Critical Care

CRITICAL CARE

Effects of steroids on reintubation and post-extubation stridor in adults: meta-analysis of randomized controlled trials

Critical Care 2009, **13**:R49 doi:10.1186/cc7772

Samir Jaber (s-jaber@chu-montpellier.fr)
Boris Jung (b-jung@chu-montpellier.fr)
Gerald Chanques (g-chanques@chu-montpellier.fr)
Francis Bonnet (francis.bonnet@tnn.ap-hop-paris.fr)
Emmanuel Marret (emmanuel.marret@tnn.ap-hop-paris.fr)

ISSN 1364-8535

Article type Research

Submission date 5 December 2008

Acceptance date 3 April 2009

Publication date 3 April 2009

Article URL http://ccforum.com/content/13/2/R49

Effects of steroids on reintubation and post-extubation stridor in adults: meta-analysis of randomized controlled trials

Samir Jaber[1], Boris Jung[1], Gérald Chanques[1],
Francis Bonnet[2], Emmanuel Marret[2]

[1]Department of Anaesthesiology and Critical Care, University Saint Eloi Hospital, 80, avenue Augustin Fliche; University of Montpellier I; 34295 Montpellier Cedex 5, France

[2]Department of Anesthesiology and Critical Care, Tenon University Hospital, Assistance Publique Hôpitaux de Paris, and INSERM U 707 Université Pierre et Marie Curie, Paris 6, Paris, France

Correspondence:
Professor Samir Jaber
E-mail: s-jaber@chu-montpellier.fr

Abstract

Introduction: The efficacy of steroid administration before planned tracheal extubation in critical care patients remains controversial with respect to the selection of patients most likely to benefit from this treatment.

Methods: We performed an extensive search for adult trials testing steroids versus placebo to prevent reintubation or laryngeal dyspnea. Studies were evaluated on a 5-point scale based on randomization, double-blinding and follow-up. Our analysis included trials having a score ≥ 3 with patients mechanically ventilated for at least 24-hours and treated with steroids before extubation, taking into account the time of their administration (early vs late), and if the population was selected at risk or not.

Results: Seven prospective, randomized, double-blinded trials, including 1846 patients, (949 of which received steroids) were selected. Overall, steroids decreased significantly the risk of reintubation (relative risk (RR), 0.58 (95%CI, 0.41-0.81) - number-needed-to-treat (NNT) = 28 (95%CI, 20-61)) and stridor (RR, 0.48 (95%CI, 0.26-0.87)-NNT= 11 (95%CI, 8-42)). The effect of steroids on reintubation and stridor was more pronounced for selected high-risk patients, as determined by a reduced cuff leak volume (respectively RR, 0.38 (95%CI, 0.21-0.72)-NNT= 9 (95%CI, 7-19) and RR, 0.40 (95%CI, 0.25-0.63) -NNT= 5 (95%CI, 4-8)). In contrast, steroid benefit was unclear when trials did not select patients for their risk of reintubation (RR, 0.67 (95%CI, 0.45-1.00) - NNT= 44 (95%CI, 26-infinity)) or stridor (RR, 0.56 (95%CI, 0.20-1.55)).

Conclusions: The efficacy of steroids to prevent stridor and reintubation was only observed in a high-risk population, as identified by the cuff-leak test and when it was administered at least 4 hours prior extubation. The benefit of steroid remains unclear when patients are not selected.

Introduction

Post-extubation stridor associated with post-extubation laryngeal edema is one of the most frequent causes of reintubation in the intensive care unit (ICU) [1-7]. Reintubation may result in increased morbidity (nosocomial infection, prolonged length of ICU stay, additional costs…) and mortality [1-4, 6, 7]. The prevalence of post-extubation stridor ranges between 6 to 37% of intubated ICU patients [5, 8-13], depending upon the studied population (at high risk or not). Controversy still exists regarding the effectiveness of prophylactic steroid therapy to prevent both post-extubation stridor occurrence and its related reintubation in both selected [8, 9, 13] and non selected patients [10-12, 14].

Two recent meta-analyses [15, 16], based on original papers published up to 2007, have been performed and report contradictory conclusions with respect to the efficacy and the safety of prophylactic steroid therapy in preventing post-extubation laryngeal edema and the need for reintubation in adult ICU patients. Fan et al. [15] have suggested, regarding the most recent clinical trials, that prophylactic steroid therapy can reduce the incidence of post-extubation laryngeal edema, and the subsequent need for reintubation, in mechanically ventilated patients. In contrast, Markovitz et al. [16] concluded that using steroids to prevent (or treat) stridor after extubation has not proven effective for neonates, children or adults. Reporting conflicting results, these recent trials [8, 9, 13] combined with the two meta-analyses [15, 16] intensify the debate surrounding the use of prophylactic steroid therapy to prevent both post-extubation stridor occurrence and reintubation. Moreover, the meta-analyses results were pooled from trials which included selected [8, 9, 13] and unselected patients [10-12, 14] with respect to the risk for post-extubation stridor development and which allowed for very different steroid administration regimes (well in advance of extubation or immediately before). Indeed, the anti-inflammatory effect of steroids, the main mechanism responsible for reduction of post-extubation laryngeal

edema, is time course dependant [17, 18]. Although the two meta-analyses [15, 16] allowed for these differences, they did not perform subgroup analyses of the early versus late steroid administration nor for selected high-risk patients versus unselected patients. Finally in 2007, two additional randomized clinical trials (RCTs) were presented in abstract form but were not included in these two meta-analysis [8, 14]. Thus, we performed a quantitative meta-analysis to evaluate the effectiveness of prophylactic steroid therapy to prevent reintubation and post-extubation stridor, taking into account the studied populations (at risk to develop post-extubation stridor or not) and the steroid administration regime (pre-extubation early versus late).

Materials and methods

QUOROM standards were followed during all phases of the design and implementation of this meta-analysis [19].

Identification of the Studies

Three electronic databases were searched *via* the Internet for studies published between January 1966 and November 2008: PubMed® (MEDLINE/*Index Medicus*), the Cochrane Controlled Trials Register published by the Cochrane Library and EMBASE. The Medical Subject Heading terms used for the search were *steroids* and *extubation, adults and randomized controlled trials*. Supplementary manuscripts were searched by changing the Medical Subject Heading term *steroids* to *dexamethasone*, *prednisolone*, *methylprednisolone*, or *hydrocortisone*. Additional references were retrieved by clicking on hyperlinks "related articles" in Medline and by manually searching reference lists in original published articles, review articles, and correspondence. To complete the search with the inclusion of non published trials, abstracts presented in different critical care meetings (American Thoracic Society, Society of Critical Care Medicine, American Society of Anesthesiology, European Society of Anesthesiology, European Society of Intensive Care Medicine, International Symposium on Intensive Care and Emergency Medicine, Societé Française d'Anesthésie-Réanimation, Société de Réanimation en Langue Française) were also screened. For abstracts, only the last three years were consulted. For some trials, the authors were contacted for additional information on the results [8, 14].

Quality Assessment of the Studies

Each study was subjected to a quality assessment by two investigators (SJ, BJ), who were not blinded to the authors or results. Disagreements between the two investigators were resolved by

discussion. In the case of persistent disagreement, a third reviewer (EM) helped to reach a consensus after separately reviewing the report. Each article was scored using a five-point scale that evaluates randomization, blinding, and completeness of patient follow-up (Jadad scale) [20]. One point was given if the study was described as randomized. An additional point was given if the randomization method was described and was appropriate (*e.g.*, computer-generated table of random numbers), whereas a point was subtracted if the randomization method was described and inappropriate (*e.g.*, alternate allocation or allocation by date of birth). Similarly, one point was assigned to studies described as double-blinded, two points were assigned to studies for which the double-blinding method was described and appropriate (identical placebo, active placebo, double-dummy), and zero points were assigned to studies for which the double-blinding method was described and inappropriate. One point was given if the article specified the numbers of and reasons for withdrawals and dropouts. Thus, the minimum score for a randomized study was 1, and the highest possible score was 5. We included studies with a score of 3 or greater [20].

Selection Criteria

Criteria for study selection were as follows: randomized, double-blind design; quality assessment score of 3 or greater [20], duration of mechanical ventilation superior to 24 hours; steroids administrated for a planned extubation.

Criteria for study exclusion were a score of 2 or lower on the three-item Jadad quality five-point scale; duration of mechanical ventilation less than 24 hours (for example, mechanical ventilation for anesthesia); trials that have studied steroid administration for the prevention of pulmonary fibrosis (for example, excessive fibroproliferation or bronchopulmonary dysplasia), paediatric patients or neonates.

Outcome Measures

The primary evaluation criterion was the incidence of reintubation. Other endpoints: post-extubation stridor, duration of ICU stay and mortality were analyzed. When trials compared more than two groups, data were extracted into two groups: steroid and control. In dose-ranging studies with a placebo group, we extracted the events of the control group and pooled the steroid groups. When authors compared two types of administration with the same dose of steroids (*i.e.*, single injection *vs.* intermittent or bolus group), patients receiving steroids were pooled and compared to those receiving placebo.

Sensitivity analysis was performed to explore the effect of steroid in different populations, namely in trials which selected patients at high risk for reintubation or not. Similarly, subgroup analysis for time of administration was conducted in groups of patients who received steroids "late" (less than 2 hours before extubation) or "early" (more than 4 hours before extubation).

Statistics

Data were extracted as they were reported in the original paper or based on the answers of the authors to our queries. The Mantel-Haenszel-like procedure for relative risk (RR) was used to pool RRs [21]. Analyses were performed with Rev Man review manager (version 4.2, Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen). The RRs (and 95% confidence intervals [CIs]) were calculated, and the results were expressed graphically. All criteria were analyzed separately. A random-effects analysis was conducted in the case that the result of a Q Cochran heterogeneity test was significant ($P < 0.1$) and heterogeneity was quantified by I^2 [22]. For the significant criteria, we computed the number needed to treat (NNT) as the inverse of the difference of the proportion of patients who had any event in the steroid groups and the control groups. CIs of the NNT were constructed by inverting and exchanging the limits of the 95% CI

for the RR. The NNT and 95% CI were calculated with the Internet-based program Visual Rx. All tests were two sided, and P values less than 0.05 were considered statistically significant.

A funnel plot (plot of treatment effect against trial precision) was also created to determine the presence of publication bias and possible other biases (English language, citation, and multiple publication), true heterogeneity, data irregularities, and choice of effect measure in the meta-analysis [23]. In the presence of bias that usually leads to an overestimate of the treatment effect, the funnel plot is skewed and asymmetrical. The degree of asymmetry was measured by the Egger test [23] using WeasyMA software [24]. A *P* value less than 0.1 was considered statistically significant for asymmetry.

Results

Identification of the trials

Fifty-six relevant randomized controlled trials were identified by Medline, Cochrane Library, Embase and hand-searching. Forty-eight were excluded for the following reasons: 29 were surgical patients (evaluation of steroid neuromuscular block or steroids to prevent postoperative nausea or vomiting); 10 studies investigated the endocrine stress response, 6 trials evaluated the effect of steroids on ventilation weaning after cardiac surgery, 2 trials investigated long term administration of steroids in patients with acute respiratory distress syndrome; one trial studied the effect of steroids on healing after thoracic surgery (Fig. 1). One randomized controlled trial was excluded because the quality assessment score was less than 3 [25]. Two trials were found after consulting conference abstracts [8, 14]. Seven studies were finally selected including exclusively 1846 adult patients. Nine hundred forty-nine patients were included in the steroid group, versus 897 in the placebo group. (Fig. 1)

Study designs and patients (table 1)

The characteristics of the seven controlled trials are summarized in Table 1. All seven randomized double-blinded studies were published in or after 1992. Two trials [8, 14] were presented at the American Thoracic Society conference in 2007 and one author answered our queries concerning additional data [8]. The median quality score of data reporting was 5 (range, 3 to 5). All studies were double-blinded; the procedure of randomization was adequately described in 5 out of 7. Type of corticosteroid, doses, timing and duration of administration varied from one trial to another (Table 1). Three trials included only patients with high risk of distress after planned extubation based on a reduced cuff leak volume (CLV) [8, 9, 13]. One trial [9] had 3

arms that compared placebo versus one injection of methylprednisolone versus 4 injections of corticosteroid; these two steroid arms were thus combined for the analyses.

Post-extubation stridor was mainly defined by the occurrence of stridor after the extubation except in two trials where the authors included patients with stridor and laryngeal obstruction dyspnea defined by the occurrence of signs of upper airway obstruction, i.e. a prolonged inspiratory phase associated with recruitment of accessory respiratory muscles [10, 12]. Post-extubation laryngeal edema was confirmed by examination using bronchoscopy or laryngoscopy in two trials [9, 11].

Outcomes

Outcomes according population included in the trials: overall, unselected and selected patients at high risk to develop post-extubation stridor and reintubation as defined by a reduced cuff leak volume.

The rates of reintubation were obtained for all selected trials. Figure 2 demonstrates a significant difference in the reintubation rate after a planned extubation, with 8.7% (range, 2.6% to 30.3%) in the controls and 5.4% (range, 0% to 12.9%) in the steroid-treated patients (RR 0.58; 95%CI, 0.41-0.81; P = 0.001). This indicates a 42% decrease in the risk of reintubation. The number needed to treat overall patients (unselected and selected patients) was 28 (95%CI, 20-61) (Table 2). Subgroup analysis was performed by pooling trials that selected high-risk patients by measuring the leak around the deflated endotracheal tube cuff. The risk of reintubation was reduced by steroids even more when only trials with these high-risk patients were considered. The rate of reintubation decreased from 19.8% to 8.6% (RR 0.38; 95%CI, 0.21-0.72; P = 0.003)

NNT= 9 (95%CI, 7-19))] (Fig. 2). The number of high-risk patients needed to treat was 9 (95%CI, 7-19) (Table 2). In comparison, the risk reduction appears less well defined when trials did not select patients for risk of reintubation (RR, 0.67; 95%CI, 0.45-1.00; P = 0.05, NNT= 44 (95%CI, 26-∞)) (Table 2).

Stridor was described in the 7 RCTs. (Fig. 3). Among the 897 patients who did not receive steroid therapy before extubation, 167 experienced symptomatic post-extubation stridor (18.6%; range, 9.1% to 48.5%) (Fig. 3). In one trial [13], 9 of 11 patients had severe respiratory distress that required non-invasive positive pressure ventilation. Of the 949 patients who received corticosteroids, 77 (8.1%; range, 2.8% to 23.7%) experienced symptomatic laryngeal obstruction (RR, 0.48; 95%CI, 0.26-0.87; P = 0.02) (Fig. 3). Eleven patients needed to be treated so as to prevent one patient from developing stridor (95%CI, 8-42) in the overall population (selected and unselected patients) (Table 2). Aerosol with epinephrine (n=19) and non-invasive positive pressure ventilation (n=3) were used to treat laryngeal dyspnea in the steroid group [9, 12, 13]. Similar to reintubation, subgroup analysis was performed to evaluate patients at a higher risk for laryngeal dyspnea. In high-risk patients, based on reduced CLV, the overall incidence was 34.5% for the control groups and 12.9% in the steroid group. In this context, the relative benefit was 0.40 (95%CI, 0.25-0.63; P < 0.001 – NNT = 5 (95%CI, 4-8)) (Table 2). In contrast, steroids did not reduce significantly the incidence of post-extubation stridor when high-risk patients were not selected (RR, 0.56 (95%CI, 0.20-1.55) – Fig. 3). Moreover, the coefficient of heterogeneity (I^2) was high. Presumably, the trial performed by Francois et al. could be the respective condition. After exclusion of this study, the coefficient of heterogeneity was 0 (RR, 0,89 (95%CI, 0.61-1.30)) .A funnel plot of the treatment effect (logarithm RR of reintubation) *versus* trial precision was symmetric and centred around an RR of less than 1.0, suggesting that there is no publication bias or other biases (Fig. 4).

No additional information with respect to outcomes of patients (death, duration of ventilation, infection, and cost) that required reintubation was provided by the authors in the articles. Francois et al. [11] reported one death in each group; the reason was respiratory failure and septic shock in the placebo and corticosteroid groups respectively. Five trials found that women have a significantly higher risk of symptomatic laryngeal oedema after extubation [9-12, 14].

Outcomes according to when steroid administration was initiated before extubation: "late" as defined by starting less than 2 hours before planned extubation versus "early" administration as defined by starting steroid administration at least 4 hours (ranged 4 to 24 h) before planned extubation.

In the subgroup of patients with a high risk for post-extubation stridor, steroids were always administrated early (more than 4 hours before the planned extubation) (Fig. 2). In contrast, steroid administration initiation timing varied from one trial to another when authors did not selecting patients at high risk. Among the four studies [10-12, 14], two trials used a protocol with an early injection, namely more than 4 hours before [11, 14] extubation, and the 2 others injected steroids just before the extubation [10, 12]. Pooled together, these 2 last trials [10, 12] did not show that steroids decrease the risk of reintubation (RR, 0.88 (95%CI, 0.48- 1.61) – Fig. 5) or stridor (RR, 0.81 (95%CI, 0.53 - 1.25) – Fig. 6). However, an anticipated administration of steroids (i.e. more than 4 hours before planned extubation) decreases significantly the risk for reintubation (RR, 0.55 (95%CI, 0.32- 0.94)) – NNT= 26 (95%CI, 17-193) – Fig. 5) but not for stridor ((RR, 0.41 (95%CI, 0.05- 3.59)) – Fig. 6).

Discussion

The present meta-analysis documents that steroid administration before a planned extubation decreases the risk of post-extubation stridor and reintubation both in high-risk and unselected patients,. The benefit effect of steroids to prevent post-extubation stridor and reintubation was clear in the subgroup of patients at high-risk for development of post-extubation stridor as identified by a cuff-leak test (a low level of leak less than 110 ml or less than 25%).

The discrepancies observed in studies which evaluated the interest to administer steroids before extubation could be due to several factors including patient inclusion criteria, duration of intubation, dosage, timing of treatment and risk levels of developing stridor. Only the two last criteria (risk levels of developing stridor and timing of administration initiation) could be extensively evaluated in the present meta-analysis, allowing their importance to be reported for the first time. Post-extubation stridor is commonly the result of edema of the subglottic area or the vocal cords. The difficulty in defining the relationship between laryngo-tracheal injury and post-extubation stridor is that the presence of the endotracheal tube precludes direct visualisation of the upper airway, prior to extubation. The ability to predict which patients will develop stridor following extubation, possibly culminating in reintubation, is obviously a desirable goal. Beyond assessment of risk factors, clinicians have long used the cuff-leak test to predict post-extubation airway patency, wherein the endotracheal tube cuff is deflated and a leak of air around the tube is sought during either spontaneous ventilation (with the endotracheal tube lumen occluded) or positive-pressure ventilation. The cuff-leak test may be performed using the “qualitative method” (presence or absence of air leak around the tube when the cuff is deflated) or the “quantitative method” by reporting the leak volume (inspired minus exhaled tidal volume during positive-pressure ventilation when the cuff is deflated) or the fraction of leak volume (inspired minus exhaled volume divided by inspired tidal volume when the cuff is deflated). Several cuff-leak test

studies [5, 9, 26-29] suggest that the presence of an air leak is associated with a low likelihood of clinically important post-extubation stridor, whereas the absence or a low level of leak (less than 110 to 140 ml in absolute value or less than 12% to 25% in relative value) is associated with a high incidence of stridor and reintubation. The use of the cuff-leak test should be standardized and take into account a possible discrepancy between inspired and exhaled tidal volume measurement devices together with significant breath by breath variability. A more reliable identification of patients at high-risk to develop post-extubation stridor and reintubation would appear desirable not only to decrease the risk of reintubation, but also to avoid excessive steroid treatment as it may induce adverse effects in patients for whom there is no need. Indeed as shown in the present meta-analysis, the number needed to treat so as to prevent one stridor episode decreased from 11 in overall population (selected and unselected) to 5 in a population determined to be at high-risk to develop post-extubation stridor as determined by the cuff leak test (Fig. 3) (Table 2). However, steroids did not reduce significantly the incidence of post-extubation stridor when patients were not selected (i.e, unselected patients) for their risk of post-extubation stridor. The number needed to treat so as to avoid one reintubation decreased from 28 in overall population (selected and unselected) to 9 in patients with a high risk (Fig. 2) (Table 2). On other hand, the benefit of steroids is unclear when trials did not use the cuff-leak test to selected patients. In this case (i.e, unselected patients), the NNT increases to 44 and the upper limit of confidence interval is infinity (Fig. 2) (Table 2).

Although steroids are potentially associated with several adverse effects (such as hyperglycemia, arterial hypertension, agitation, infection) when they are administered for a few days (more than 48h)[30], side effects associated with steroid treatment for less than 24 hours are minimal [17, 18]. The studies included in the present meta-analysis reported no side effects related to steroids, but detection of steroid related adverse events was not specifically studied in these trials.

Laryngotracheal injury related to intubation may cause narrowing of the airway mainly due to inflammatory edema. The potential capacity of steroids to relieve laryngeal edema is mainly due to its anti-inflammatory effects, which inhibit the release of inflammatory mediators and decrease capillary permeability [9, 11, 13, 18]. The initial anti-inflammatory effects start at least 1 to 2 hours after intravenous administration and maximal effects appear between 2 to 24 hours, depending on steroid type and administered dose [9, 11, 17, 18]. Indeed, a single injection of dexamethasone (1 mg/kg) one hour before extubation had no effect on subglottic histological injury in a rabbit model [31, 32]. Moreover, in the two trials [10, 12] included in the present meta-analysis in which steroids were administered 1 h before extubation, no significant difference was observed between control and steroid groups for post-extubation stridor and reintubation rates. The same is true for the Gaussorgues study [25] for which steroids were also administered 1 h before extubation and no significant difference was observed between control and steroid groups for post-extubation stridor and reintubation rates. Although the Gaussorgues study [25] was excluded because the quality assessment score was less than 3, the inclusion of the Gaussorgues study [25] will not change the conclusions of the present meta-analysis. Save one trial, presented in abstract form in congress [14], all the published RCTs in which steroids were administered at least 4 to 24 h before extubation (Table 1 and Figs. 5 and 6) reported a significant decrease in post-extubation stridor [8, 9, 11, 13] and reintubation [8, 9, 11].

Some might argue that the use of corticosteroids in adult critical care for planned extubation is unnecessary, since objectively the incidence of reintubation is low and symptomatic laryngeal edema has self-limited symptoms. However, stridor and laryngeal dyspnea increase care needs due to the institution of epinephrine or corticosteroid aerosol and associated nursing time. Similarly, reintubation increases cost, morbidity, care needs, and both ICU and hospital lengths of stay. Unfortunately, trials included in the current meta-analysis evaluated the benefit of

corticosteroids only during the first 48 hours and no information on the outcome of reintubated patients was provided. Further studies on this topic are needed; using standard criteria for the assessment of readiness to extubate and a well define evaluation on the relation between post extubation laryngeal oedema and re-intubation.

The quality of the trials included in a systematic review may alter the results [33], because meta-analysis are often handicapped by the heterogeneity of the included trials. Moher et al. [33] demonstrated that meta-analyses with low quality trials (Jadad assessment scale ≤ 2) compared with high quality trials (assessment scale > 2) were associated with a 33% increase in the estimated benefit. Similarly, trials using inadequate allocation concealment may also overestimate the benefit of treatment by as much as 37% [33]. Therefore, multiple scales have been proposed to assess the quality of trials included in a meta-analysis in order to decrease bias due to the inclusion of low quality trials. We used the Jadad composite scale [20] to assess quality, using the following items : randomization, double-blinding and patient withdrawals. Meta-analyses of trials with low quality, as evaluated with this scale, significantly exaggerate benefits [19, 33]. All seven trials selected for our systematic review have a scale reflecting high quality [33] and, consequently were double-blinded and randomized. Patients included in trials have variable risks for post-extubation stridor or reintubation. Interestingly, the reduction of risk for stridor appears to be similar (approximately 50%), regardless of the risk of post-extubation laryngeal dyspnea, suggesting that the effect is the same in the presence of edema. Dosage, duration and type of corticosteroids differed from one trial to another. Pooling RCTs with varying designs may be interesting since the current meta-analysis appears to demonstrate that the timing of the first administration influences the risk of reintubation.

The current meta-analysis suggests an effect of administration timing on the efficacy of corticosteroids, since steroids appear to prevent reintubation more effectively if they are

administrated at least 4 hours before planned extubation. As stridor and reintubation, secondary to upper obstruction airway obstruction, occur soon after extubation [5, 11], it may be reasonable to suggest starting steroid treatment at least 4 hours before planned extubation so as to prevent prolongation of weaning from mechanical ventilation.

Further studies should address to better define the optimal use of steroids to prevent extubation failure. In patients selected at high risk for postextubation stridor (traumatic intubation, low cuff-leak value, previous extubation failure…), steroid should be used but the optimal steroid use before extubation without delaying it, remains to be establishing (steroid type, dosing regimes, administration timing and duration). Dose-response should be also established to know the lowest effective dose. Moreover, the risk of steroid use remains a source of concern in critical care patients. The side effects of steroids administration to prevent reintubation are unknown and were not investigated clearly in all trials included in this meta-analysis. The current meta-analysis did not show a benefit when trials that did not selected patients at risk for reintubation were pooling. In this group, only one trial [5, 11] has found a significant benefit of steroid but the others did not. The study of Francois [11] appears to be the main cause of heterogeneity between the trials that did not selected patients at risk. The timing of administration does not seem to be the major reason for heterogeneity since the study of Shih et al. [14] have administrated steroid more sooner than Francois et al. [11] (24 hours versus 12 hours). Another hypothesis may be the dose of steroid used by Francois et al. [11] because they have administrated the highest. Finally, all trials have a risk to observe a significant result despite there is none (Type I error). Thus, the evidence for steroid administrated in unselected patients remains unclear and additional studies are warranted to determine clearly the benefit but also the potential adverse events of this drug.

Conclusions

The present meta-analysis suggests, first that the beneficial effects of steroids to prevent post-extubation stridor and reintubation were observed in the subgroup of patients with a high risk to develop post-extubation stridor, as identified by the cuff-leak test, and second that steroid treatment before a planned extubation decreases the risk of reintubation only if intravenous steroid administration was performed at least 4 before planned extubation. The benefit of steroid remains unclear when patients are not selected.

Key messages

- A high risk population to develop post-extubation stridor and reintubation can be identified by a cuff-leak test (a low level of leak less than 110 ml or less than 25%).

- There is convincing evidence for giving steroid therapy, at least 4 hours prior to extubation to prevent stridor and reintubation in a high risk population.

- The steroid benefit remains unclear when patients are not selected.

Abbreviations

ICU = intensive care unit; RCT = randomized clinical trial; RR = relative risk; CI = confidence interval; NNT = number needed to treat; CLV = cuff leak volume.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Samir Jaber, MD, PhD designed and supervised the research, collected, analyzed, and interpreted the data, drafted and revised the manuscript. Boris Jung, MD contributed to the conception of the study and approved the final version of the manuscript. Gérald Chanques, MD made substantial contributions to the conception and design of the study and approved the final version of the

manuscript. Francis Bonnet, MD, PhD participated in the design of the study and helped to draft the manuscript. Emmanuel Marret, MD, PhD co-designed and supervised the research, collected, analyzed, and performed the statistical analysis. All authors read and approved the final manuscript.

Acknowledgements

The authors gratefully acknowledge Patrick McSweeny for his assistance with the English editing manuscript.

REFERENCES

1. de Lassence A, Alberti C, Azoulay E, Le_Miere E, Cheval C, Vincent F, Cohen Y, Garrouste-Orgeas M, Adrie C, Troche G, Timsit JF, OUTCOMEREA Study Group: **Impact of unplanned extubation and reintubation after weaning on nosocomial pneumonia risk in the intensive care unit: a prospective multicenter study.** *Anesthesiology* 2002, **97**:148-156.
2. Epstein SK, Ciubotaru RL: **Independent effects of etiology of failure and time to reintubation on outcome for patients failing extubation**. *Am J Respir Crit Care Med* 1998, **158**:489-493.
3. Epstein SK, Ciubotaru RL, Wong JB: **Effect of failed extubation on the outcome of mechanical ventilation**. *Chest* 1997, **112**:186-192.
4. Jaber S, Amraoui J, Lefrant J, Arich C, Cohendy R, Landreau L, Calvet Y, Capdevila X, Mahamat A, Eledjam J: **Clinical practice and risk factors for immediate complications of endotracheal intubation in intensive care unit: a prospective multicenter study**. *Crit Care Med* 2006, **34**:2355-2361.
5. Jaber S, Chanques G, Matecki S, Ramonatxo M, Vergne C, Souche B, Perrigault PF, Eledjam JJ: **Post-extubation stridor in intensive care unit patients. Risk factors evaluation and importance of the cuff-leak test**. *Intensive Care Med* 2003, **29**:69-74.
6. Seymour CW, Martinez A, Christie JD, Fuchs BD: **The outcome of extubation failure in a community hospital intensive care unit: a cohort study**. *Crit Care* 2004, **8**:R322-327.
7. Torres A, Gatell J, Aznar E: **Re-intubation increases the risk of nosocomial pneumonia in patients needing mechanical ventilation**. *Am J Respir Crit Care Med* 1995, **152**:137-141.
8. Cheng KC, Chen CM, Tan CK, Lin SC, Chen HM, Zhang H: **Methylprednisolone Reduces the Incidence of Postextubation Stridor Associated with Downregulation of IL-6 in Critical Ill Patients**. *Am J Respir Crit Care Med* 2007:A593.
9. Cheng KC, Hou CC, Huang HC, Lin SC, Zhang H: **Intravenous injection of methylprednisolone reduces the incidence of postextubation stridor in intensive care unit patients**. *Crit Care Med* 2006, **34**:1345-1350.

10. Darmon JY, Rauss A, Dreyfuss D, Bleichner G, Elkharrat D, Schlemmer B, Tenaillon A, Brun-Buisson C, Huet Y: **Evaluation of risk factors for laryngeal edema after tracheal extubation in adults and its prevention by dexamethasone. A placebo-controlled, double-blind, multicenter study**. *Anesthesiology* 1992, **77**:245-251.
11. Francois B, Bellissant E, Gissot V, Desachy A, Normand S, Boulain T, Brenet O, Preux PM, Vignon P: **12-h pretreatment with methylprednisolone versus placebo for prevention of postextubation laryngeal oedema: a randomised double-blind trial**. *Lancet* 2007, **369**:1083-1089.
12. Ho LI, Harn HJ, Lien TC, Hu PY, Wang JH: **Postextubation laryngeal edema in adults. Risk factor evaluation and prevention by hydrocortisone**. *Intensive Care Med* 1996, **22**:933-936.
13. Lee CH, Peng MJ, Wu CL: **Dexamethasone to prevent postextubation airway obstruction in adults: a prospective, randomized, double-blind, placebo-controlled study**. *Crit Care* 2007, **11**:R72.
14. Shih CM, Chen W, Tu CY, Chen HJ, Lee JC, Tsai WK, Hsu WH: **Multiple injections of hydrocortisone for the prevention of post-extubation stridor in acute respiratory failure**. *Am J Respir Crit Care Med* 2007:A593.
15. Fan T, Wang G, Mao B, Xiong Z, Zhang Y, Liu X, Wang L, Yang S: **Prophylactic administration of parenteral steroids for preventing airway complications after extubation in adults: meta-analysis of randomised placebo controlled trials**. *BMJ* 2008, **337**:a1841.
16. Markovitz BP, Randolph AG, Khemani RG: **Corticosteroids for the prevention and treatment of postextubation stridor in neonates, children and adults (Review)**. *Cochrane Database of Systematic Reviews Art No: CD001000 DOI:101002/14651858CD001000pub2* 2008.
17. Marik PE, Pastores SM, Annane D, Meduri GU, Sprung CL, Arlt W, Keh D, Briegel J, Beishuizen A, Dimopoulou I, Tsagarakis S, Singer M, Chrousos GP, Zaloga G, Bokhari F, Vogeser M, American College of Critical Care Medicine: **Recommendations for the diagnosis and management of corticosteroid insufficiency in critically ill adult patients: consensus statements from an international task force by the American College of Critical Care Medicine**. *Crit Care Med* 2008, **36**:1937-1949.

18. Prigent H, Maxime V, Annane D: **Clinical review: corticotherapy in sepsis**. *Crit Care* 2004, **8**:122-129.
19. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF: **Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses**. *Lancet* 1999, **354**:1896-1900.
20. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ: **Assessing the quality of reports of randomized clinical trials: is blinding necessary?** *Control Clin Trials* 1996, **17**:1-12.
21. Greenland S, Robins JM: **Estimation of a common effect parameter from sparse follow-up data**. *Biometrics* 1985, **41**:55-68.
22. Higgins JP, Thompson SG: **Quantifying heterogeneity in a meta-analysis, Stat. Med. 21 (2002), pp. 1539–1558**. *Stat Med* 2002, **21**:1539–1558.
23. Egger M, Davey Smith G, Schneider M, Minder C: **Bias in meta-analysis detected by a simple, graphical test**. *BMJ* 1997, **315**:629-634.
24. Cucherat M, Boissel JP, Leizorovicz A, Haugh MC: **EasyMA: a program for the meta-analysis of clinical trials**. *Comput Methods Programs Biomed* 1997, **53**:187-190.
25. Gaussorgues P, Boyer F, Piperno D, Gerard M, Leger P, Robert D: **Laryngeal edema after extubation. Do corticosteroids play a role in its prevention?** *Presse Med* 1987, **16**:1531-1532.
26. De Bast Y, De Backer D, Moraine J, Lemaire M, Vandenborght C, Vincent J: **The cuff leak test to predict failure of tracheal extubation for laryngeal edema**. *Intensive Care Med* 2002, **28**:1267-1272.
27. Miller R, Cole R: **Association between reduced cuff leak volume and postextubation stridor**. *Chest* 1996, **110**:1035-1040.
28. Prinianakis G, Alexopoulou C, Mamidakis E, Kondili E, Georgopoulos D: **Determinants of the cuff-leak test: a physiological study**. *Crit Care* 2005, **9**:24-31.
29. Sandhu R, Pasquale M, Miller K, Wasser T: **Measurement of endotracheal tube cuff leak to predict postextubation stridor and need for reintubation**. *J Am Coll Surg* 2000, **190**:682-687.
30. Sprung CL, Annane D, Keh D, Moreno R, Singer M, Freivogel K, Weiss YG, Benbenishty J, Kalenka A, Forst H, Laterre PF, Reinhart K, Cuthbertson BH, Payen D,

Briegel J, CORTICUS Study Group: **Hydrocortisone therapy for patients with septic shock**. *N Engl J Med* 2008, **358**:111-124.

31. Kil H, Alberts M, Liggitt H, Bishop M: **Dexamethasone treatment does not ameliorate subglottic ischemic injury in rabbits**. *Chest* 1997, **111**:1356-1360.

32. Kil HK, Kim WO, Koh SO: **Effects of dexamethasone on laryngeal edema following short-term intubation**. *Yonsei Med J* 1995, **36**:515-520.

33. Moher D, Pham B, Jones A, Cook DJ, Jadad AR, Moher M, Tugwell P, Klassen TP: **Does quality of reports of randomised trials affect estimates of intervention efficacy reported in meta-analyses?** *Lancet* 1998, **352**:609-613.

Figure legends

Figure 1. Flowchart of controlled trials selected for the meta-analysis.

Figure 2. Risk for reintubation according to the studied population. Risk Ratio (RR) of reintubation rate for the individual randomized controlled trials comparing steroids versus control groups. Vertical line, "no difference" point between the two groups; squares, risk ratios (the size of each square denotes the proportion of information given by each trial); diamonds, pooled risk ratios for randomized controlled trials that did not select patients at high risk (upper) and trials that did select patients at high risk, based on a reduced cuff leak volume (lower); horizontal lines, 95% confidence intervals (CI).

Figure 3. Risk ratio for post-extubation stridor according to the studied population. Risk ratios (RR) of post-extubation stridor rate for the individual randomized controlled trials comparing steroids versus control groups and the pooled analysis. Vertical line, "no difference" point between the two groups; squares, risk ratios (the size of each square denotes the proportion of information given by each trial); diamonds, pooled odds ratios for randomized controlled trials that did not select patients at high risk (upper) and trials that did selected patients at high risk, based on a reduced cuff leak volume (lower); horizontal lines, 95% confidence intervals (CI).

Figure 4. Funnel plot for outcome reintubation to detect bias or systematic heterogeneity in trials according to the studied population (selected vs unselected patients at risk based on a reduced cuff-leak volume). Each point represents one trial.

Figure 5. Risk for reintubation according to the steroid administration initiation timing before extubation in unselected patients. Risk ratios (RR) of reintubation rate for the individual randomized controlled trials comparing steroids versus control groups and the pooled analysis. Vertical line, "no difference" point between the two groups; squares, odds ratios (the size of each square denotes the proportion of information given by each trial); diamonds, pooled odds ratios for randomized controlled trials with for which steroid administration was started less than 2 hours before planned extubation (upper) and trials for which steroid administration was started at least 4 hours (ranged 4 to 24 h) before planned extubation (lower); horizontal lines, 95% confidence intervals (CI).

Figure 6. Risk for post-extubation stridor according to the timing steroid administration initiation before extubation in unselected patients. Risk ratios (RR) of post-extubation stridor rate for the individual randomized controlled trials comparing steroids versus control groups and the pooled analysis. Vertical line, "no difference" point between the two groups; squares, odds ratios (the size of each square denotes the proportion of information given by each trial); diamonds, pooled odds ratios for randomized controlled trials for which steroid administration was started less than 2 hours before planned extubation (upper) and trials for which steroid administration was started at least 4 hours (ranged 4 to 24 h) before planned extubation (lower); horizontal lines, 95% confidence intervals (CI).

Table 1: Characteristics of the seven adult studies included in the meta-analysis

Author Year	Jadad scale	Overall sample size analyzed (n)	ICU population and inclusion criteria	Duration of ventilation (days) (steroid vs placebo)	Steroid dose and regime administration	Overall equivalent dose of Hydrocortisone (mg)
Cheng 2007 [8]	3	71	Medical and surgical MV for more than 24 hours High risk of stridor (CLV < 24%)	NR	Methylprednisolone IV 40 mg, 4 hours before extubation	200
Cheng 2006 [9]	5	128	Medical and surgical MV for more than 24 hours High risk of stridor (CLV < 24%)	7.3 ± 3.9 (1 inj) 6.3 ± 3.8 (4 inj) vs 7.1 ± 4.1 (placebo)	Methylprednisolone IV 40 mg/6 h x 4 vs Methylprednisolone IV 40 mg - 1 injection vs placebo Started 24 hours before extubation	800 or 200
Darmon 1992 [10]	5	694	Medical and surgical MV for more than 36 hours Not selected at high-risk	9.6 ± 9.7 vs 10.3 ± 10.9	Dexamethasone IV 8 mg one hour before extubation	213
Francois 2007 [11]	5	698	Medical, surgical and trauma MV for more than 36 hours Not selected at high-risk	Duration of MV < 7 days: 51 vs 49% Duration of MV > 7 days : 49 vs 51%	Methylprednisolone IV 20 mg/4h starting 12 h before planned extubation (last dose just before extubation)	400
Ho 1996 [12]	5	77	Medical and surgical Not selected at high-risk	6.1 ± 3.8 vs 4.6 ± 4.7	Hydrocortisone IV 100 mg one hour before extubation	100
Lee 2007 [13]	5	86	Medical MV for more than 48 hours High risk of stridor (CLV <110 ml)	7.0 ± 2.0 vs 6.6 ±2.0	Dexamethasone IV 5 mg/6 hours x 4 – started 24 h before extubation, last dose just before extubation	533
Shih 2007 [14]	3	98	Medical and surgical MV for more than 24 hours	Between 10 to 15	Hydrocortisone IV 4 injections/6 h Started 24 hours before	NR

ICU: intensive care unit; MV: mechanical ventilation; CLV: cuff-leak volume; IV: intra-venous; NR: not reported.

Table 2: Number needed to treat (NNT) with steroids to reduce reintubation and stridor in unselected, selected and overall population

	Unselected	**Selected**	**Overall (= unselected+selected)**
NNT so as to prevent one reintubation episode	44 [95% CI, 26-∞]	9 [95% CI, 7-19]	28 [95% CI, 20-61]
NNT so as to prevent one stridor episode	Not calculated	5 [95% CI, 4-8]	11 [95% CI, 8-42]

Selected population is defined by patients at high risk to develop post-extubation stridor and reintubation in which the cuff leak-test showed absence or a low level of leak (less than 110 to 140 ml in absolute value or less than 12% to 25% in relative value).
Unselected population is defined by patients included in trials did not use the cuff-leak test to selected patients.
Overall population is defined by patients included in both trials which did use and did not use the cuff-leak test to selected patients (= unselected+selected).
The NNT was calculated only when a significant result was observed.

Figure 1

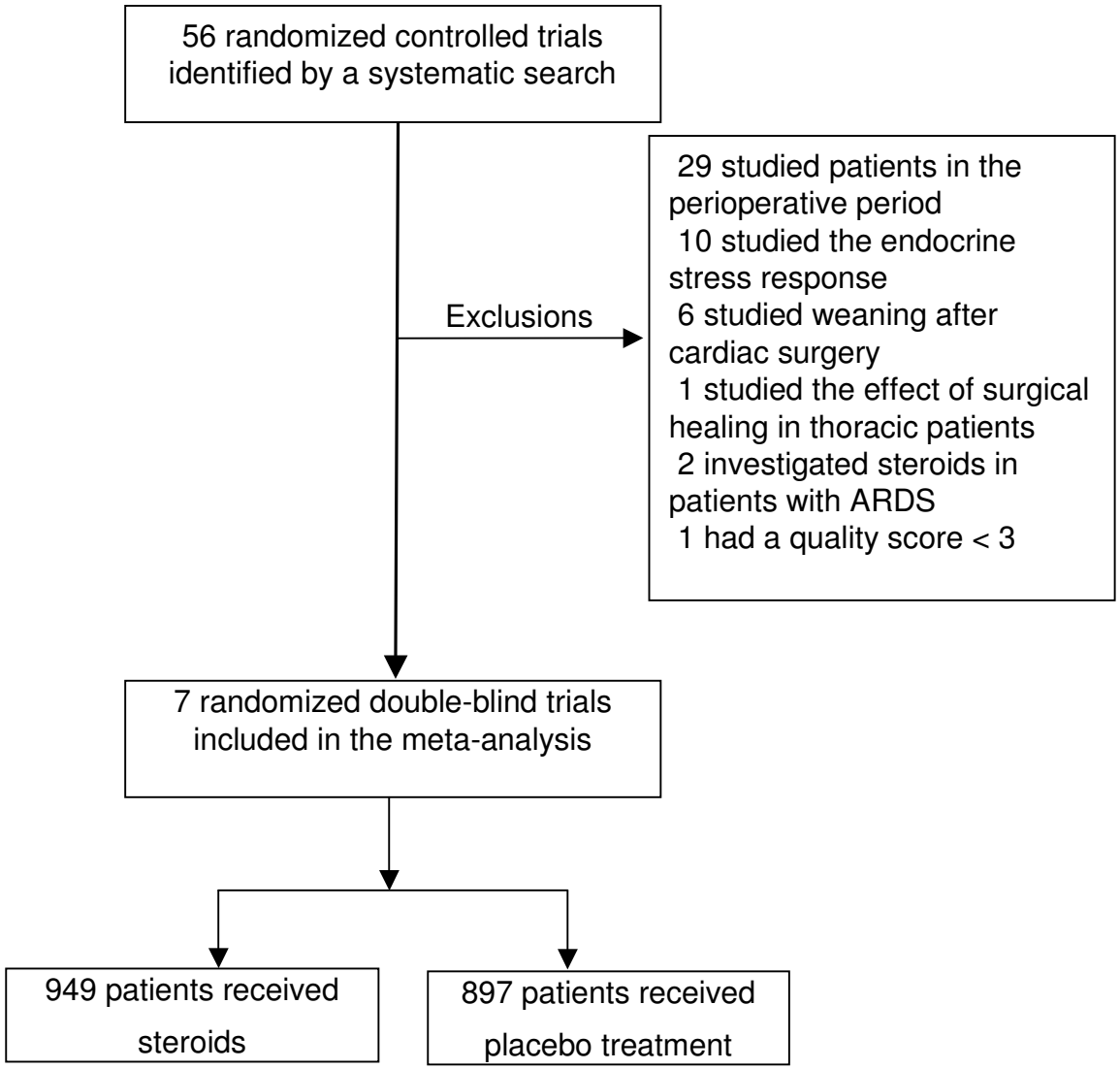


Figure 1

Figure 2

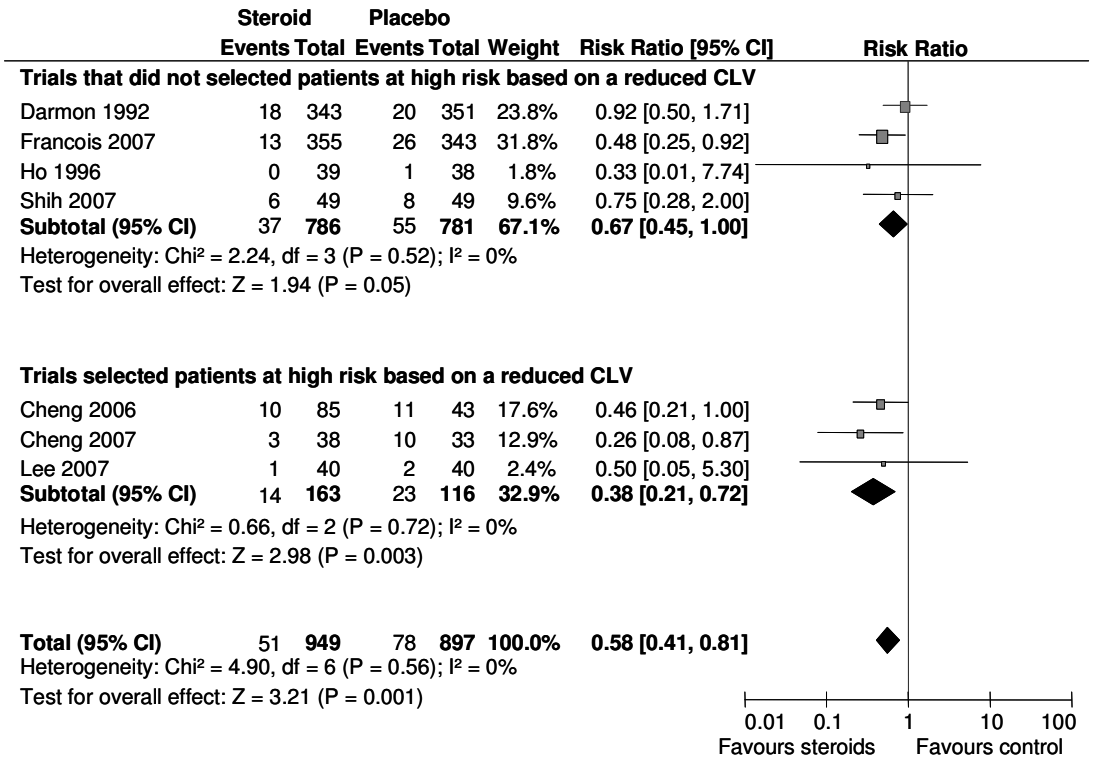


Figure 2

Figure 3

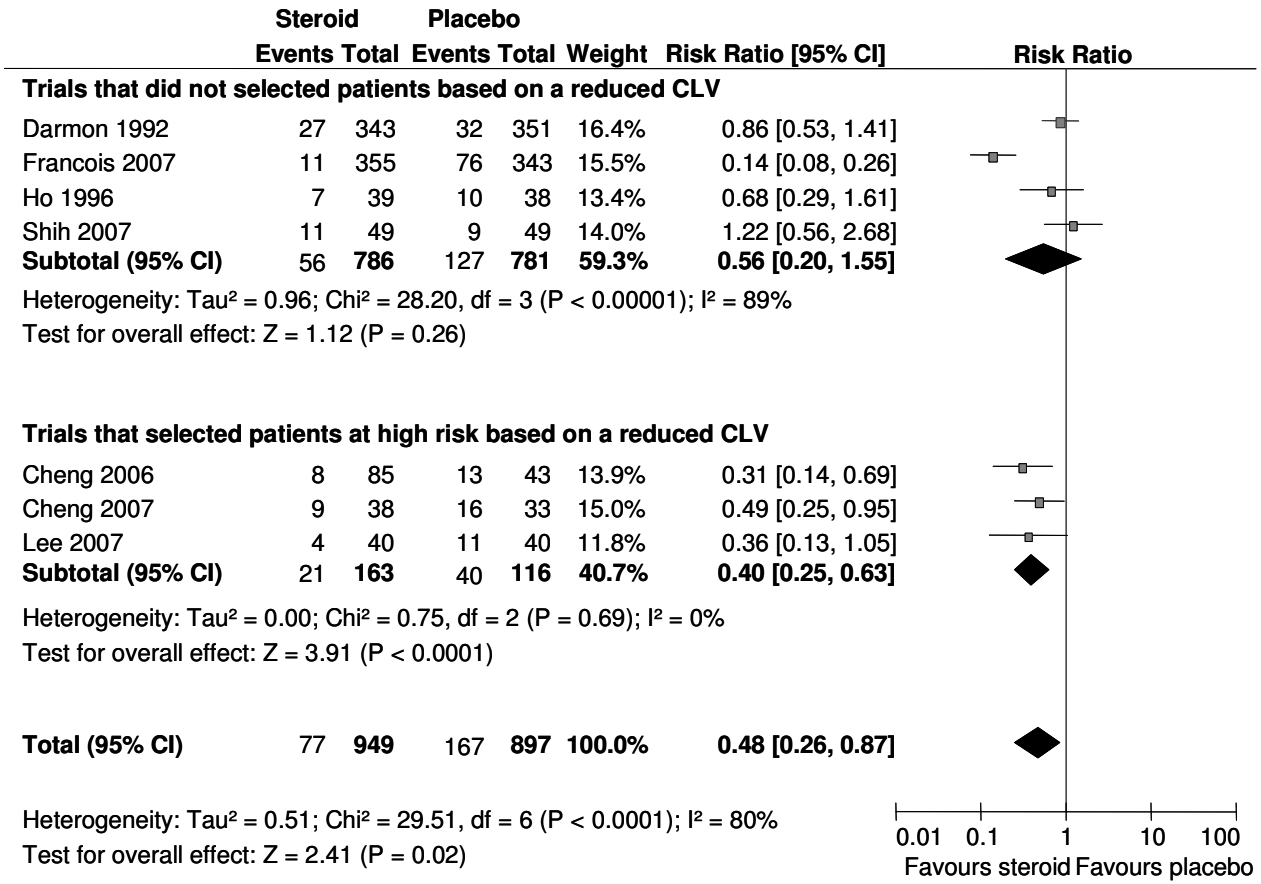

Steroid
Placebo
Events Total Events Total Weight Risk Ratio [95% CI]
Risk Ratio
Trials that did not selected patients based on a reduced CLV
Darmon 1992 27 343 32 351 16.4% 0.86 [0.53, 1.41]
Francois 2007 11 355 76 343 15.5% 0.14 [0.08, 0.26]
Ho 1996 7 39 10 38 13.4% 0.68 [0.29, 1.61]
Shih 2007 11 49 9 49 14.0% 1.22 [0.56, 2.68]
Subtotal (95% CI) 56 786 127 781 59.3% 0.56 [0.20, 1.55]
Heterogeneity: Tau² = 0.96; Chi² = 28.20, df = 3 (P < 0.00001); I² = 89%
Test for overall effect: Z = 1.12 (P = 0.26)
Trials that selected patients at high risk based on a reduced CLV
Cheng 2006 8 85 13 43 13.9% 0.31 [0.14, 0.69]
Cheng 2007 9 38 16 33 15.0% 0.49 [0.25, 0.95]
Lee 2007 4 40 11 40 11.8% 0.36 [0.13, 1.05]
Subtotal (95% CI) 21 163 40 116 40.7% 0.40 [0.25, 0.63]
Heterogeneity: Tau² = 0.00; Chi² = 0.75, df = 2 (P = 0.69); I² = 0%
Test for overall effect: Z = 3.91 (P < 0.0001)
Total (95% CI) 77 949 167 897 100.0% 0.48 [0.26, 0.87]
Heterogeneity: Tau² = 0.51; Chi² = 29.51, df = 6 (P < 0.0001); I² = 80%
Test for overall effect: Z = 2.41 (P = 0.02)
0.01 0.1 1 10 100
Favours steroid Favours placebo

Figure 4

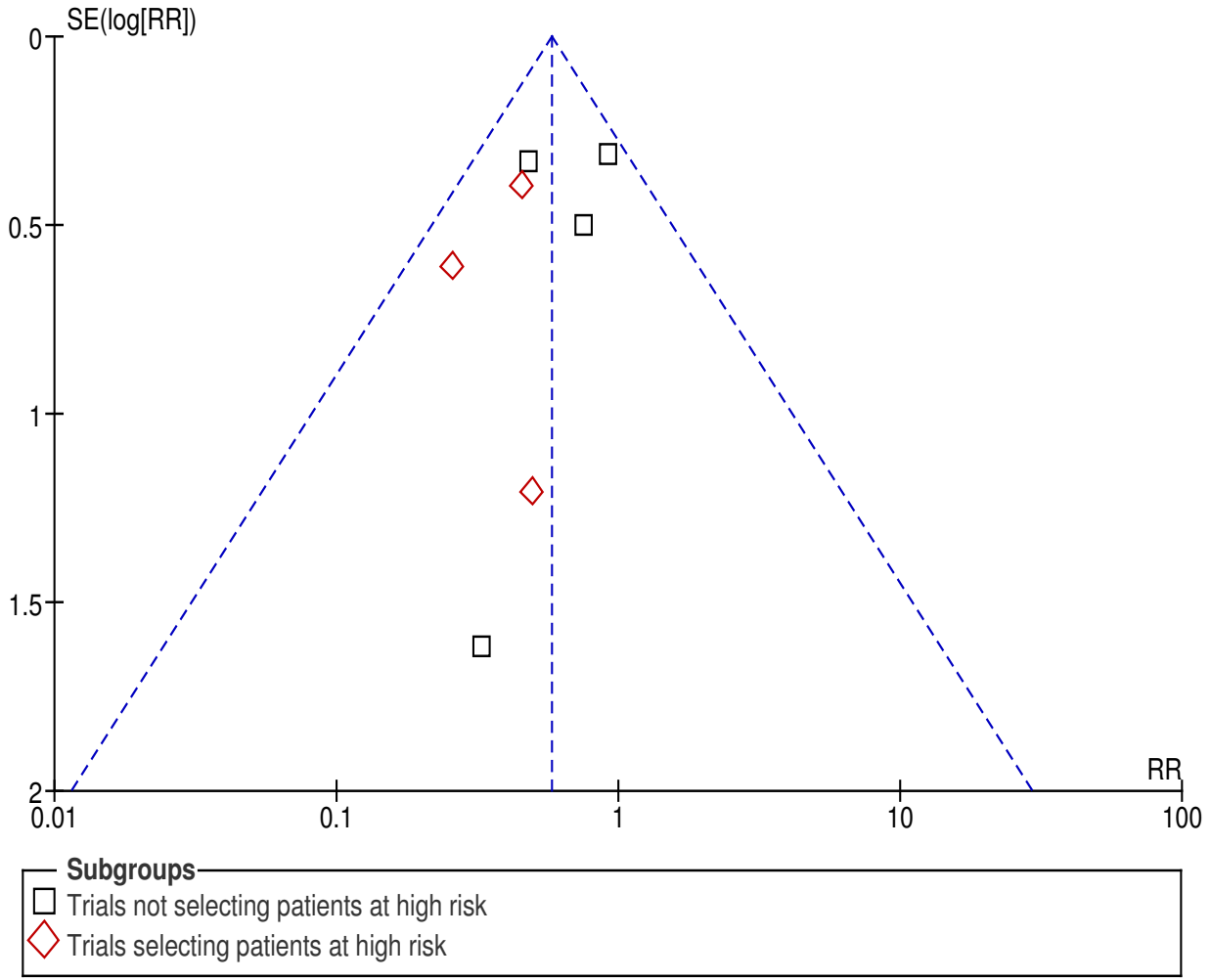

SE(log[RR])
0
0.5
1
1.5
2
0.01
0.1
1
10
100
RR
Subgroups
Trials not selecting patients at high risk
Trials selecting patients at high risk

Figure 5

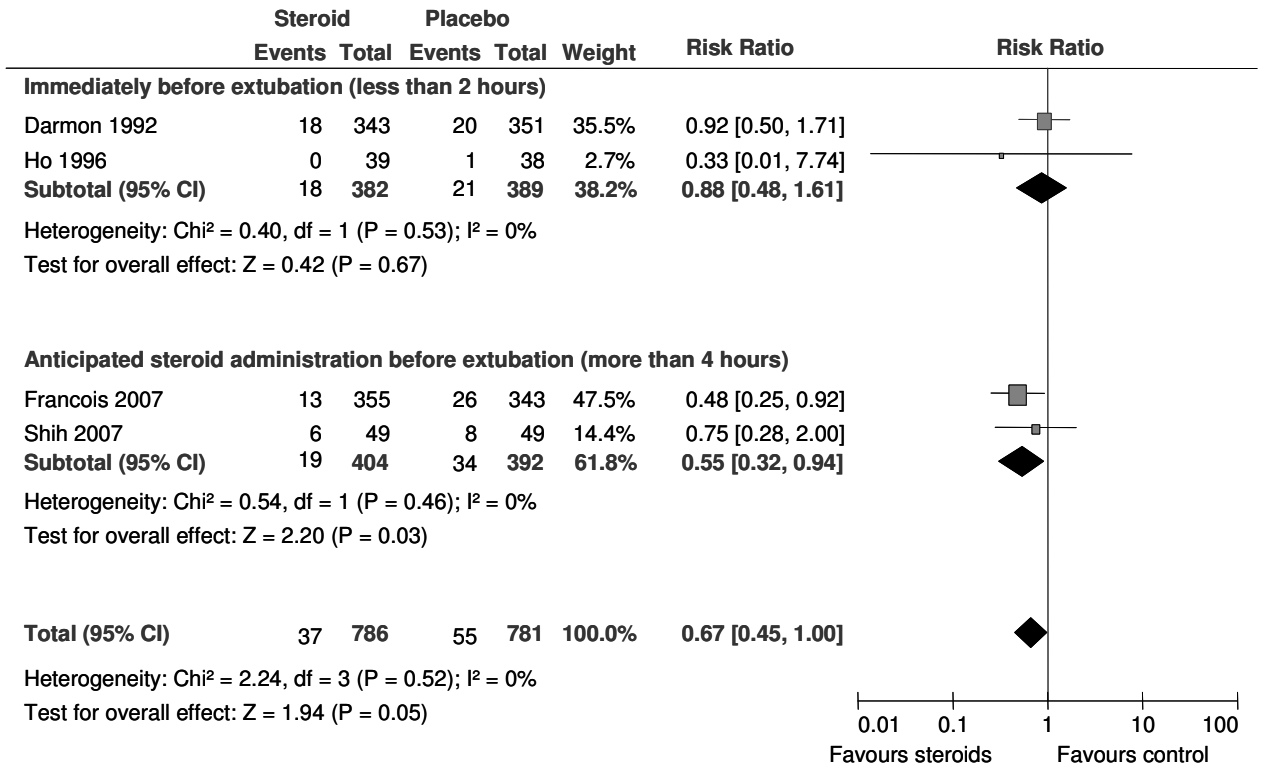
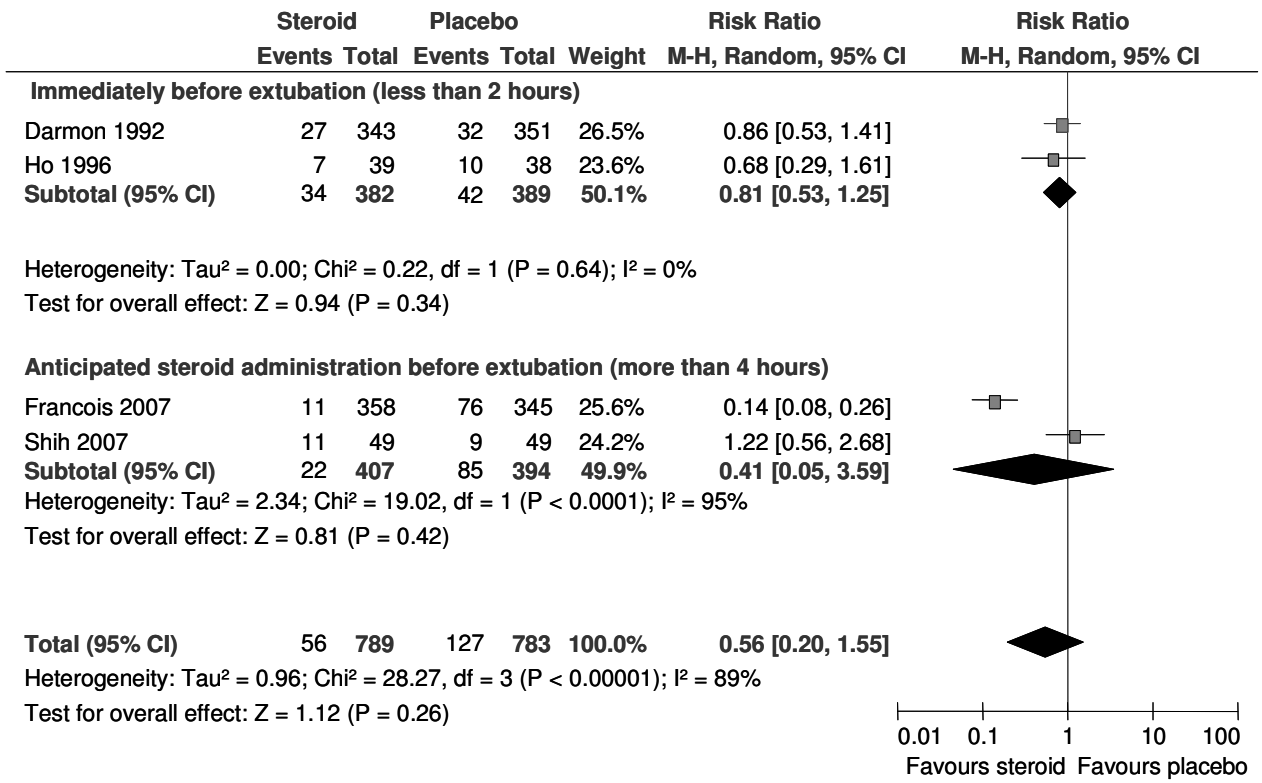


Figure 5

Figure 6


Steroid
Placebo
Risk Ratio
Risk Ratio
Events Total Events Total Weight M-H, Random, 95% CI
M-H, Random, 95% CI
Immediately before extubation (less than 2 hours)
Darmon 1992 27 343 32 351 26.5% 0.86 [0.53, 1.41]
Ho 1996 7 39 10 38 23.6% 0.68 [0.29, 1.61]
Subtotal (95% CI) 34 382 42 389 50.1% 0.81 [0.53, 1.25]
Heterogeneity: Tau² = 0.00; Chi² = 0.22, df = 1 (P = 0.64); I² = 0%
Test for overall effect: Z = 0.94 (P = 0.34)
Anticipated steroid administration before extubation (more than 4 hours)
Francois 2007 11 358 76 345 25.6% 0.14 [0.08, 0.26]
Shih 2007 11 49 9 49 24.2% 1.22 [0.56, 2.68]
Subtotal (95% CI) 22 407 85 394 49.9% 0.41 [0.05, 3.59]
Heterogeneity: Tau² = 2.34; Chi² = 19.02, df = 1 (P < 0.0001); I² = 95%
Test for overall effect: Z = 0.81 (P = 0.42)
Total (95% CI) 56 789 127 783 100.0% 0.56 [0.20, 1.55]
Heterogeneity: Tau² = 0.96; Chi² = 28.27, df = 3 (P < 0.00001); I² = 89%
Test for overall effect: Z = 1.12 (P = 0.26)
0.01 0.1 1 10 100
Favours steroid Favours placebo