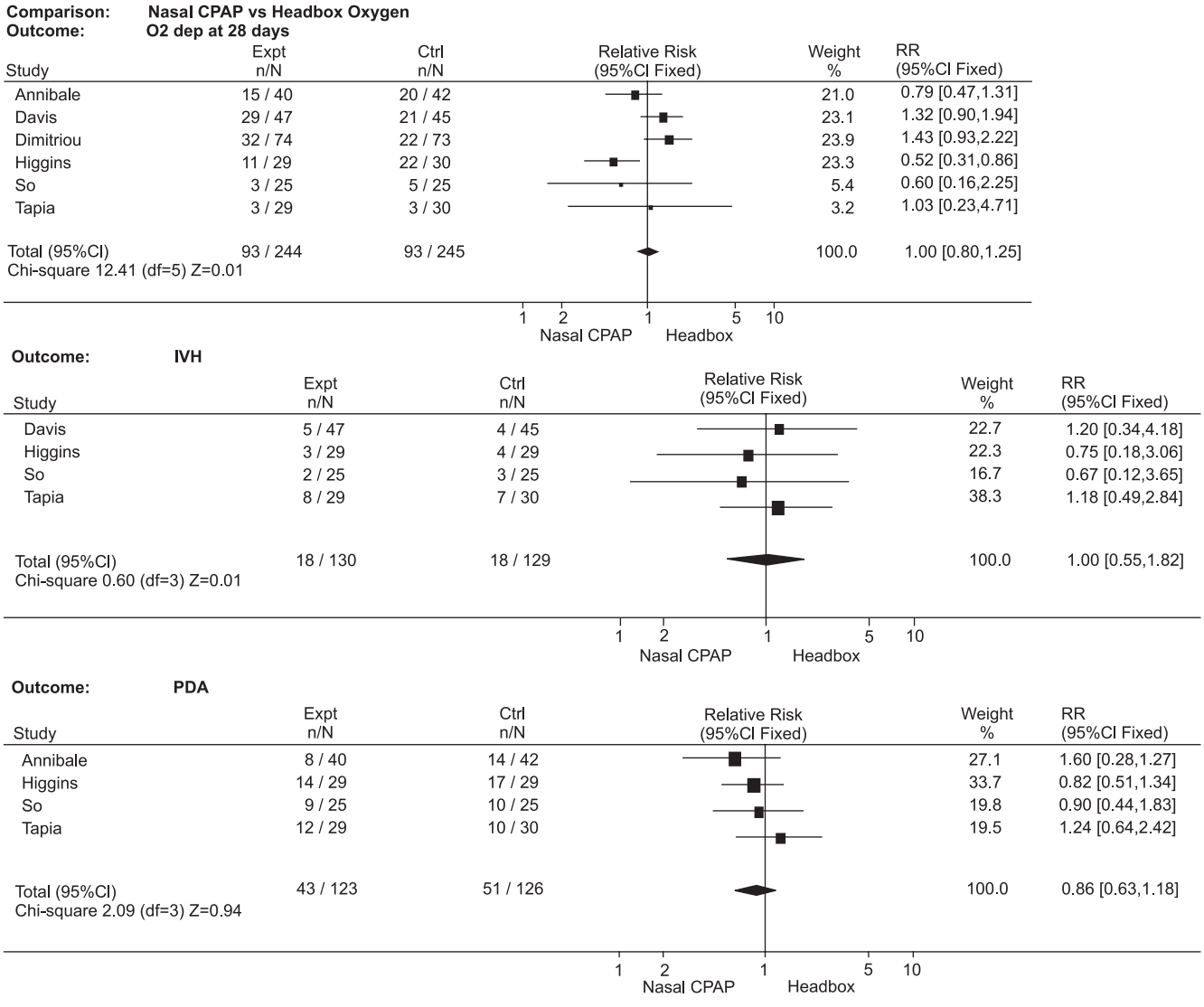

Fig. 3 Results from randomized studies comparing extubation on nCPAP or headbox oxygen. The results of IVH, PDA rate and oxygen dependency at 28 days are given as the relative risk (95% CI)

Table 4 Outcome of trials included in the review. Certain outcome data were not reported in all trials. (*ROP* retinopathy of prematurity)

Reference		Death	PDA	Oxygen dependency at 28 days	Oxygen dependency at 36 weeks post-conceptional age	IVH	ROP	Sepsis	Feeding intolerance
[4]	CPAP	2	–	31	13	5	11	18	23
	Headbox	2	–	21	12	4	12	13	20
[6]	CPAP	–	9	–	–	–	–	–	–
	Headbox	–	10	–	–	–	–	–	–
[11]	CPAP	–	–	3	–	2	2	–	–
	Headbox	–	–	5	–	3	2	–	–
[3]	CPAP	–	–	–	–	–	–	–	–
	Headbox	–	–	–	–	–	–	–	–
[12]	CPAP	–	12	3	–	8	–	8	–
	Headbox	–	10	3	–	7	–	8	–
[2]	CPAP	1	8	15	–	–	–	–	–
	Headbox	1	14	20	–	–	–	–	–
[7]	CPAP	–	14	11	–	3	–	–	–
	Headbox	–	17	22	–	4	–	–	–
Present study	CPAP	2	–	32	11	–	–	–	–
	Headbox	1	–	22	9	–	–	–	–

variety of methods to deliver CPAP. Thus, although we cannot confidently exclude that the use of one CPAP method may generate different results, our results reflect the efficacy of CPAP as it is currently delivered.

An earlier meta-analysis demonstrated elective use of nCPAP post-extubation would reduce oxygen dependency at 28 days [5]. That analysis, however, only included approximately 60% of the sample currently investigated. The two trials subsequently reported demonstrated a tend for use of nCPAP to increase oxygen dependency, although in neither did the effect reach statistical significance (Table 3). This result reversal [5], as further small studies were added into a meta-analysis, stresses the superiority of information obtained from one large well designed multicentre randomized trial.

Hyperoxia occurred in a small proportion of the infants studied despite nursing them in air supplied by nCPAP. Effective delivery of CPAP results in lung volume recruitment and hence hyperoxia can occur despite use of air in infants with minimal or no respiratory distress. This problem may be compounded by use of the infant flow driver (IFD) which delivers 2% more oxygen than a single nasal prong and ventilator system [1]. Use of an alternative CPAP delivery system may, therefore, reduce the number of infants who become hyperoxic on CPAP. The IFD has become a popular choice, as its use has been associated with a decreased work of breathing [8]. Caution should be exercised when contemplating long-term use, however, as this may expose infants to the risk of nasal deformities [8]. CPAP had to be discontinued in two trials because the infants were intolerant, becoming extremely agitated. Sedation in such circumstances would be an inappropriate response. Other possible adverse effects, including sepsis and feeding intolerance, did not differ significantly between infants who were supported by CPAP or nursed in a headbox, but such complications were reported only in three studies. In total CPAP was only prematurely discontinued in 10% of infants.

The results of a randomized trial and a meta-analysis demonstrate that nCPAP used electively post-extubation significantly reduces the need for increased respiratory support. We only included infants < 28 days of age and thus cannot make any statement regarding the value of nCPAP following prolonged mechanical ventilation.

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