

The role of non-invasive positive pressure ventilation in post-extubation respiratory failure: An evaluation using meta-analytic techniques

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Abstract

Background: The use of non-invasive positive pressure ventilation (NIPPV) in post-extubation respiratory failure is not well-established. Meta-analytic techniques were used to assess the effects of prophylactic application of NIPPV (prior to the development of respiratory failure) and therapeutic application of NIPPV (subsequent to the development of respiratory failure). **Materials and Methods:** Randomized controlled trials (RCTs) from 1966 to May 2010 were identified using electronic databases. RCTs, which reported the use of NIPPV in post-extubation respiratory failure with defined assessable endpoints: reintubation, mortality and length of stay, were included. **Results:** Reintubation was the primary outcome, mortality and lengths of stay were the secondary outcomes. Risk ratios (RR) were calculated for discrete outcomes and weighted mean differences (WMD) for continuous measures. There were 13 trials with 1420 patients; 9 prophylactic with 861 patients and 4 therapeutic with 559 patients. In the prophylactic group, NIPPV was associated with lower rates of reintubation: RR 0.53 (95% confidence interval [CI], 0.28-0.98), $P = 0.04$. In the therapeutic group, NIPPV showed a null effect on reintubation: RR 0.79 (95% CI, 0.50-1.25), $P = 0.31$. The analysis on the secondary outcomes suggested significant reduction of hospital mortality with prophylactic application of NIPPV: RR 0.62 (95% CI 0.4-0.97), $P = 0.03$, with no effect on the other outcomes. Therapeutic application of NIPPV reduced intensive care unit length of stay: WMD -1.17 (95% CI -2.82 to -0.33), $P = 0.006$, but no effect on the other secondary outcomes. **Conclusions:** The results of this review suggested prophylactic NIPPV was beneficial with respect to reintubation and the therapeutic use of NIPPV showed a null effect.

Keywords: Bi-level positive airway pressure ventilation, continuous positive airway pressure ventilation, non-invasive ventilation, post-extubation, reintubation, respiratory failure

Access this article online

Website: www.ijccm.org

DOI: 10.4103/0972-5229.118477

Quick Response Code:



Introduction

Respiratory failure after a planned extubation is reported to be a common event, leading to reintubation and can occur in as many as 3-20% of extubated patients.^[1-7] These reintubated patients have higher

morbidity, mortality, hospitalization charges and an increased length of hospital stay.^[6-9]

Non-invasive positive pressure ventilation (NIPPV), which includes continuous positive airway pressure ventilation (CPAP) and bi-level ventilation^[10] has assumed an important role in the treatment of acute respiratory failure, owing to its particular features of avoiding intubation and its associated complications and the physiological benefits,^[11] which it shares with invasive ventilation. NIPPV has been used with success in patients with the chronic obstructive pulmonary

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disease (COPD)^[12-14] and acute cardiogenic pulmonary edema,^[15-17] but its usefulness in other causes of acute hypoxemic respiratory failure is under evaluation.

Strategies to prevent reintubation have led to non-randomized^[18] and randomized controlled trials (RCTs)^[19,20] from 1998 to 2004, assessing the efficacy of NIPPV in post-extubation respiratory failure and the results from these clinical trials have shown conflicting outcomes. The negative results from two of these initial RCTs^[19,20] on mixed patient population, discouraged the use of NIPPV in treating post-extubation respiratory failure. However, it was postulated in the trial by Keenan *et al.*^[19] that NIPPV if applied immediately after a planned extubation, may be beneficial.

Immediate application of NIPPV on identified high risk patients was implemented in the trials by Nava *et al.* (2005)^[21] and Ferrer *et al.* (2006),^[22] and was found to be beneficial.

The overall evidence supporting the use of NIPPV in the post-extubation period does not appear to be well-established. Three systematic reviews about this topic have been conducted.^[23-25] The two reviews by Burns *et al.* in 2003^[23] and 2009,^[25] assessed the role of NIPPV in early weaning of invasively ventilated patients. The third review by Agarwal *et al.* (2007)^[24] assessed the benefits of NIPPV in post-extubation respiratory failure. This review did not include trials,^[26-33] which had been identified in an abstract by Krishna *et al.* (2007).^[34]

The aim of this review was to conduct an extended search and identify all relevant articles, where NIPPV was used in the post-extubation period. The analytic strategy was to assess the benefits of prophylactic application of NIPPV (that is, before the patient developed respiratory failure) and therapeutic application of NIPPV (that is, after patient developed respiratory failure).^[34]

Materials and Methods

NIPPV was defined as ventilatory support delivered without establishing an endotracheal airway.^[10]

Search strategy: A preliminary search using the search software OVID[®] was carried out for the period 1966 to May 2010 using the search terms "Non-invasive ventilation" and "post-extubation" in the MEDLINE[®] database. These search terms were then expanded and combined in a more detailed search [Appendix 1] using the "Highly sensitive search strategy" described by Robinson.^[35] Medline, Embase, Scopus, Web of Science,

Science direct and springer databases were electronically searched between the years 1950 and May 2010. Trials that were retrieved through the electronic search were reviewed for inclusion and trials of interest were examined in full text. References and review articles were further searched for relevant articles.

Inclusion criteria were: (i) RCTs, (ii) NIPPV used as a means of ventilatory support in the post-extubation period, (iii) NIPPV used for a minimum period of 2 h in a day^[10] and (iv) trials which reported reintubation or intensive care unit (ICU) and hospital; mortality and length of stay. Exclusion criteria were: (i) Non-randomized trials, (ii) trials where NIPPV was used as a means of chest physiotherapy, (iii) NIPPV used for weaning from ventilator, (iv) trials, which reported only physiological end points and (v) trials where NIPPV was used in varying duration in the study and control groups.

The data was extracted by the first two authors (BK and SS). RCTs were classified as prophylactic and therapeutic trials. Independent quality assessment was performed by the first two authors using the Down's and black quality assessment scale (score ranging from 0 [worst] to 31).^[36] Differences in opinion were settled by consensus.

The primary outcome of interest was episodes of reintubation and secondary outcomes of interest were ICU and hospital length of stay and ICU and hospital mortality. The effect of prophylactic and therapeutic NIPPV was assessed separately on the outcome measures.

The efficacy of NIPPV on the outcome variables were assessed as risk ratio ([RR], random effects estimator) for binary events and weighted mean difference for continuous measures. Results were expressed graphically as forest plots. The number needed to treat for a favorable outcome was also calculated. The heterogeneity was calculated using the I^2 test.^[37] Meta-regression was performed with the fraction of patients with COPD, or cardiac failure and the presence or absence of a non-operative versus post-operative status in the current admission as predictor variables, in the prophylactic and therapeutic groups. Publication bias was assessed using funnel plots and "trim and fill" tests. The analysis was carried out using the program Stata[™] (Version 10, College station TX) using the commands "metan,"^[38] "metareg"^[39] and "metabias."^[40]

Results

The highly sensitive search strategy revealed a total of 402 articles from Medline and no additional articles

were retrieved from Embase, Scopus, Web of Science, Science direct and Springer databases. The details of the exclusions are shown in Figure 1 and 13 trials were available for this systematic review.

Table 1 summarizes the baseline characteristics of the patients. There were 1420 patients in the 13 trials. There were 9 prophylactic trials^[21,22,26-31,41] with a total of 861 patients; 427 patients in the study group and 434 patients in the control group. The mean (standard deviation) age was 61.5 (10.5) years in the NIPPV group and 61.7 (10.8) years in the control group with male/female ratio of 317/110 and 307/127 respectively. There were 4 therapeutic trials^[19,20,32,33] with a total of 559 patients, 282 subjects in the study and 277 in the control groups. The patients were aged 63.55 (12.3) in the NIPPV and 63.6 (12.6) in the control group, with male/female ratio of 138/81 and 124/87 respectively.

Table 2 summarizes the baseline characteristics of the selected trials. The median (range) quality score was 16 (13-24) in the prophylactic trials and median (range) of quality score was 21 (20-23) in the therapeutic trials. The method, duration and interfaces used for delivery of NIPPV were variable. Most trials used either the bi-level positive airway pressure ventilation ([BiPAP] Vision, Respironics) or CPAP for delivery of NIPPV with varying pressure supports and for varying durations in 24 h. Full face mask was the most common type of interface used. Patients assigned to the control group in all the trials received supplemental oxygen through a

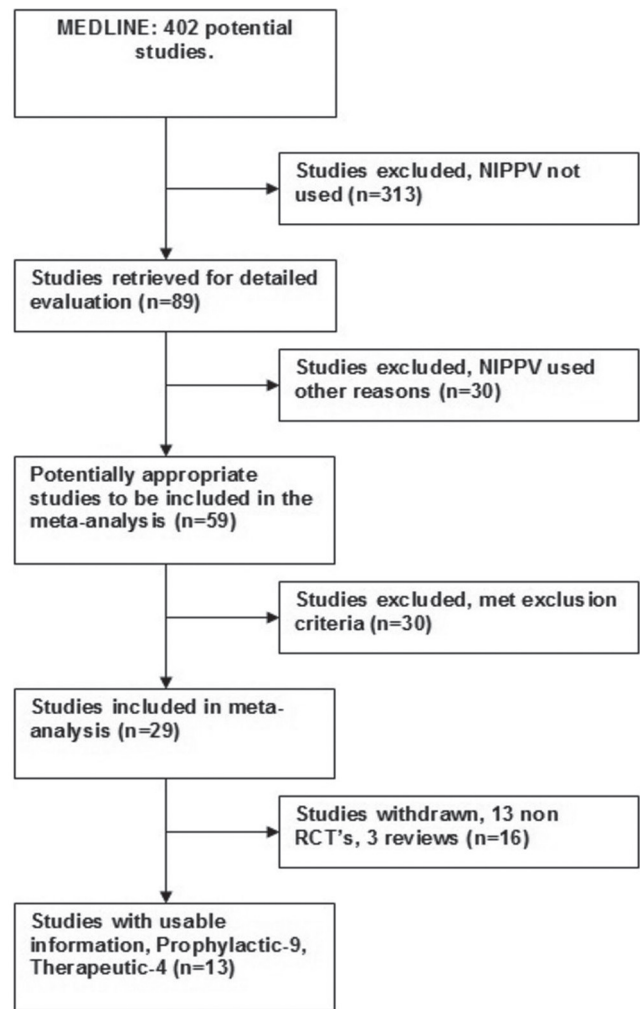


Figure 1: Flow chart of selected trials

Table 1: Baseline characteristics of patients

Study (year of publication) (references)	Journal	Prophylactic (P)/therapeutic (T)	Total number of subjects	Number in study group	Number in control group	Age in study group (sd)	Age in control group (sd)	Male:Female in study group	Male:Female in control group
Pinilla et al. (1990) ^[26]	Crit Care Med	P	58	32	26	56.2 (6.6)	59.4 (7.2)	30/2	23/3
Jiang et al. (1999) ^[27]	Respirology	P	93	47	46	73.4 (13.7)	72.11 (15.8)	27/20	32/14
Auriant et al. (2001) ^[32]	Am J Respir Crit Care Med	T	48	24	24	58.9 (10)	63 (9)	-	-
Fagevik et al. (2002) ^[28]	British Journal of Surgery	P	70	34	36	62 (14.3)	64.1 (9.7)	29/5	31/5
Böhner et al. (2002) ^[29]	Langenbecks Arch Surg	P	204	99	105	64.1 (12.3)	64.5 (11.3)	84/15	82/23
Ebeo et al. (2002) ^[30]	Respiratory Medicine	P	21	9	12	37 (6)	35 (10)	1/8	0/12
Keenan et al. (2002) ^[19]	JAMA	T	81	39	42	68.3 (13.1)	68.6 (12.4)	-	-
Esteban et al. (2004) ^[20]	N Engl J Med	T	221	114	107	61 (17)	58 (19)	67/47	60/47
Kindgen et al. (2005) ^[31]	Chest	P	50	25	25	66 (3)	67 (4)	15/10	14/11
Nava et al. (2005) ^[21]	Crit Care Med	P	97	48	49	56 (19.3)	53.2 (19.5)	31/17	30/19
Squadroni et al. (2005) ^[33]	JAMA	T	209	105	104	66 (9)	65 (10)	71/34	64/40
Ferrer et al. (2006) ^[22]	Am J Respir Crit Care Med	P	162	79	83	72 (10)	70 (11)	56/23	59/24
Ferrer et al. (2009) ^[41]	Lancet	P	106	54	52	67 (10)	70 (9)	44/10	36/16

face mask or nasal cannula, along with varying durations of physiotherapy or inhaled pharmacotherapy.

There were 255 (17.95%) COPD patients reported in 7 trials,^[19-22,27,31,41] 207 (14.5%) patients with cardiac failure in 7 trials^[19-22,27,29,32] and 729 (51.3%) post-operative patients reported in 11 trials.^[19-22,26,28-33]

Effect of NIPPV on the clinical outcomes in the prophylactic trials: There were 7 trials^[21,22,27-29,31,41] reporting on reintubation with a total of 782 patients. The trials by Pinilla *et al.*^[26] and Ebeo *et al.*^[30] did not report reintubation as an outcome. There were 35 reintubations in the study group and 63 reintubations in the control group. NIPPV was associated with a significantly lower rate of reintubation as compared with the control group, with a relative risk reduction of 0.53 (95% confidence interval [CI], 0.28-0.98) and $P = 0.04$ [Figure 2]. There was evidence of moderate heterogeneity ($I^2 = 48.5\%$).^[37] The number needed to treat for one favorable outcome (avoiding reintubation) was 14.

The pooled analysis on the secondary outcomes of interest suggested significant reduction of hospital mortality with prophylactic application of NIPPV with null effect on the other outcomes [Table 3].

Effect of NIPPV on the clinical outcomes in the therapeutic trials: There were 4 therapeutic trials^[19,20,32,33]

with 559 patients, 89 reintubations in the study group and 102 reintubations in the control group. The pooled analysis suggested that NIPPV when applied therapeutically was neither beneficial nor harmful on the outcome reintubation. The relative risk was 0.79 (95% CI, 0.50-1.25) and $P = 0.31$ [Figure 3]. The heterogeneity between the 4 trials was substantial ($I^2 = 70\%$).^[37]

Therapeutic application of NIPPV reduced ICU length of stay, but had no effect on the secondary outcomes [Table 3].

Meta-regression and publication bias: None of the co-morbidities such as COPD, cardiac failure or post-operative status showed a significant effect across both prophylactic and therapeutic trials. No evidence of publication bias was demonstrated in the prophylactic and therapeutic groups.

Discussion

The pooled results from this review suggested that NIPPV when used prophylactically on extubated patients, decreased reintubation and hospital mortality. The ICU mortality, ICU and hospital length of stay were unchanged. The use of NIPPV after development of respiratory failure suggested that the length of ICU stay decreased and there was null effect with respect to the other outcomes.

Earlier reviews had studied the efficacy of NIPPV and other respiratory supportive techniques (that is, incentive

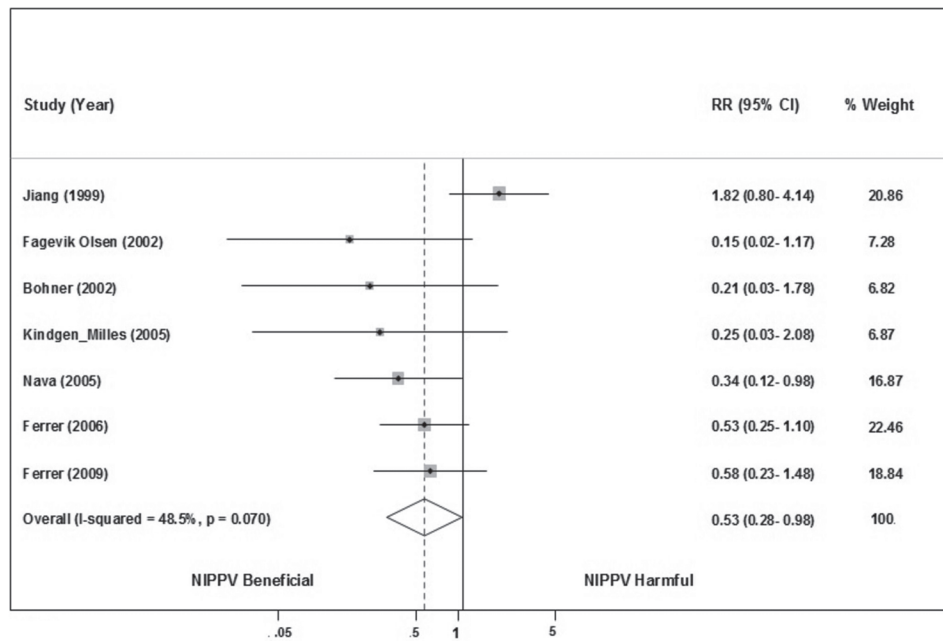


Figure 2: Effect of non-invasive positive pressure ventilation on reintubation in prophylactic trials. (Vertical solid line = null effect, vertical dotted line = overall mortality effect of treatment, boxes and horizontal lines = relative risk [95% confidence interval])

Table 2: Baseline characteristics of trials

Study (references)	Extubation reintubation criteria defined	Inclusion exclusion criteria	Quality scoring	Case definition	Delivery of NIPPV	Primary outcome	Secondary outcome
Pinilla <i>et al.</i> (1990) ^[26]	No	Yes	16	Post-operative coronary bypass ^b	CPAP	LOS, duration of ventilation	Physiological parameters
Jiang <i>et al.</i> (1999) ^[27]	Yes	No	13	Extubated patients-respiratory ICU	BiPAP	Reintubation	-
Auriant <i>et al.</i> (2001) ^[32]	Yes	Yes	20	Post-operative lung resection	BiPAP	Reintubation	Mortality, duration of ICU stay, hospital stay
Fagevik <i>et al.</i> (2002) ^[28]	Yes	No	16	Post-operative thoraco-abdominal surgery ^b	CPAP	Reintubation	Time mobilization, 30 day hospital mortality
Böhner <i>et al.</i> (2002) ^[29]	No	Yes	16	Post-operative lap for vascular surgery ^b	CPAP	Physiological parameters, reintubation	Cardiac and pulmonary complications, LOS ^a
Ebeo <i>et al.</i> (2002) ^[30]	No	Yes	13	Morbidly obese-gastric by-pass surgery ^b	BiPAP	Physiological parameters	LOS ^a of hospital stay
Keenan <i>et al.</i> (2002) ^[19]	Yes	Yes	21	Extubated after 48 h of mechanical ventilation	BiPAP	Reintubation	LOS ^a ICU and hospital, ICU survival, hospital survival
Esteban <i>et al.</i> (2004) ^[20]	Yes	Yes	23	Extubated after 48 h of mechanical ventilation	Not mentioned	Mortality in the ICU	Reintubation, LOS ^a ICU
Kindgen <i>et al.</i> (2005) ^[31]	Yes	Yes	17	Thoraco-abdominal surgery ^b	CPAP	Reintubation	LOS ^a ICU and hospital
Nava <i>et al.</i> (2005) ^[21]	Yes	Yes	20	Ventilated >48 h and at risk of extubation failure ^b	BiPAP	Reintubation	ICU and hospital mortality, LOS ^a hospital
Squadrone <i>et al.</i> (2005) ^[33]	Yes	Yes	21	Post-operative laparotomy	CPAP	Reintubation	LOS ^a ICU and hospital, hospital mortality
Ferrer <i>et al.</i> (2006) ^[22]	Yes	Yes	22	Ventilated >48 h and risk of extubation failure ^b	BiPAP	Reintubation	LOS ^a ICU and hospital, ICU and hospital mortality
Ferrer <i>et al.</i> (2009) ^[41]	Yes	Yes	24	Chronic respiratory disorders intubated ≥nt h ^b	BiPAP	Reintubation, decreased pulmonary oxygen transfer, nosocomial pneumonia	ICU mortality, hospital mortality and 90 day mortality

^aLOS: Length of stay; ^bHigh risk category; ICU: Intensive care unit; NIPPV: Non-invasive positive pressure ventilation; CPAP: Continuous positive airway pressure; BiPAP: Bi-level positive airway pressure

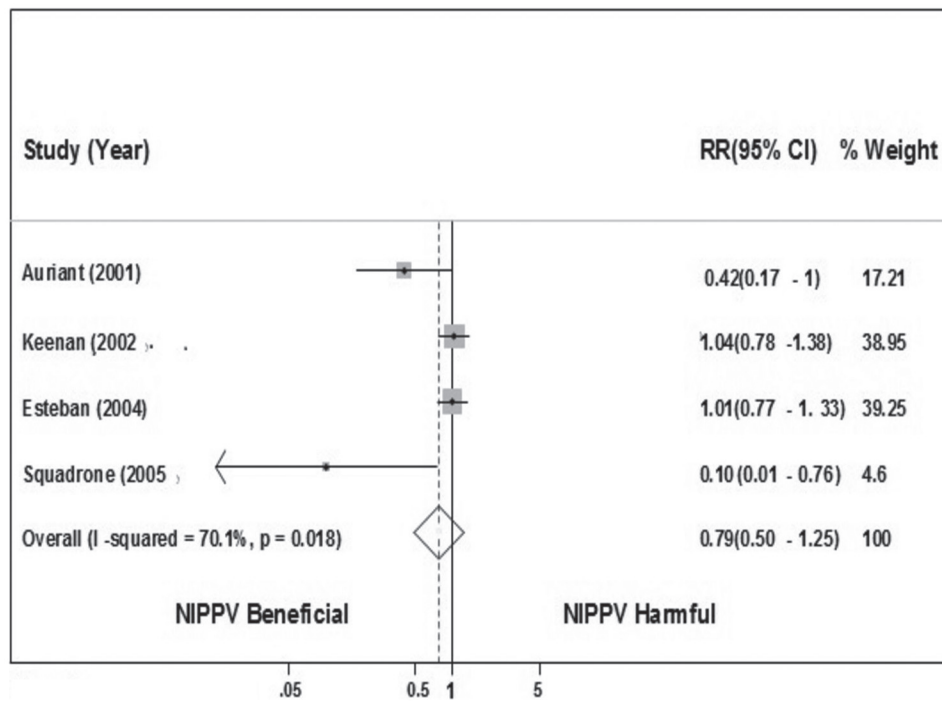


Figure 3: Effect of non-invasive positive pressure ventilation on reintubation in therapeutic trials. (Vertical solid line = null effect, vertical dotted line = overall mortality effect of treatment, boxes and horizontal lines = relative risk [95% confidence interval])

Table 3: Secondary outcome results

Outcomes (References)	Subjects (trials)	RR ^a /WMD ^b (95% CI)	P value	I ² Heterogeneity (%)
Prophylactic trials				
ICU mortality ^[21,22,31,41]	569 (4)	RR 0.53 (0.16-1.75)	0.296	54.1
Hospital mortality ^[21,22,28,31,41]	485 (5)	RR 0.62 (0.4-0.97)	0.037	0
ICU length of stay ^[21,22,26,28,29,31,41]	747 (7)	WMD-1.35 (-3.33-0.62)	0.180	93.8
Hospital length of stay ^[21,22,28-31,41]	710 (7)	WMD-2.18 (-8.44-4.07)	0.494	98.8
Therapeutic trials				
ICU mortality ^[19,20]	302 (2)	RR 1.14 (0.43-3.00)	0.795	70
Hospital mortality ^[19,32,33]	338 (3)	RR 0.55 (0.20-1.53)	0.251	49.3
ICU length of stay ^[19,20,32,33]	559 (4)	WMD-1.17 (-2.82 to-0.33)	0.006	0
Hospital length of stay ^[19,32,33]	338 (3)	WMD-0.74 (-4.10-2.61)	0.663	0

^aRR: Relative risk for binary events; ^bWMD: Weighted mean difference for continuous measures; ^cValues of I² are percentages, a value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. ICU: Intensive care unit

spirometry and deep breathing exercises); as a means of post-operative chest physiotherapy;^[42] for preventing post-operative pulmonary complications;^[43] for early weaning from ventilator;^[23,25] and for post-extubation respiratory failure on a mixed population.^[24]

The meta-analysis by Agarwal *et al.*^[24] included 4 trials with 2 trials assessing role of NIPPV in patients “at risk” for post-extubation failure and 2 trials where NIPPV was used in established post-extubation respiratory failure. NIPPV when used on “at risk” patients, reintubation and ICU mortality was reduced, but hospital mortality was unchanged. NIPPV usage after the development of respiratory failure did not show any evidence of benefit. The subset of patients who have been identified as high risk of developing an extubation failure are: Age above 65 years, more than one consecutive failure to wean or extubation, cardiac failure, PaCO₂ >45 mmHg, weak cough, Apache II score >12 on the day of extubation, stridor not requiring immediate reintubation,^[6,7] thoracic or abdominal surgeries,^[44] and obesity body mass Index >40 kg/m².^[45]

In this review, there were 9 more trials with 859 patients. Eight of the nine trials included high risk patients.^[21,22,26,28-31,41] The trial by Jiang *et al.*^[27] was excluded by Agarwal *et al.*^[24] because it did not include patients who were at risk of developing respiratory failure, but included in this review as it met the inclusion criteria. There were 7 post-operative trials^[26,28-33] included in this review. Post-operative patients differ from patients who were extubated in the ICU after a period of acute respiratory failure. The reasons for including these

post-operative trials in this review are; the physiological rationale for post-operative NIPPV use is the same as for post-extubation NIPPV use.^[10,44] The patient-related risk factors for post-operative pulmonary complications, are similar to the risk factors for post-extubated patients and trials, which included a mixed population have considered post-operative patients.^[19-22]

The results from this review supports the beneficial effect of prophylactic application of NIPPV found in an earlier review.^[24] No definite inferences could be drawn on the effect of NIPPV on secondary outcomes in this review as only 4 of the 9 trials (569 patients) reported on ICU mortality and 5 trials (485 patients) reported on hospital mortality. Only in the trials by Jiang^[27] and Böhner *et al.*^[29] the direction of the treatment effect differed from the overall estimate. The trial by Jiang *et al.*^[27] where reintubation rates were increased, had a significant number of self extubated patients and was one of the earliest studies. The trial by Böhner *et al.*,^[29] where ICU mortality was increased due to surgical complications and unrelated to NIPPV.

The large therapeutic trial by Esteban *et al.*^[20] found that the NIPPV group had increased mortality in the ICU as compared with the standard therapy group. The rates of reintubation in both the NIPPV and the standard therapy group were the same. The delay in reintubation (12 h for NIPPV vs. 2.5 h for the standard therapy group) was the apparent cause of increased mortality. It is interesting to note that this trial was interrupted after an interim analysis and 28 patients were crossed over to receive NIPPV. These crossed over patients were not included in the analysis and the apparent success of NIPPV in this group was also not mentioned. Multiple regression analysis undertaken by Hess *et al.*^[46] indicated that both assignment to NIPPV and reintubation were independent predictors of mortality in this trial and the reason for increased mortality in the NIPPV group was uncertain. Our results in the therapeutic group (4 trials and 559 patients) suggested that no definite conclusion can be drawn regarding the benefits or harm associated with NIPPV in preventing reintubation, ICU and hospital mortality and hospital length of stay. ICU length of stay was reduced, which could be explained by the fact that use of NIPPV decreased the number of days of ventilation and early mobilization out of ICU.

The composition of the study populations may also have been determinate; hence, meta-regressions were performed in each group to assess the significance of COPD, cardiac failure or post-operative status as predictor variables. Neither COPD nor cardiac failure

affected the primary outcome (reintubation) in either group. This could be explained by the relatively small number overall of, COPD (17.95%) and cardiac failure (14.5%) patients. The trials by Nava *et al.*^[21] and Ferrer *et al.*^[22] had a high number of COPD patients; 36% and 51% respectively; and the more recent trial by Ferrer *et al.*^[41] included 70% of COPD patients. This may explain the apparent success of NIPPV noted in the prophylactic trials.

A recent systematic review was performed by Ferreyra *et al.*^[43] assessing the efficacy of CPAP in treating post-operative pulmonary complications after abdominal surgery. The results supported the use of CPAP in treating post-operative pulmonary complications, atelectasis and pneumonia and in preventing intubation. There were 2 RCTs^[29,33] with 413 patients reporting on intubation as an outcome and the pooled estimate was beneficial: RR 0.85 (95% CI 0.34-0.97) and these 2 RCTs have been included in the current review. The current review included 729 post-operative patients, 660 from 7 post-operative trials^[26,28-33] and 69 from 4 trials^[19-22] of mixed etiology. Post-operative status had a null effect on any outcome in a meta-regression with NIPPV use, either prophylactically or therapeutically. The varied result could be explained by, larger number of trials and patients in the current review; different outcomes of interest between the two reviews; and the inclusion of trials using both CPAP and BiPAP, in the current review.

In a secondary analysis with reintubation as the outcome and with respect to the type of NIPPV, there appeared to be some evidence that CPAP was more efficacious in prophylactic trials: RR 0.199 (95% CI 0.059-0.667); $P = 0.009$, but this estimate was (i) quite small in its scalar value compared with the overall estimate: RR 0.53 (95% CI, 0.28-0.98) and $P = 0.04$ (ii) probably unbelievable with respect to its efficacy and (iii) subject to repeated testing and small numbers. CPAP usage was also significantly more in post-operative patients in the prophylactic trials (Pearson Chi-squared = 5.76; $P = 0.016$).

There are several limitations to this review. The benefits of decreasing reintubation in the prophylactic subgroup did not translate into consistent reductions in mortality and length of stay. This could be due to NIPPV improving only a segment in the span of the disease process and all trials not reporting on the primary and secondary outcomes of interest. The time to initiation of NIPPV after extubation would have been a better tool in assessing the role of NIPPV in post-extubation failure but was not reported in a majority of the studies. Subgroup analysis based on the type of trial (post-operative/non post-operative) was

also not possible as the number of trials in each group were too few. The quality scoring of the trials ranged from 13 to 24 (median 20), earlier studies having lower scores. There was significant statistical and clinical heterogeneity. The trials varied in the patient selection, the mode of NIPPV, duration and levels of pressure support used. The type of interface and the skill of the supportive staff and patient selection criteria would also influence the results, but these factors could not be addressed in this review.

A sample size calculation, as recommended by Flather *et al.*^[47] was done to assess the power of the meta-analysis using reintubation as the outcome of interest. The number of patients in the prophylactic group (782) was adequate to give a power of 89% while the number in the therapeutic group (559) was inadequate with a power of only 55%. These estimates were obtained using a significance level of 0.05. Flather *et al.*^[47] have pointed that a significance level of 0.01 would be more appropriate in meta-analysis. Using a value of $P = 0.01$, both groups are underpowered to detect significant differences, (prophylactic 74% and therapeutic 31%). The number of events for the secondary outcomes was also inadequately powered to detect significant differences.

Conclusions

The results of this systematic review suggested that prophylactic NIPPV is beneficial with respect to reintubation and the therapeutic use of NIPPV has no demonstrable effect. Larger trials evaluating the therapeutic role of NIPPV are indicated as no large trial has been published in the last 5 years.

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How to cite this article: Krishna B, Sampath S, Moran JL. The role of non-invasive positive pressure ventilation in post-extubation respiratory failure: An evaluation using meta-analytic techniques. *Indian J Crit Care Med* 2013;17:253-61.

Source of Support: Nil, **Conflict of Interest:** None declared.

Appendix

Appendix 1: Search done on 14/6/2010 with date limits (01/01/1966-31/05/2010) and age limits > 19 years (randomized controlled trial (pt) OR controlled clinical trial (pt) OR randomized controlled trials (mh) OR random allocation (mh) OR double-blind method (mh) OR single-blind method (mh) OR clinical trial (pt) OR clinical trials (mh) OR ("clinical trial"[tw]) OR ([singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR ("latin square"[tw]) OR placebos (mh) OR placebo* (tw) OR random* (tw) OR research design (mh) OR comparative study (mh) OR evaluation studies (mh) OR follow-up studies (mh) OR prospective studies (mh) OR cross-over studies (mh) OR control* (tw) OR prospectiv* (tw) OR volunteer* [tw]) NOT (animal [mh] NOT human [mh]) AND (non-invasive positive-pressure ventilation OR non-invasive positive pressure ventilation OR non-invasive positive pressure ventilation OR positive-pressure ventilations, non-invasive OR ventilation, non-invasive positive-pressure OR ventilations, non-invasive positive-pressure OR positive-pressure non-invasive ventilation OR positive pressure non-invasive ventilation OR positive-pressure ventilation, non-invasive OR positive pressure

ventilation, non-invasive OR non-invasive ventilation, positive-pressure OR non-invasive ventilation, positive pressure OR non-invasive ventilation, positive-pressure OR positive pressure non-invasive ventilation OR ventilation, positive-pressure non-invasive OR ventilations, positive-pressure non-invasive OR continuous positive airway pressure ventilation (CPAP) ventilation OR ventilation, cpap OR nasal continuous positive airway pressure OR ncpap ventilation OR ventilation, ncpap OR biphasic continuous positive airway pressure OR bilevel continuous positive airway pressure) AND (Unplanned extubation OR extubation OR extubation failure OR early extubation OR post extubation OR extubation criteria OR extubation stridor OR tracheal extubation OR accidental extubations OR post extubation stridor OR self extubation OR extubation cardiac surgery OR weaning extubation OR extubation readiness OR failed extubation OR endotracheal extubation OR dexamethasone extubations OR early extubation cardiac surgery OR deep extubations) AND (English [lang] AND (adult [MeSH: noexp] OR middle age [MeSH] OR (middle age [MeSH] OR aged [MeSH]) OR aged [MeSH] OR aged, 80 and over [MeSH]) AND ("1966/01/01"[PDat]: "2010/05/31"[PDat])