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SYSTEMATIC REVIEW

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Noninvasive ventilation in chest trauma: systematic review and meta-analysis

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Abstract *Purpose:* Single studies of Noninvasive Ventilation (NIV) in the management of acute respiratory failure in chest trauma patients have produced controversial findings. The aim of this study is to critically review the literature to investigate whether NIV reduces mortality, intubation rate, length of stay and complications in patients with chest trauma, compared to standard therapy. *Methods:* We performed a systematic review and meta-analysis of randomized controlled trials, prospective and retrospective observational studies, by searching PubMed, EMBASE and bibliographies of articles retrieved. We screened for relevance studies that enrolled adults with chest trauma who developed mild to severe acute respiratory failure and were treated with NIV. We included studies reporting at least one clinical outcome of interest to perform a meta-analysis. *Results:* Ten studies (368 patients) met the inclusion criteria and were included for the meta-analysis. Five studies (219 patients) reported mortality and results were quite homogeneous across studies, with a summary relative risk for patients treated with NIV compared with standard care (oxygen therapy and invasive mechanical ventilation) of 0.26 (95 % confidence interval 0.09–0.71, $p = 0.003$). There was no advantage in mortality of continuous positive airway pressure over noninvasive pressure support ventilation. NIV significantly increased arterial oxygenation and was associated with a significant reduction in intubation rate, in the incidence of overall complications and infections. *Conclusions:* These results suggest that NIV could be useful in the management of acute respiratory failure due to chest trauma.

Keywords Noninvasive ventilation · Chest trauma · Acute respiratory failure · Meta-analysis · Outcomes

Introduction

Chest trauma is reported to occur in 20 % of multiple trauma patients [1] and accounts for 20–40 % of all trauma deaths, second only to head and spinal injuries. Elderly patients and patients with poor respiratory function are the most likely to develop acute respiratory failure [1–3]. The most common injuries associated with chest trauma are rib fractures, pneumothorax, hemothorax, flail chest and pulmonary contusion [2, 4–6]. Lung function is impaired after chest trauma primarily by direct parenchymal damage resulting in hemorrhage and lung disruption, and subsequently, by the activation of systemic inflammation that causes alveolar capillary barrier dysfunction and increases extravascular lung water. All these pathophysiologic events in addition to excessive bronchial secretions and airway colonization can promote alveolar collapse, ventilation perfusion mismatch, lung consolidation and lung infection, causing mild hypoxemia to severe acute respiratory distress syndrome (ARDS). The incidence of post-traumatic ARDS is between 8 and 37 % of trauma patients [7–11] with the highest percentage within 3 days after the traumatic event [9] and the associated mortality ranging from 16 to 29 % [7, 8, 12]. Patients who developed ARDS had a significantly higher mortality rate [8, 13], longer hospital and intensive care length of stay and higher hospital cost than trauma patients without ARDS [12].

Clinical management of less severely injured patients generally involves only supplemental oxygen therapy, aggressive chest physiotherapy and pain relief, without any ventilator support [14–16]. In 40–60 % of patients, however, cardiovascular failure, flail chest, pulmonary contusion and the need for major surgery are risk factors for intubation and mechanical ventilation [17, 18]. However, invasive mechanical ventilation lasting more than 5 days increases the risk of late-onset pneumonia and bacteremia, which in turn rises morbidity and mortality [19, 20]. Noninvasive ventilation (NIV) reduced the need for intubation and improved the outcome in selected patients with acute cardiogenic pulmonary edema [21, 22], exacerbation of chronic obstructive pulmonary disease (COPD) [23], and hypoxemic respiratory failure [24]. NIV also significantly lowered the incidence of ventilator-associated pneumonia [25, 26] and the requirement for sedatives, with better patient comfort compared to invasive mechanical ventilation [27].

Since the first report by Uretzky et al. [28] on the use of NIV in chest trauma patients, several randomized controlled trials, prospective observational studies and case reports have described the application of NIV in trauma [27]. In a multicenter survey of post-traumatic patients with acute respiratory failure the rate of treatment failures with NIV was 18 %, similar to those observed in patients with cardiogenic pulmonary edema [20]. However, the British Thoracic Society Guidelines suggested, with a low grade of recommendation, the use of NIV in patients with chest trauma who remain hypoxic despite adequate regional anesthesia and high oxygen flow [29]. Thus, irrespective of the widespread use of NIV and its unique benefits compared to mechanical ventilation, there is no clear consensus on its use in chest trauma [27].

These considerations led us to conduct a systematic review and a meta-analysis to investigate whether NIV in the form of either continuous positive airway pressure (CPAP), bi-level positive airway pressure (BiPAP) or noninvasive pressure support ventilation (NIPSV) reduced mortality, intubation rate, length of stay and complications compared to standard medical therapy (oxygen therapy or invasive mechanical ventilation).

Materials and methods

Search strategy

We performed a computerized search of MEDLINE/PubMed and EMBASE. All databases were searched from inception until July 2012. Our search was limited to studies on humans and those published in English. We used the following search keywords and terms: (chest trauma OR abdominal trauma OR pulmonary contusion OR posttraumatic hypoxemic respiratory failure OR trauma patients OR pneumothorax OR rib fractures) AND (noninvasive ventilation OR NIV OR continuous positive airway pressure OR CPAP). Three reviewers (DC, SC, SF) screened citation titles and abstracts independently. We reviewed the references of all articles retrieved and reviewed articles to identify additional potentially eligible studies. In case of disagreement the authors reviewed the article in question together until they reached a consensus. We identified and deleted any duplicate papers. All potentially eligible papers were retrieved in full.

Data were collected in a datasheet including the following: publication (first author's name, year, journal), study design, number of patients enrolled and outcomes.

Study selection

We screened for relevance studies that enrolled adults with chest trauma who developed mild to severe acute respiratory failure, were admitted to a trauma service, emergency department or intensive care unit (ICU) and were treated with NIV strategy.

Then we made a quantitative synthesis performing a meta-analysis. For this purpose we selected the following study designs: randomized controlled trials (RCTs), prospective observational trials (before and after treatment) and retrospective observational studies.

NIV was applied as CPAP or BiPAP (noninvasive intermittent positive pressure ventilation with two different levels of positive pressure) or NIPSV (noninvasive intermittent pressure support ventilation).

We considered the use of CPAP or BiPAP or NIPSV delivered using any interface as experimental strategy, compared to mechanical ventilation or unassisted supplemental oxygen therapy.

We included studies reporting at least one of the following clinical outcomes: gas exchange, respiratory rate, length of stay in ICU or hospital, complications, intubation rate, infections and mortality.

Statistical analysis

We ran our meta-analysis including all studies (observational and RCTs). For continuous outcomes (gas exchange, respiratory rate, length of stay in ICU or hospital), we extracted the mean responses, standard deviations (SD), and the group sizes, then we calculated the DerSimonian and Laird random effect mean weighted difference (WMD) using the pooled SDs of the treatment and control groups [30]. When the mean and SDs were not available we calculated the SD with the formula: SD = (max – min)/(2 × 1.96) [31]. (We could have used a larger divisor, e.g. 6, but we preferred a more conservative approach). Some were before-after studies, but since we did not have access to individual (matched) values, we could not calculate the correct SD of the mean difference. Therefore we considered them (conservatively) as unmatched studies.

For dichotomous outcomes (adverse events including infections, intubation rate, complications and mortality) we calculated summary relative risk (RR) estimates using DerSimonian and Laird random—effect models [30]. When a study contained a zero cell we added 0.5 to each cell to obtain finite variance estimators. The heterogeneity across studies was measured by the I^2 statistic [32]. I^2 values of 25–50 % indicate moderate inconsistency, whereas larger values reflect large inconsistencies among studies. We evaluated the possibility of publication bias using funnel plots and Begg's and Egger's test [30]. Statistical analyses were performed with Stata 12 (StataCorp. 2011. Stata: Release 12. Statistical Software. College Station, TX: StataCorp LP).

Results

Search and study selection

We identified 263 articles using the search strategy. The selection process is shown in Fig. 1.

After screening titles and abstracts for relevance and compliance with our inclusion criteria we excluded 224 articles that were considered as not relevant or that involved enrolling newborn and pediatric patients (Fig. 1) We added one other study from the reference list of the articles retrieved.

After examination of the full text of the selected papers we included 10 studies (observational studies and RCTs) for the meta-analysis (Tables 1 and 2). These studies enrolled patients admitted to ICUs and emergency departments in different countries: Italy [33, 34], USA [42], Spain [35, 36], Greece [37], South Africa [38, 39], Turkey [40] and Australia [41].

The total number of patients was 368. Selection criteria for the quantitative synthesis are presented in Fig. 1. Seven studies enrolled chest trauma patients with acute respiratory failure. In the majority the criteria for acute respiratory failure were a combination of impairment of oxygenation and increase in respiratory rate.

All studies used a face mask. Noninvasive positive pressure was delivered as CPAP [38–43], BiPAP [35–37, 41, 43] and as noninvasive pressure support ventilation (NIPSV) [33, 34, 37, 41, 43].

Effect of NIV on mortality

Five studies (219 patients) reported information on mortality. The pooled results are shown in Fig. 2. There were 3/101 (3.0 %) deaths in the NIV group compared to 27/118 (22.9 %) in the control group. There was no heterogeneity across studies.

The estimate of the RR for mortality in patients treated with NIV compared with standard care was 0.26 (95 % confidence interval 0.09 to 0.71, $p = 0.003$).

Effect of NIV on intubation rate, complications and length of stay

NIV significantly reduced the intubation rate [RR 0.32 (95 % confidence interval 0.12 to 0.86, $p = 0.023$)], overall complications and infection [RR 0.37 (95 % confidence interval 0.24 to 0.57, $p < 0.001$) and RR 0.34 (95 % confidence interval 0.20 to 0.58, $p < 0.001$), respectively] (Table 3).

The length of ICU stay was also significantly shorter: WMD −2.4 (95 % confidence interval −3.9 to −1.0, $p = 0.001$). Hospital length of stay was shorter, but without reaching significance: WMD −4.0 (95 % confidence interval −9.7 to 1.6, $p = 0.162$), although significant heterogeneity existed among studies ($I^2 = 94.9$ %) (Table 3).

Effect of NIV on gas exchange and respiratory rate

NIV increased the arterial oxygenation WMD of 101.0 (95 % confidence interval 10.6 to 191.5, $p = 0.029$), but did not affect the arterial carbon dioxide WMD of −1.03 (95 % confidence interval −5.19 to 3.13, $p = 0.627$) (Fig. 3, upper and middle panel). The respiratory rate was lower in the NIV group WMD of −9.25 (95 % confidence interval −15.72 to −2.79, $p = 0.005$) (Fig. 3, lower panel).

Discussion

To our knowledge this is the first systematic review and meta-analysis of the effect of NIV on chest trauma patients. We found that NIV significantly reduced mortality, requirement for tracheal intubation, length of ICU stay and improved oxygenation.

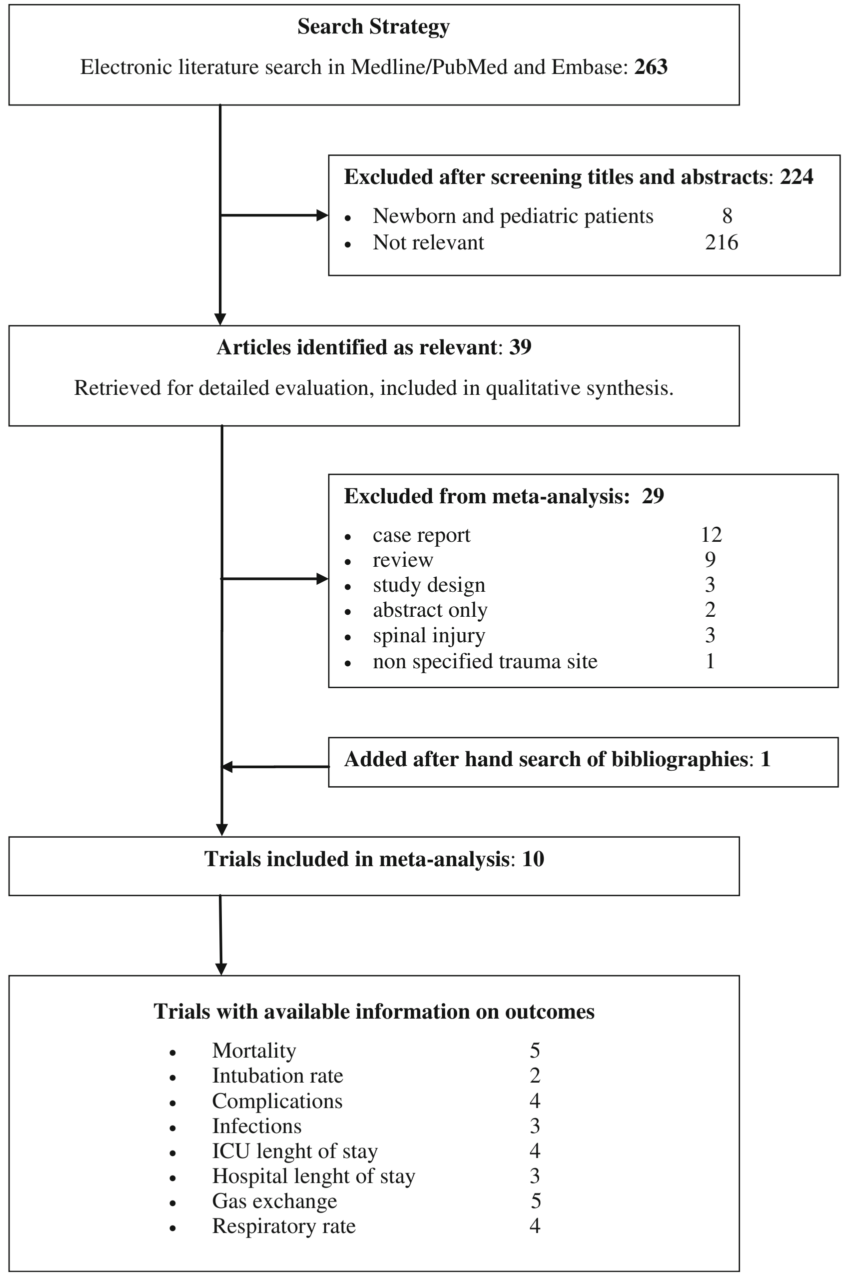

Fig. 1 Flow chart of the study selection process

In severe chest trauma patients, a lung lesion (i.e. pulmonary contusion, pneumothorax) and/or thoracic injury (hemothorax, rib fractures, flail chest) with inadequate pain relief and systemic inflammatory activation can promote acute respiratory failure due to alveolar collapse and impaired alveolar fluid clearance [44]. Therefore for several decades now, invasive mechanical ventilation with positive end-expiratory pressure (PEEP) has been suggested as the only possible ventilator support to improve gas exchange [45, 46]. Invasive mechanical ventilation has been used in up to 50 % of chest trauma patients [17, 18]. Although tracheal intubation and mechanical ventilation are life-saving tools, they can induce barotrauma, ventilator-associated infections and other complications relating to sedation and immobility [27].

NIV promotes a wider and earlier use of mechanical ventilation outside the ICU [27, 47–50], thus limiting "lung collapse" and the risk of early-onset pneumonia [51]. Several trials and meta-analysis indicate a beneficial effect of NIV on outcome in patients with acute cardiogenic pulmonary edema and exacerbations of COPD [23, 52]. Although some studies reported that NIV reduced mortality in patients with ARDS and severe community-

Table 1 Randomized controlled trials

Study	Study design	Inclusion criteria	Experimental strategy	Control strategy	Sample size		Outcomes
					Experimental	Control	
Bolliger and Van Eeden [38]	RCT	Chest trauma with multiple rib fractures	Face mask CPAP regional analgesia	CPPV	36	33	Complications, infections, ICU/hospital stay and ICU mortality
Gunduz et al. [40]	RCT	Chest trauma with multiple rib fractures and ARF	Face mask CPAP	CPPV	21	22	Gas exchange, infections, ICU/hospital stay and ICU mortality
Ferrer et al. [35]	RCT	Chest trauma with ARF	BiPAP face mask	High flow oxygen therapy	6	17	Intubation rate and ICU mortality
Hernandez et al. [36]	RCT	Chest trauma with ARF	BiPAP face mask	High flow oxygen therapy	25	25	Intubation rate, infections, ICU/hospital stay and mortality

RCT randomized controlled trial, *CPAP* continuous positive airway pressure, *BiPAP* bi-level positive airway pressure, *CPPV* continuous positive pressure ventilation, *ARF* acute respiratory failure, *ICU* intensive care unit

Table 2 Observational studies

Study	Study design	Inclusion criteria	Experimental strategy	Sample size	Outcomes
Hurst et al. [42]	Prospective observational	Trauma patients with ARF	Face mask CPAP	33	Gas exchange, respiratory rate and intubation rate
Xirouchaki et al. [37]	Prospective observational	Blunt thoracic trauma patients with ARF	Face mask BiPAP combined with regional analgesia	22	Gas exchange, respiratory rate and intubation rate
Gregoretti et al. [34]	Prospective observational	Trauma patients with ARF weaned from mechanical ventilation	Face mask NIPSV	22	Gas exchange, respiratory rate, intubation rate
Linton and Potgieter [39]	Retrospective observational	Blunt thoracic trauma patients	Face mask CPAP with regional analgesia	26	Complications and ICU stay
Beltrame et al. [33]	Retrospective observational	Trauma patients with ARF	Face mask NIPSV	46	Gas exchange, respiratory rate and intubation rate
Vidhani [41]	Retrospective non randomized	Trauma patients	Face or nasal CPAP/BiPAP	40	ICU mortality

CPAP continuous positive airway pressure, *BiPAP* bi-level positive airway pressure, *NIPSV* noninvasive pressure support ventilation, *ARF* acute respiratory failure, *ICU* intensive care unit

acquired pneumonia [22, 24], its use is still debated [53, 54].

The mortality rate in ARDS due to trauma is lower than for ARDS due to pneumonia or sepsis [10, 11], although the development of ARDS per se increases mortality. NIV may significantly lower the risk of ARDS developing, because of its role in lung recruitment (i.e. limiting lung collapse) and/or in preventing lung infections [27, 51]. Among the studies we analyzed only Hernandez et al. [36] did not find a lower mortality rate. Interestingly, NIV's effects on mortality were not related to the treatment modality. CPAP provides constant positive pressure throughout the respiratory cycle, while BiPAP or NIPSV provides intermittent positive pressure during inspiration, above the PEEP level. Theoretically BiPAP and NIPSV are more able to reduce the respiratory work of breathing and respiratory rates [55]. However, PEEP seems to influence the patient's final outcome more than intermittent positive pressure.

In trauma patients the risk for intubation depends not only on the severity of gas exchange impairment, but also on the severity of trauma [14, 56], on the extension of lung contusion and on the hemodynamic status [56]. Early use of NIV, by favoring chest stabilization and lung recruitment, might prevent the failure of spontaneous breathing and avoid the need for intubation. In a prospective multicenter cohort study of hypoxemic patients after pulmonary contusion, the intubation rate was 18 %, significantly lower than in patients with community-acquired pneumonia or ARDS [20]. The risk of failure

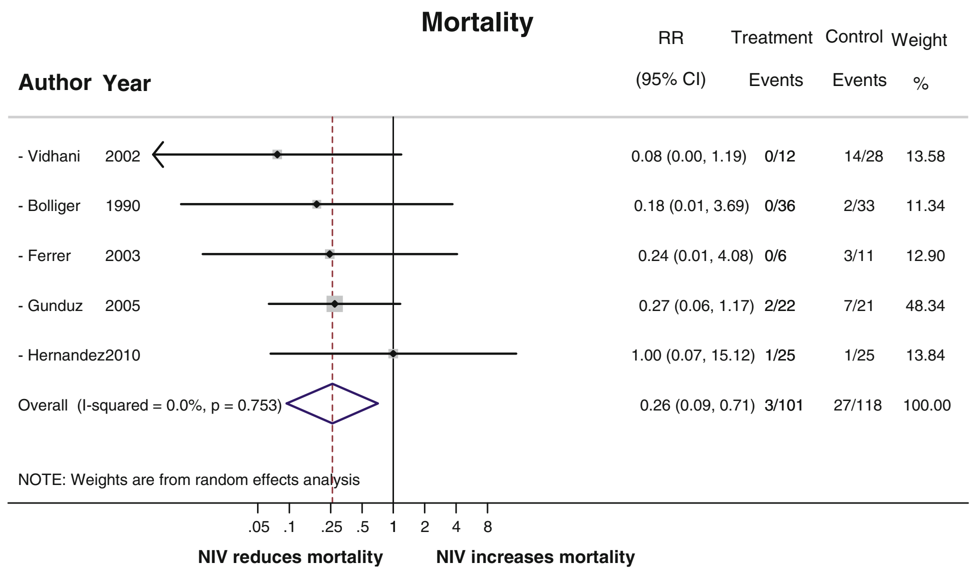

Fig. 2 Effect of Noninvasive Ventilation (NIV) on mortality in chest trauma patients. Treatment group represents the use of NIV. Control group represents mechanical ventilation or unassisted supplemental oxygen therapy. *Vertical solid line* null effect, *Vertical dotted line* overall mortality effect of treatment, *Boxes and horizontal lines* relative risk (RR) and 95% confidence interval, *CI* confidence interval, *NIV* noninvasive ventilation

Table 3 Summary estimates of outcomes of noninvasive ventilation in chest trauma patients

Outcomes	N° studies (N° patients)	Summary estimate (95 % CI)	*p* value (summary estimate)	*p* value (heterogeneity)	I^2 (%)
Adverse events					
Intubation rate	2 (67)	0.32# (0.12 to 0.86)	0.023	0.860	0.0
Complications	4 (188)	0.37# (0.24 to 0.57)	<0.001	0.722	0.0
Infections	3 (162)	0.34# (0.20 to 0.58)	<0.001	0.619	0.0
Length of stay (days)					
Intensive care	4 (188)	−2.4* (−3.9 to −1.0)	0.001	0.081	53.3
Hospital	3 (162)	−4.0* (−9.7 to +1.6)	0.162	<0.001	94.9

Complications identified by the authors refer to: pneumothorax, subcutaneous emphysema, broncopleural fistula, lung collapse, extrapleural hematoma, tracheal stenosis, respiratory and nosocomial infections, sepsis and multi-organ failure

* Weighted mean difference (DerSimonian and Laird Random effect)

\# Relative Risk (DerSimonian–Laird and Mantel–Haenszel random effect)

with NIV was associated with a higher SAPS II score and with persistent hypoxemia after 1 h of NIV [20]. Peter et al. [57] reported in a meta-analysis that NIV was associated with a significant reduction in the need for mechanical ventilation in all studies. However, the fact that no trauma patients were enrolled precluded any analysis in this subgroup.

The present meta-analysis found a significant reduction in the intubation rate with NIV (mean failure 14.5 %) and in the ICU length of stay as well as a lower infection rate. All except two of the studies [35, 42] were performed in ICUs, limiting the risk of bias from different locations, timing and nursing assistance [47].

The incidence of nosocomial pneumonia because of differences in the definition of pneumonia, patients' characteristics and risk factors, was not homogeneous, ranging from 20 to 40 % [15, 19, 20, 58, 59]. Prolonged ventilation (>24 h) and PEEP significantly raised the risk of nosocomial pneumonia [59]. In a clinical survey, Nourdine et al. [26] reported that the incidence of nosocomial pneumonia and ventilator-associated pneumonia (VAP) was respectively 14.2 versus 30.3 and 4.4 vs 13.2 per 1,000 patients—days when noninvasive positive pressure ventilation was compared to endotracheal intubation. Among the cofactors related to nosocomial infection and VAP, trauma significantly raised the risk of infection compared to medical or surgical reasons for hospital admission [26]. In the present meta-analysis, NIV had a beneficial effect in reducing the infection rate and ICU length of stay.

After a direct or indirect lung insult, chest trauma patients can develop increased lung permeability and parenchymal collapse with ventilation-perfusion mismatch. NIV, by raising transpulmonary pressure, should recruit the collapsed and poorly ventilated lung regions, both reducing the work of breathing and ameliorating gas exchange. Like previous meta-analysis which found that NIV improved gas exchange in acute cardiogenic pulmonary edema, acute exacerbation of COPD and acute respiratory failure [23, 24, 60], we also found that NIV

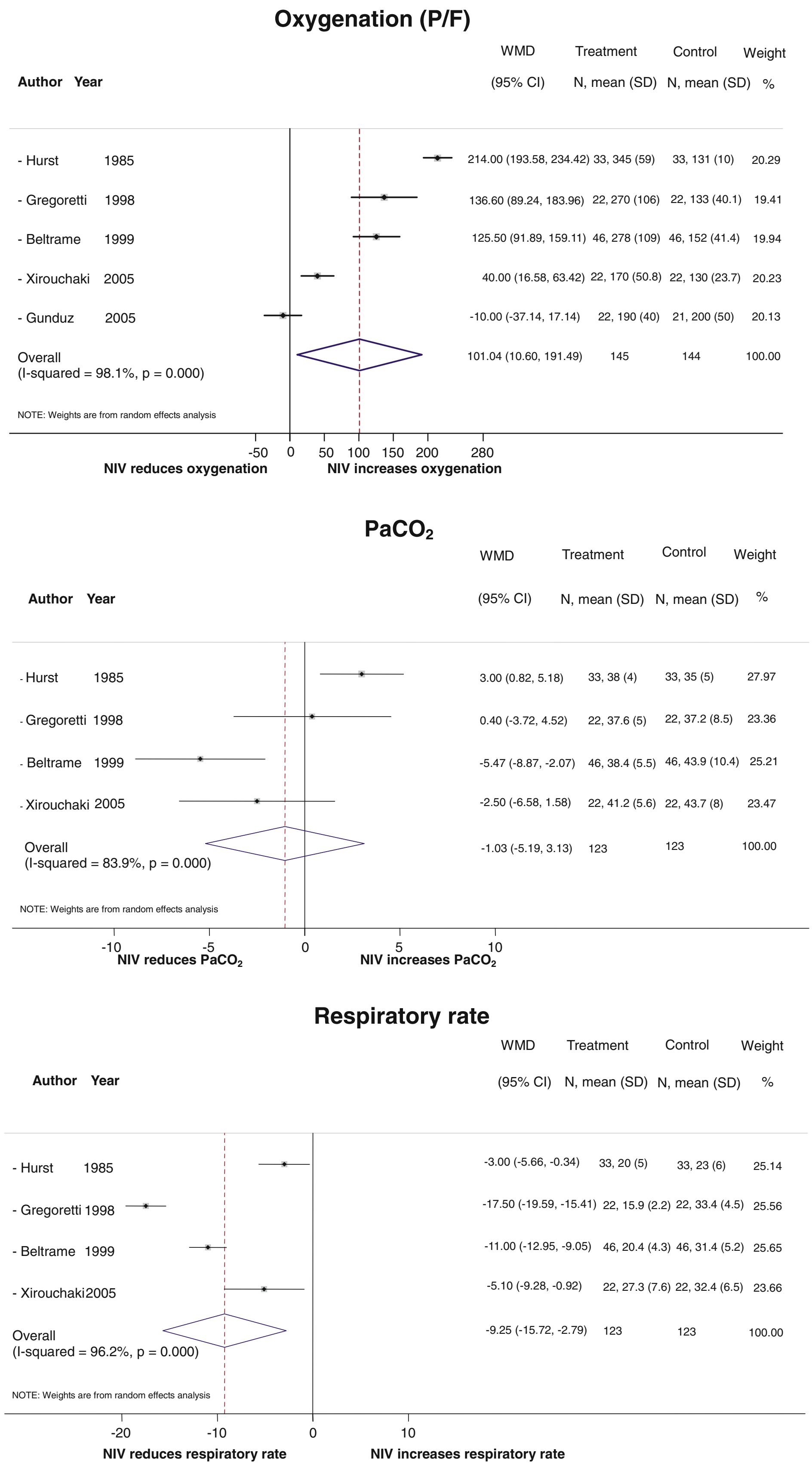

Fig. 3 Effect of Noninvasive Ventilation on respiratory parameters in chest trauma patients. *Upper panel* oxygenation (P/F)—ratio of arterial oxygen concentration to the fraction of inspired oxygen, *Middle panel* $PaCO_2$, *Lower panel* respiratory rate. Treatment group represents the use of NIV. Control group represents mechanical ventilation or –unassisted supplemental oxygen therapy. *Vertical solid line* null effect, *Vertical dotted line* overall effect of treatment, *Boxes and horizontal lines* weighted mean difference (WMD) and 95% confidence interval, *CI* confidence interval, *SD* standard deviation, *NIV* noninvasive ventilation, *N* number of patients

significantly ameliorated gas exchange in trauma patients. We found evidence of oxygenation improvement also when we restricted the meta-analysis to three studies [34, 37, 40] focusing on isolated chest trauma patients: WMD was 52.6 (versus 101.0 when considering all studies). For the other continuous outcomes the effect estimates (WMD or RR) were similar to those calculated in all the studies. Finally, binary outcomes were only evaluated among patients with isolated chest trauma.

Lung contusions are frequently associated with pneumothorax so any positive pressure ventilation might increase the entity of pneumothorax and eventually lead to hypertensive pneumothorax. In our analysis NIV use was not associated with any significant increase in the incidence of pneumothorax. Because CPAP involves a lower physiological risk of barotrauma with no less effect than NIPSV, it should be used as first-line treatment in patients with severe chest trauma [29].

The present meta-analysis has several limitations. First, the criteria for use of NIV in chest trauma differed among studies. Second, NIPSV—BiPAP pressure and ventilator characteristics were not homogeneous [47]. Third it was not possible to separate the effects of CPAP, BiPAP and NIPSV because of the paucity of studies for each group and moreover in one case these modalities were indifferently applied. Fourth, the number of eligible studies was relatively small. However, we found some possible evidence of publication bias only for length of hospital stay [36, 38, 40], for which we found $p = 0.30$ from Begg's and $p = 0.03$ from Egger's test, while for all other outcomes p values from either tests were always >0.40. We found high heterogeneity of effect across studies for the following continuous variables: oxygenation, $PaCO_2$, respiratory rate, length of hospital stay. For these analyses, we tried to explain heterogeneity by stratifying the studies by potentially important variables (type of study, type of comparison, site of trauma, severity of hypoxemia, patients' age, length of NIV treatment). However, due to the small number of studies, analysis was often not feasible or yielded unreliable results. For length of ICU stay, heterogeneity was mild (I^2: 53.3 %, $p = 0.09$). For binary outcomes (complications, infections, intubation rate, mortality), there was a remarkable homogeneity of effect across studies (Table 3 and Fig. 2), with $I^2 = 0$ and p values always >0.60.

Conclusion

This systematic review and meta-analysis indicates that the early use of NIV in chest trauma patients, facilitating stabilization of the chest and promoting the recruitment of collapsed lung regions, significantly reduces mortality and the intubation rate without increasing complications. However, NIV must be integrated with other medical and surgical clinical therapies.

Conflicts of interest Dr. Gregoretti received fees for lectures from Vivisol, SapoLife and Covidien. He also received fees for consultancies from Covidien and Smith Medical.

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