ORIGINAL ARTICLE

Noninvasive positive pressure ventilation

Effect on mortality in acute cardiogenic pulmonary edema: a pragmatic meta-analysis

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KEY WORDS

bi-level positive airway pressure, continuous positive airway pressure, positive pressure ventilation, pulmonary edema

ABSTRACT

INTRODUCTION In contrast to a series of recent meta-analyses (MAs), the 3CPO (Three Interventions in Cardiogenic Pulmonary Oedema) randomized controlled trial (RCT) reported in 2008 did not find a significant mortality benefit of noninvasive positive pressure ventilation (NPPV) in acute cardiogenic pulmonary edema (ACPE).

OBJECTIVES This paper combines data collected in the 3CPO trial together with data from recent MAs and calculates a revised risk ratio for NPPV in ACPE. Reasons for the discrepancy in mortality estimates are identified and discussed through contrasting the methodology and results of the 3CPO trial with previous RCTs.

PATIENTS AND METHODS Patients included adults with ACPE secondary to a variety of insults such as hypertension, acute coronary syndromes, dietary indiscretion, arrhythmias and valvular lesions and assessed by clinical parameters (respiratory rate, crackles, oxygen saturation) and chest radiograph. Data was collected from MAs published after 2005 and their respective RCTs. As opinions regarding RCTs worthy of inclusion in the analyses were varied, 3 sets of RCTs were combined with the 3CPO data. The first set of data duplicated the RCTs chosen in the Cochrane; the second set, a comprehensive set, included all RCTs cited in any of the MAs reviewed; and the third set, a high quality RCT set, assessed data from only those RCTs included in at least 4 out of the 5 MAs reviewed. Data were analyzed with both fixed and variable effect modes using Revman software.

RESULTS All combinations of RCTs and modes of analysis predict a significant mortality benefit. The combined data predicts a risk ratio for mortality using NPPV of 0.75 (95% CI: 0.61–0.92).

CONCLUSIONS An analysis of the existing RCT data, inclusive of the 3CPO trial, predicts a continued and significant mortality benefit of NPPV in ACPE.

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INTRODUCTION Acute cardiogenic pulmonary edema (ACPE) can be caused by a variety of insults including, among others, dietary indiscretion, medication non-compliance, hypertensive crisis, arrhythmias, acute coronary syndromes and valvular lesions. A variety of modalities exist to treat ACPE such as standard medical care including venodilators, after load reduction, inotropic medications and diuretics; insult specific modes like rate controlling agents in tachyarrhythmia; noninvasive positive pressure ventilation modes (NPPV) including continuous positive airway pressure (CPAP) and bi-level positive airway pressure (BiPAP); and finally, invasive ventilation/intubation.

Several recent meta-analyses (MAs) concluded that NPPV provided a significant mortality benefit in patients with ACPE.[1-5] However, the 3CPO (Three Interventions in Cardiogenic Pulmonary Oedema) trial published in 2008, the largest randomized controlled trial (RCT) of its kind (n = 1069), found no significant mortality benefit from this intervention.[6] This disagreement presents clinical concern – a physiologically sensible and widely used method of immediate preload, shunt, work of breathing and after load reduction in ACPE is now questioned regarding its effectiveness. This analysis integrates the 3CPO trial mortality data into recent MAs, and presents a modified prediction of the effect on mortality of NPPV

TABLE 1 Randomized control trials included in meta-analyses and in modified meta-analyses

RCT	Year	Crossover	Meta-analysis					Modified meta-analysis		
			Vital 2008 (Cochrane)	Masip 2005	Peter 2006	Collins 2006	João 2006	3CPO+ (Cochrane)	3CPO+ all trials	3CPO + agreed trials
Bersten	1991	–	Y	Y	Y	Y	Y	Y	Y	Y
Crane	2004	–	Y	Y	Y	Y	Y	Y	Y	Y
Delclaux	2000	+	Y		Y			Y	Y	
Ferrer	2004	+			Y				Y	
Kelly	2002	–	Y	Y	Y	Y	Y	Y	Y	Y
L'Her	2004	?	Y	Y	Y	Y	Y	Y	Y	Y
Levitt	2001	–	Y	Y	Y	Y	Y	Y	Y	Y
Lin	1991	+	Y					Y	Y	
Lin	1995	–	Y	Y	Y		Y	Y	Y	Y
Masip	2000	–	Y	Y	Y		Y	Y	Y	Y
Nava	2003	–	Y	Y	Y	Y	Y	Y	Y	Y
Park	2001	–	Y	Y	Y		Y	Y	Y	Y
Park	2004	–	Y	Y	Y	Y	Y	Y	Y	Y
Räsänen	1985	–	Y	Y	Y		Y	Y	Y	Y
Sharon	2000	–	Y					Y	Y	
Takeda	1997	–	Y	Y	Y		Y	Y	Y	Y
Takeda	1998	–	Y		Y		Y	Y	Y	
Thys	2002	+	Y					Y	Y	
3CPO	2008	+						NEW	NEW	NEW

+ allowed, – not allowed, ? unclear from article, Y – included

Abbreviations: RCT – randomized controlled trial, 3CPO – Three Interventions in Cardiogenic Pulmonary Oedema

TABLE 2 Mortality estimate for modified meta-analyses

Modified meta-analysis (30 and 7 day mortality)	Risk ratio (CI)			
	fixed (30 day)	random (30 day)	fixed (7 day)	random (7 day)
3CPO + Cochrane	0.75 [0.61, 0.92]	0.78 [0.63, 0.96]	0.72 [0.57, 0.92]	0.75 [0.59, 0.96]
3CPO + all trials	0.75 [0.60, 0.92]	0.75 [0.62, 0.96]	0.72 [0.57, 0.91]	0.75 [0.59, 0.95]
3CPO + agreed trials	0.75 [0.60, 0.94]	0.75 [0.62, 0.97]	0.73 [0.56, 0.94]	0.75 [0.57, 0.97]

Abbreviations: see TABLE 1

in ACPE. Possible reasons for the RCT-MA incongruence are discussed below.

PATIENTS AND METHODS Five MAs were used to provide a comprehensive set of RCTs available at approximately the beginning of 2005.[1-5] Based on their assessment and ranking of the quality of each RCT, the MA authors selected a slightly different set of RCTs to include in each individual MA. However, TABLE 1 shows that most MAs are based on a very similar set of RCTs. Collins et al.[3] included the fewest number of trials, and when their MA was excluded from TABLE 1 there was a high level of agreement among the remaining MAs. The Cochrane review by Vital et al. is the most recent and comprehensive of the MAs.[4] TABLE 1 further reveals that many authors have not included the RCTs by Delclaux 2000, Ferrer 2004, Lin 1991, Sharon 2000 and Thys 2002 in their analyses. Reviewing individual MAs revealed that the exclusion of these trials was not based on lack of awareness of their existence but rather on concern regarding their quality, methodology and appropriateness for inclusion.

To avoid the possibility that the choice of studies included in this modified analysis might influence its result, three sets of RCTs were used and combined with the 3CPO data. TABLE 1 shows those RCTs included in 3 separate analyses: the first duplicated the Cochrane analysis (Cochrane Set); the second included all trials identified within any of the MAs (Comprehensive Set); and the third included only those trials agreed to among four out of the five of the MAs (Quality Set).

All statistical analyses were performed with Review Manager (Revman Version 5) utilizing both fixed and variable effect models.[7] In hospital, mortality was the end point of all previous MAs, but the 3CPO trial reported only 7 and 30 day mortality. Therefore, the combined MA/3CPO data was analyzed with both 7 and 30 day mortality data.

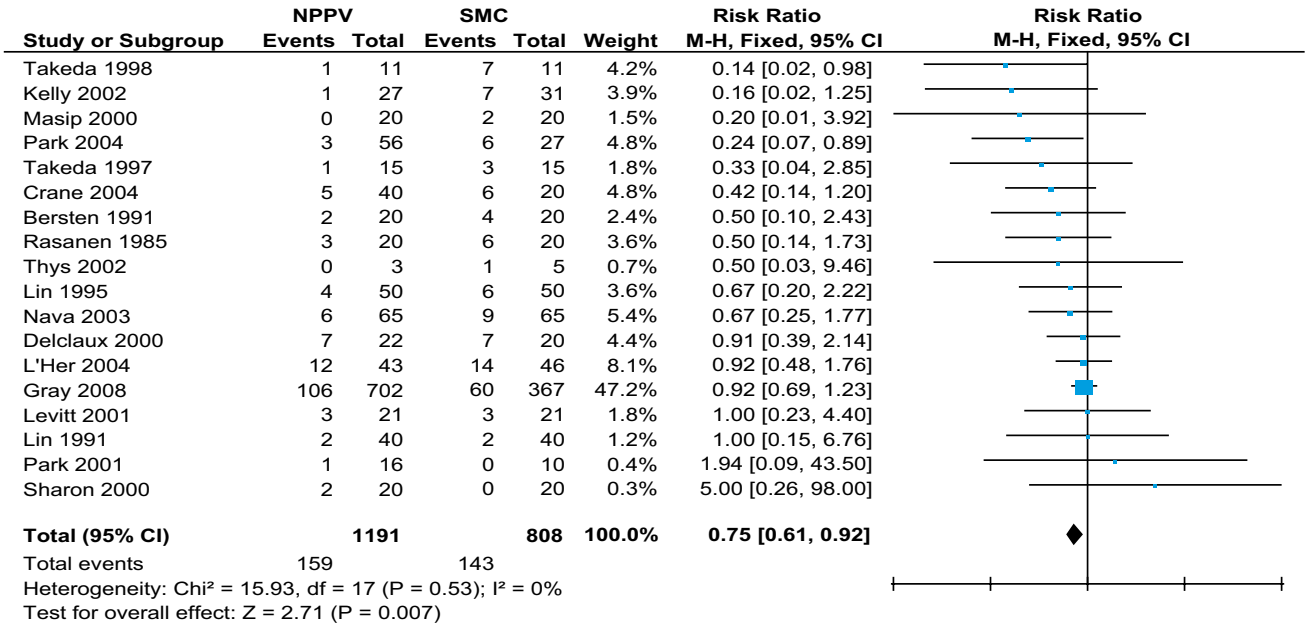

FIGURE Mortality Risk Ratio – NPPV vs. SMC – Modified Cochrane Analysis (Fixed Effect)

Abbreviations: NPPV – noninvasive positive pressure ventilation, SMC – standard medical care

RESULTS The FIGURE shows that when the 3CPO data (30 day mortality) is added to the Cochrane MA, there continues to be a significant mortality benefit of NPPV in ACPE (fixed effect model, risk ratio 0.75, CI 0.61–0.92). TABLE 2 gives the results of all the analyses identified in TABLE 1. A sensitivity analysis, taking into account all modes of analysis and combinations of RCTs, continues to predict a statistically significant mortality benefit of NPPV in ACPE. Significant heterogeneity was not observed in any of the analyses performed (all I^2 below 10%).

DISCUSSION While the modified analysis predicts a continued mortality benefit, it remains of interest to examine reasons for the RCT-MA incongruence. The post 3CPO trial discussion identifies many reasons for the incongruence.[8] Among these reasons, two overlapping and key factors are crossover and intubation rates. Only a rigid trial not allowing crossover from the standard medical care (SMC) group into the NPPV group can accurately estimate mortality benefit. This was not the case in the 3CPO trial which allowed, after only 2 hours of separate randomization, full clinical discretion in patient management. Furthermore, within 2 hours of randomization, 19% of SMC patients (those with worsening respiratory parameters) had their therapy escalated to NPPV and intubation (only 1% were intubated, the other 18% were rescued with NPPV). The paper does not reveal how many patients crossed into the NPPV group after the 2 hour trial period. Considering the degree of crossover and rescue NPPV within the 3CPO trial, rather than address the mortality benefit of NPPV in ACPE, the trial simply evaluates whether in patients who clinically merit NPPV, a short delay in initiating NPPV increases mortality.

The high crossover/early rescue NPPV within the 3CPO trial likely reflects evidence of the benefit of NPPV that had accumulated at the time of the trial. With this evidence, there was no ethical opportunity to design the trial in the rigorous non-crossover fashion that would accurately estimate the mortality benefit of NPPV. This limitation and restriction in trial design did not exist in the earlier RCTs completed before the evidence for the benefit of NPPV was so compelling. High rates of crossover/rescue NPPV were explicit exclusion criteria in some MAs. Owing to its design and crossover, the 3CPO trial would not have been included in Masip's MA. TABLE 1 shows that very few of the RCTs included within the MAs allowed crossover within the trial methodology.

The influence of NPPV/rescue NPPV/crossover on avoiding intubation and the mortality benefit of avoiding any intubation are overlapping variables that merit individual consideration in assessing the benefit of NPPV. The risks of intubation include ventilator associated pneumonia, tracheal injury and prolonged intensive care unit and hospital stay.[4] Peter et al. estimated that in ACPE it is only necessary to treat 6 or 7 with NPPV to avoid one intubation.[2] Peter's MA found intubation rates in the SMC and NPPV groups of 27% and 12%, respectively.[2] In dramatic contrast to all of the MAs identified in this paper, the 3CPO trial had very low intubation rates that were the same (3%) in both the SMC and NPPV groups. Did the crossover allowed within the 3CPO trial reduce intubations in the SMC group and did this in turn affect the predicted mortality benefit of NPPV?

Significant differences found between the 3CPO trial and previous MAs include: the high degree of crossover/rescue NPPV found in the 3CPO trial; the overall low rate of intubation in the 3CPO trial; and the equivalent rate of intubation between the SMC and NPPV groups in the 3CPO trial. These differences help explain the important

RCT-MA incongruence addressed in this paper. Prior to the 2008 3CPO trial there was a state of agreement within the literature, and at least five separate MAs concluded, that NPPV in ACPE provided a strong, significant mortality benefit. Although the 3CPO trial did not confirm this mortality benefit, when its data is analyzed together with a comprehensive set of RCTs (at the end of 2005), in varying combinations and analysis modes (fixed and variable), in every instance there continues to be a statistically significant mortality benefit of NPPV in ACPE. The high rate of crossover and low intubation rates within the 3CPO trial were in part responsible for its lack of mortality benefit. Therefore, the combined mortality estimate of this modified MA is an underestimation of the true mortality benefit. The results of this modified MA together with a review of the methodology of the 3CPO trial support an important and significant mortality benefit of NPPV in ACPE.

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Nieinwazyjna wentylacja mechaniczna dodatnim ciśnieniem

Wpływ na śmiertelność w ostrym kardiogennym obrzęku płuc: metaanaliza pragmatyczna

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SŁOWA KLUCZOWE

dwupoziomowe dodatnie ciśnienie w drogach oddechowych, obrzęk płuc, stałe dodatnie ciśnienie w drogach oddechowych, wentylacja mechaniczna ciśnieniem dodatnim

STRESZCZENIE

WPROWADZENIE W odróżnieniu od wielu ostatnio przeprowadzonych metaanaliz (*meta-analysis* – MA), randomizowane badanie kliniczne (*randomized controlled trial* – RCT) pod nazwą 3CPO (Three Interventions in Cardiogenic Pulmonary Oedema) ogłoszone w 2008 roku, nie wykazało znamiennego zmniejszenia śmiertelności podczas stosowania nieinwazyjnej mechanicznej wentylacji dodatnim ciśnieniem (*noninvasive positive pressure ventilation* – NPPV) w ostrym kardiogennym obrzęku płuc (*acute cardiogenic pulmonary edema* – ACPE). Znaleziono i przedyskutowano przyczyny rozbieżności w ocenie śmiertelności poprzez porównanie metodologii i wyników dla badania 3CPO z poprzednimi RCTs.

CELE Raport ten łączy dane zebrane w trzech próbach CPO razem z danymi pochodzącymi z ostatnich MA w celu obliczenia poprawionego współczynnika ryzyka NPPV w ACPE.

PACJENCI I METODY Do grupy ocenianych pacjentów włączano osoby dorosłe z ACPE wtórnym, wywołanym przez szereg czynników takich jak nadciśnienie tętnicze, ostre zespoły wieńcowe, błędy dietetyczne, arytmie, uszkodzenie zastawek, ocenianym poprzez parametry kliniczne (częstość oddychania, trzeszczenia nad płucami, wysycenie krwi tętniczej tlenem) oraz zdjęcie RTG klatki piersiowej. Dane uzyskano z MA opublikowanych po 2005 roku i odpowiadających im RCT. Opinie odnoszące się do RCT wartych włączenia do analiz różniły się, więc utworzono 3 zbiory RCT, które połączono z danymi z 3CPO. Pierwszy zbiór danych kopiuje RCT wybrane w recenzji Cochrane; drugi (obszerny) zbiór obejmuje wszystkie RCT wymienione we wszystkich rewidowanych MA; trzeci, zbiór RCT o wysokiej jakości, ocenia dane tylko z tych RCT, które były zawarte w przynajmniej 4 z 5 rewidowanych MA. Dane zostały zanalizowane przy zastosowaniu zarówno stałych, jak i zmiennych trybów efektu przy użyciu oprogramowania Revman.

WYNIKI Wszystkie kombinacje RCT i tryby analizy wzięte pod uwagę w niniejszej pracy przewidują znamienne zmniejszenie ryzyka zgonu. Połączone dane przewidują stosunek ryzyka dla zgonu w przypadku zastosowania NPP wynoszący 0,75 (95% CI: 0,61–0,92).

WNIOSKI Analiza istniejących danych RCT, włącznie z próbą 3CPO, przewiduje ciągłe i znamienne zmniejszenie śmiertelności dzięki zastosowaniu NPPV w ACPE.

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