β_2 Agonist for the Treatment of Acute Lung Injury: A Systematic Review and Meta-analysis

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BACKGROUND: The use of β_2 agonist as an intervention for acute lung injury (ALI) and ARDS patients is controversial, so we performed a systematic review and meta-analysis of the published randomized controlled trials of using β_2 agonists to improve outcomes (mortality and ventilator free days) among patients with ALI/ARDS. METHODS: A comprehensive search of 7 major databases (Ovid MEDLINE In-Process and other non-indexed citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials (CENTRAL), Ovid Cochrane Database of Systematic Reviews, Web of Science, and Scopus) for randomized controlled trials using β_2 agonists for ALI from their origin to March 2013 was conducted. The effect size was measured by relative risk for dichotomous outcomes, and mean difference for continuous outcomes, with 95% CI. The statistical heterogeneity between the studies was assessed with the Cochran Q test and I^2 statistic. The heterogeneity of > 50% was considered significant for the analysis. The Cochrane risk of bias tool was used to ascertain the quality of the included studies. RESULTS: Out of 219 studies screened, 3 randomized controlled trials reported mortality and ventilator-free days, in 646 ALI/ARDS subjects. Of the 646 subjects, 334 (51.7%) received β_2 agonist and 312 (48.3%) received placebo. There was no significant decrease in 28-day mortality or hospital mortality in the β_2-agonist group: relative risk 1.04, 95% CI 0.50–2.16, and relative risk 1.22, 95% CI 0.95–1.56, respectively. The ventilator-free days and organ-failure-free days were significantly lower for the ALI subjects who received β_2 agonists: mean difference −2.19 days (95% CI −3.68 to −1.99 d) and mean difference −2.04 days (95% CI −3.74 to −0.35 d), respectively. CONCLUSIONS: In subjects with ALI/ARDS, β_2 agonists were not only nonbeneficial in improving the survival, but were harmful and increased morbidity (reduced organ-failure-free days and ventilator-free days). The current evidence discourages the use of β_2 agonist in ALI/ARDS patients. (International Prospective Register of Systematic Reviews, http://www.crd.york.ac.uk/prospero, 2012:CRD42012002616.)

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Introduction

Acute lung injury (ALI) and ARDS are characterized by the inflammation of the pulmonary vasculature, resulting in increased vascular permeability, leading to noncardiogenic pulmonary edema.[1] β_2-agonist therapy has been traditionally considered to be beneficial in patients suffering from ALI/ARDS, because β_2 agonists promote

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salt and water transport by increasing intracellular c-AMP (c-adenosine monophosphate) and thereby improve alveolar fluid clearance.[2,3] Impaired alveolar fluid clearance in ALI patients may increase the risk of death.[4] Other β_2 agonist properties that have been proposed to improve the outcomes in ALI patients are their ability to improve the permeability of lung endothelium to proteins,[5] and anti-inflammatory properties.[6]

In a retrospective study by Manocha et al,[7] inhaled β_2 agonists were associated with shorter duration and low severity of ALI. However, the use of β_2 agonists as an intervention for ALI/ARDS is controversial. Lack of consensus about using β_2 agonists in the treatment of ALI/ARDS patients represents one of the growing controversial issues in the critical care community.[6,8-11] This challenging topic has been addressed in physiologic studies[12-15] and randomized controlled trials (RCTs)[16-18] However, 2 of the RCTs (the Aerosolized β_2 Agonist for Treatment of Acute Lung Injury[16] [ALTA] trial, and the second β Agonist Lung Injury trial[17] [BALTI-2]) were stopped early because of futility and patient intolerance of the β_2 agonists. Therefore, we performed a systematic review and meta-analysis of the published RCTs, on the effects of β_2 agonists on hospital mortality, 28-day mortality, and ventilator free-days in patients with ALI/ARDS. Some of the results have been reported in an abstract.[19]

Methods

This study was performed at Mayo Clinic, Rochester, Minnesota. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.[20] The protocol for the systematic review and meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO, http://www.crd.york.ac.uk/prospero, 2012: CRD42012002616).

Study Eligibility and Outcomes

The study eligibility criteria were: RCT; β_2 agonists were compared against a control/placebo group; reported a risk estimate or data from which a risk estimate could be calculated; and reported hospital mortality or 28-d mortality and ventilator-free days. We did not include non-randomized trials or cohort or case control studies.

The primary outcomes of our study were mortality and ventilator free-days. The secondary outcomes were organ-failure-free days and adverse events. ALI was defined as a $P_{aO_2}/F_{IO_2} \leq 300$ mm Hg, and ARDS was defined as a $P_{aO_2}/F_{IO_2} \leq 200$ mm Hg, with bilateral pulmonary infiltrates consistent with edema, and the absence of clinically evident left atrial hypertension, according to the American-European Consensus Conference Committee definition.[21] Ventilator-free days was defined as "the number of calendar days after subjects started unassisted breathing until day 28 after randomization for subjects who survived at least 48 consecutive hours after start of unassisted breathing."[22] Organ-failure-free days were defined as "the number of days in the first 28 days after randomization that the subject received no cardiovascular, renal, liver, or neurological support."[23]

Search Strategy

We comprehensively searched the following databases, from their origin to March 2013 (any language, any population): Ovid MEDLINE In-Process and other non-indexed citations, Ovid MEDLINE, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials (CENTRAL), Ovid Cochrane Database of Systematic Reviews, Web of Science, and Scopus. The search strategy was designed and conducted by an experienced librarian (PJE), with input from the study's principal investigator (BS). Controlled vocabulary, supplemented with key words, was used to search for studies of β_2 agonist in subjects with ALI/ARDS. Two reviewers independently identified the eligible studies and extracted data. For additional information we contacted the study authors via e-mail. We searched by hand the references of found articles, abstracts of major congresses/conferences of pulmonary and critical care medicine (Society of Critical Care Medicine, American Thoracic Society, International Symposium on Intensive Care and Emergency Medicine, and European Society of Intensive Care Medicine), to minimize the risk of publication bias. Clinical trials registries (eg, http://www.controlled-trials.com and http://clinicaltrials.gov) were also searched to identify potential eligible studies. The search strategy is more thoroughly described in the supplementary materials at http://www.rcjournal.com).

Study Selection

Study selection was done by 2 reviewers (AA and BS), independently, in 2 phases. First, articles were screened on the basis of title and abstracts. Next, eligible articles were reviewed in full and selected according to the study eligibility criteria. The agreement between the 2 reviewers was measured using the Cohen weighted kappa value during both the phases.[24] Any disagreement was resolved via consensus in the presence of a third investigator (PMF).

Data Extraction

Two reviewers (BS and PMF) independently used standardized forms to abstract the data from the eligible

studies. The corresponding authors of eligible articles were contacted via e-mail to request any missing data. The following data were extracted from each study: author, country, publication year, number of subjects, description of study participants, inclusion and exclusion criteria, dates of enrollment, severity of illness scores, use of β_2 agonist, outcome definition, adverse reactions to β_2 agonist (eg, severe tachycardia leading to stoppage of the drug), duration of follow-up, and loss to follow-up.

Quality Assessment

For the assessment of risk of bias in estimating the study outcomes, we used the Cochrane risk of bias tool.[25] Each study was assessed for adequate sequence generation, allocation concealment, blinding of participants and personnel, blinding for patient-related outcomes and mortality, incomplete outcome data addressed, freedom from selective reporting, and freedom from other bias. Two reviewers (BS and PMF) conducted the quality assessment, independently, and in duplicate. Any disagreement was resolved via consensus, in the presence of the principal investigator.

Statistical Analysis

Categorical variables are reported as number and percent. Continuous variables are reported as means ± SD or median and IQR. The effect size was summarized by the relative risk for mortality and mean difference for ventilator-free days, along with 95% CI. The statistical heterogeneity between the studies was assessed with the Cochran Q test and I^2 statistic. A P value $< .10$ on the Cochran Q test and an I^2 value of $> 50\%$ suggest that the heterogeneity is beyond random error or chance.[26,27] We used the random DerSimonian and Laird effects model for analysis,[28] and present the results in forest plots. Heterogeneity $> 50\%$ was considered significant for the analysis.[27] The Cochrane risk of bias tool was used to ascertain the quality of the included studies, with each variable answered as high risk, low risk, or uncertain.[25] Data analyses were performed with meta-analysis software (RevMan 5.1, Cochrane Collaboration, http://www.cochrane.org).[29] $P < .05$ was considered significant in all the analyses.

Results

We identified 219 studies through various databases, of which 44 were excluded as duplicate studies. Another 163 were excluded for: non-relevance ($n = 99$), not based on original research ($n = 59$), not randomized trials ($n = 3$), and study protocols ($n = 2$). Twelve studies were included for full-text review, and 3 studies were finally included for the meta-analysis (Fig. 1). The interviewer agreement for study selection (from abstract and title) in phase I and the complete article reviews in phase II were excellent: Cohen weighted kappa values 0.92 (95% CI 0.80–1.00), and 1.0 (95% CI 1.0–1.0), respectively.

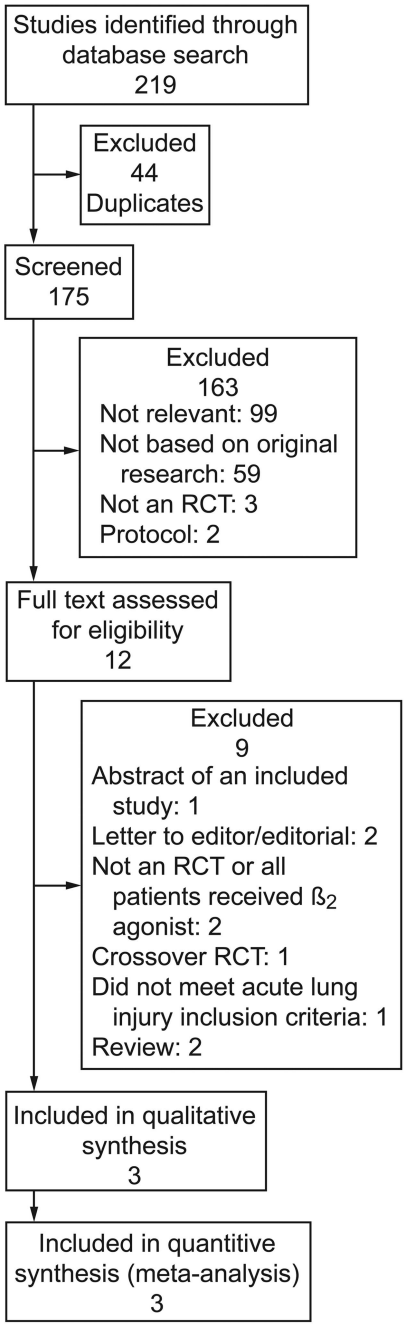

Fig. 1. Flow chart. RCT = randomized controlled trial.

The 3 RCTs included 646 ALI/ARDS patients, of whom 334 (51.7%) received β_2 agonist and 312 (48.3%) received placebo.[16-18] The detailed description of the included studies is given in the Table 1. The 3 RCTs used

Table 1. Characteristics of the Included Randomized Controlled Trials

	BALTI-1[18]		ALTA[17]		BALTI-2[16]	
Year published	2006		2011		2012	
Country	United Kingdom		United States		United Kingdom	
Setting	Single center		Multi-center: NHLBI ARDS Clinical Trials Network		Multi-center: 46 United Kingdom ICUs	
Inclusion criteria	Mechanically ventilated adults ($\geq$ 18 y), within 48 h of ALI or ARDS onset		Intubated and mechanically ventilated, frontal chest radiograph with bilateral pulmonary infiltrates consistent with edema, $P_{aO_2}/F_{IO_2} \leq 300$ mm Hg		Intubated and mechanically ventilated, age $\geq$ 16 y, within 72 h of ARDS onset. ARDS defined by the criteria of the American-European consensus conference on ARDS	
Blinding	Double		Double		Double	
Route for intervention	Intravenous		Inhaled		Intravenous	
Outcome definition	Extravascular lung water reduction in the salbutamol group at day 7, via thermodilution		Primary outcome: number of ventilator-free days from randomization to day 28		Primary outcome: 28-day mortality Secondary outcomes: ICU or hospital mortality; ventilator-free days, organ-failure-free days	
	β_2 Agonist Group	Placebo Group	β_2 Agonist Group	Placebo Group	β_2 Agonist Group	Placebo Group
P_{aO_2}/F_{IO_2}, mean $\pm$ SD mm Hg	117 $\pm$ 49.5	102.8 $\pm$ 36.8	170 $\pm$ 84	171 $\pm$ 75	103.5 $\pm$ 36.8	103.5 $\pm$ 36.8
Age, mean $\pm$ SD y	68.7 $\pm$ 16.0	57.0 $\pm$ 14.7	52 $\pm$ 16	51 $\pm$ 16	55.8 $\pm$ 17.2	54.2 $\pm$ 17.5
Number of subjects	21	19	152	130	161	163
Male, no. (%)	ND	ND	85 (56)	72 (55)	102 (63)	110 (67)
APACHE II score, mean $\pm$ SD	24.9 $\pm$ 6.4	22.5 $\pm$ 6.5	ND	ND	19.5 $\pm$ 6.2	18.9 $\pm$ 6.7
APACHE III score, mean $\pm$ SD	ND	ND	94.1 $\pm$ 28.7	91.5 $\pm$ 29.6	ND	ND
SAPS II score, mean $\pm$ SD	55.6 $\pm$ 15.1	49.3 $\pm$ 14.7	ND	ND	ND	ND
Lung injury severity score, mean $\pm$ SD	2.8 $\pm$ 0.7	3.0 $\pm$ 0.4	ND	ND	ND	ND
28-day mortality, no. (%)	11 (58)	14 (66)	ND	ND	55 (34)	38 (23)
60-day mortality, no. (%)	ND	ND	35 (23.0)	23 (17.7)	ND	ND
90-day mortality, no. (%)	ND	ND	37 (24.3)	24 (18.5)	ND	
ICU mortality, no. (%)	ND	ND	30 (19.7)	18 (13.8)	58 (36)	45 (28)
Mortality at hospital discharge, no. (%)	ND	ND	35 (23)	23 (17)	62 (39)	53 (33)
Extravascular lung water at day 7, mean $\pm$ SD mL/kg/L	9.2 $\pm$ 6	13.2 $\pm$ 3	ND	ND	ND	ND
Ventilator-free days, mean $\pm$ SD	6.2 $\pm$ 8.9	5.3 $\pm$ 8.6	14.4 $\pm$ 11.1	16.6 $\pm$ 10.3	8.5 $\pm$ 8.8	11.1 $\pm$ 9.3
Organ-failure-free days, mean $\pm$ SD	ND	ND	14.2 $\pm$ 11.1	15.9 $\pm$ 11.1	16.2 $\pm$ 10.7	18.5 $\pm$ 9.8
Follow-up period, d	28	28	90	90	Until discharged to a ward, or day 28	
Lost to follow-up, %	0	0	0	0	0	0

BALTI = β Agonist Lung Injury Trial
ALTA = Aerosolized β_2 Agonist for Treatment of Acute Lung Injury
NHLBI = National Heart, Lung, and Blood Institute
ALI = acute lung injury
ND = no data available
APACHE = Acute Physiology and Chronic Health Evaluation
SAPS = Simplified Acute Physiology Score

salbutamol (albuterol) as the β_2 agonist, and placebo in the control group. Two studies[16,18] used intravenous salbutamol, and the other used nebulized salbutamol.[17] The BALTI-1[18] and ALTA trials[17] included ALI patients. BALTI-2[16] included only ARDS patients. ALTA and BALTI-2[16,17] were multicenter trials. BALTI-1 was a single-center study.[18]

BALTI-1[18] and BALTI-2[16] reported 28-day mortality as an outcome. There was no significant decrease in 28-day mortality in the β_2-agonist group: relative risk 1.04 (95% CI 0.50–2.16). There was substantial heterogeneity between the studies (I^2 = 83%). A post hoc subgroup analysis was conducted to assess the between-study heterogeneity, based on the severity of ALI (ALI vs ARDS). The subgroup

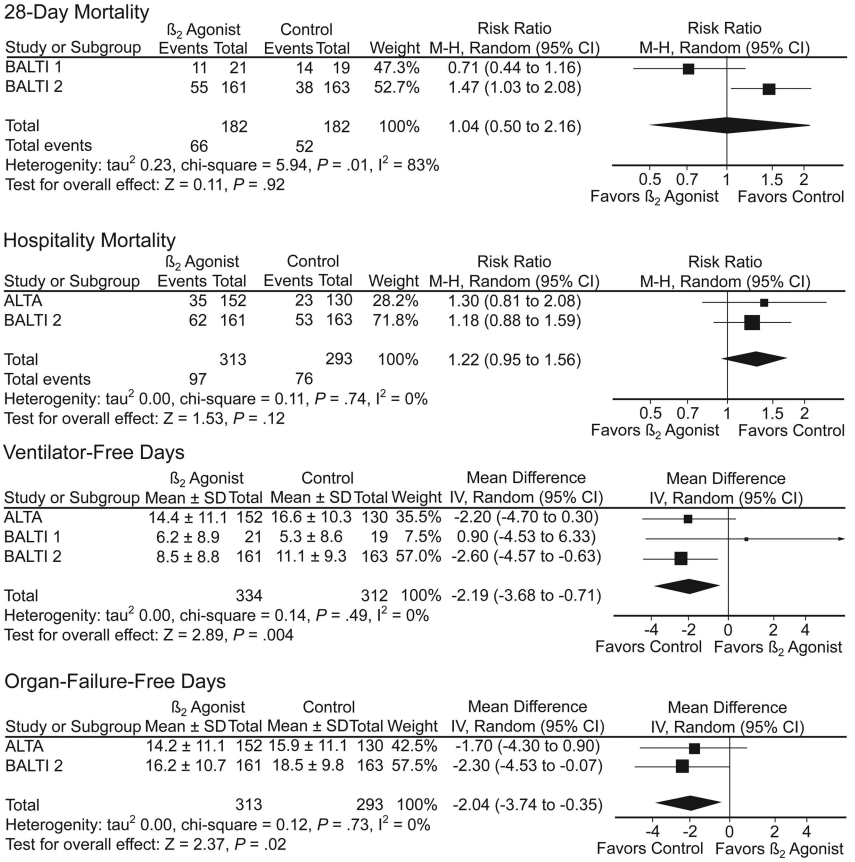

Fig. 2. Meta-analysis of outcomes in patients with acute lung injury/acute respiratory distress syndrome, who received β_2 agonist. M-H = Mantel-Haenszel test. BALTI = β agonist Lung Injury trial. ALTA = Aerosolized β_2 Agonist for Treatment of Acute Lung Injury trial. IV = inverse variance.

analysis showed a statistically significant difference in 28-day mortality among the ARDS subjects (relative risk 1.47, 95% CI 1.03–2.08), compared to the ALI subjects (relative risk 0.71, 95% CI 0.44–1.16) who were on β_2 agonists ($P = .02$) (see the supplementary materials at http://www.rcjournal.com). Although, this difference explains the heterogeneity, the small sample size of BALTI-1 could be the reason behind the low 28-day mortality in the ALI subjects. Two studies[16,17] reported hospital mortality as an outcome. There was a trend toward higher hospital mortality in the subjects who received β_2 agonists (relative risk 1.22, 95% CI 0.95–1.56), as compared to the placebo groups. However, that difference was not significant and had no heterogeneity ($I^2 = 0\%$). Figure 2 summarizes the evidence on 28-day mortality, hospital mortality, ventilator-free days, and organ-failure-free days.

In all the studies,[16-18] ventilator-free days were significantly lower in the subjects on β_2 agonist: mean difference −2.19 days (95% CI −3.68 to −1.99) (see Fig. 2). In 2 studies,[16,17] organ-failure-free days were significantly lower in the subjects who received β_2 agonists: mean difference −2.04 days (95% CI −3.74 to −0.35 d), $I^2 = 0\%$ (see Fig. 2).

Adverse Events

Figure 3 shows the major adverse events in the studies. The incidence of tachycardia (severe enough to stop/change the dose of medication) among subjects who received β_2 agonists was significantly higher than in the subjects who received placebo: pooled risk ratio 3.95 (95% CI 1.41–11.06). There was moderate heterogeneity ($I^2 = 44\%$). There was a higher incidence of arrhythmias among the ALI subjects who received β_2 agonists, compared to the subjects who received placebo: relative risk 1.97 (95% CI 0.70–5.54). There was substantial heterogeneity ($I^2 = 61\%$, $P = .08$), which could be explained by the differences in the severity of ALI and the route of drug administration (see the supplementary materials at http://www.rcjournal.com). On subgroup analysis, there was a statistically significant difference in arrhythmias among the ARDS subjects (relative risk 4.72, 95% CI 1.38–16.13), compared to

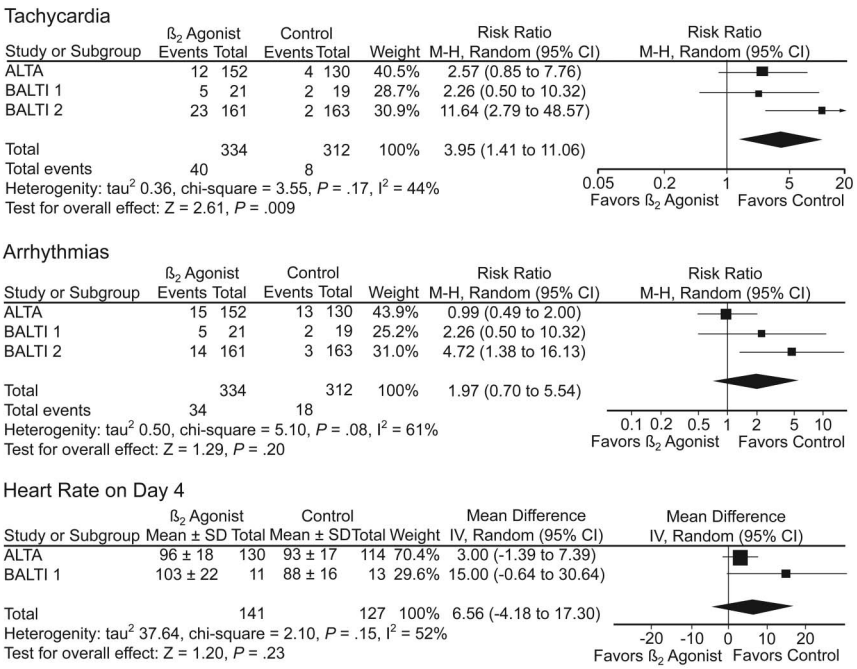

Fig. 3. Meta-analysis of adverse effects of β_2 agonist in patients with acute lung injury/acute respiratory distress syndrome. M-H = Mantel-Haenszel test. ALTA = Aerosolized β_2 Agonist for Treatment of Acute Lung Injury trial. BALTI = β agonist Lung Injury trial. IV = inverse variance.

the ALI subjects (relative risk 1.41, 95% CI 0.60–2.17) who received β_2 agonist ($P = .04$) (see the supplementary materials at http://www.rcjournal.com). The arrhythmogenic effect of β_2 agonists was significantly higher in ALI subjects who received intravenous β_2 agonist, as compared to inhaled β_2 agonist: relative risk 3.57 (95% CI 1.09–11.67), which explains the observed heterogeneity in the analysis. Two studies[17,18] reported the heart rate variation on day 4 after initiation of β_2 agonists in the ARDS/ALI subjects, and there was no statistically significant mean difference between the day-4 heart rates in the ARDS/ALI subjects who received β_2 agonists versus placebo.

Number Needed to Harm

The numbers needed to harm for tachycardia and arrhythmias (severe enough to stop/change the dose of medication among the subjects who received β_2 agonists) were 11 (95% CI 8–18) and 23 (95% CI 2–38), respectively. In other words, 11 ALI subjects need to be treated with β_2 agonists for one additional subject to have tachycardia. Twenty-three ALI subjects need to be treated with β_2 agonists for one additional subject to have arrhythmias, in comparison to the ALI subjects who received placebo.

Quality Assessment

All 3 studies were of high quality, with mostly low or unclear risk of biases. One study had an unclear risk of performance bias,[17] and in 2 there was an uncertainty about the detection bias (ALTA and BALTI-1).[17,18] The detailed quality assessment of the included studies is shown in Table 2.

Discussion

ALI and ARDS are associated with non-cardiogenic pulmonary edema, and several drugs have been proposed to manage these patients.[9,30-35] In spite of recent advances, the mortality remains high, at $\geq$ 30%.[36,37] There has been an interest in the role of β_2 agonists in managing patients with ALI and ARDS. We performed a literature search and meta-analysis of the available literature to assess the efficacy and role of β_2 agonists in improving the outcomes among patients with ALI/ARDS. Our meta-analysis results indicate that β_2 agonists do not improve mortality or ventilator free-days. This finding adds β_2 agonists to the list of drugs, such as aspirin and statins, that initially showed promise but failed to live up to the expectations.[38,39]

In the present literature review and meta-analysis, our evidence established that β_2 agonists were not only nonbeneficial in improving the survival, but were harmful among the patients with ALI/ARDS. β_2 agonists increased morbidity (reduced organ-failure-free days and ventilator-free days) and thus added to the cost of hospitalization. Critical illness is a strong stimulator of sympathetic drive in itself, which leads to rise in the catecholamine levels.[40]

Table 2. Quality Assessment of the Included Studies*

Quality Assessment Criteria	BALTI-1[18] 2006 United Kingdom	ALTA[17] 2011 United States	BALTI-2[16] 2012 United Kingdom
Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence	1	1	1
Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment	1	1	1
Performance bias due to knowledge of the allocated interventions by subjects and personnel during the study	1	0.5	1
Detection bias due to knowledge of the allocated interventions by outcome assessors	0.5	0.5	1
Attrition bias due to amount, nature, or handling of incomplete outcome data	1	1	1
Reporting bias due to selective outcome reporting	1	1	1
Bias due to problems not covered elsewhere	0.5	0.5	1

* Risk of bias: 1 = low, 0.5 = unclear, 0 = high.
BALTI = β Agonist Lung Injury Trial
ALTA = Aerosolized β_2 Agonist for Treatment of Acute Lung Injury

Catecholamine-induced myocardial stunning can reduce stroke volume and cause hypoperfusion of various organs. β agonists may further accentuate the harmful effects on the cardiovascular system; excessive sympathetic drive demonstrates its harmful effects systemically and due to its arrhythmogenic properties.[41] High catecholamine levels may lead to venous and arterial thrombosis. In addition, β_2 stimulation can cause lactic acidosis and hypokalemia and its related effects on various systems, such as ventricular arrhythmias, which can be life-threatening.[41-43] β_2 agonists increase myocardial oxygen demand and may have a detrimental effect in hypoxic ALI patients, leading to increased organ-failure days and longer mechanical ventilation.[8,16] Thus, the side effects of β_2 agonist can outweigh its benefits in a critically ill patient. The risk of arrhythmia was higher in ARDS patients than in ALI patients, and if the β_2 agonists were given intravenously, compared to the inhalation route. The risk of severe tachycardia (to stop or modify the dosage of medication) was almost 4 times higher in the patients on β_2 agonist than in those who received placebo. The safety profile of β_2 agonists raises questions on the use of β_2 agonist in the trials and as a treatment option for critically ill ALI patients.[8]

BALTI-1 was the first phase II, randomized, double blind, placebo-controlled, single-center trial of the efficacy, tolerability, and safety of intravenous β_2 agonist to treat pulmonary edema in adult patients with ALI.[18] Intravenous salbutamol (15 μg/kg/h) was administered to 40 subjects with ALI, for 7 days. The results suggested that salbutamol reduced extravascular lung water. BALTI-1 was one of the first human studies of the effect of β_2 agonist on lung water.[18] However, there was no statistically significance difference in 28-day mortality ($P = .40$) between the β_2 agonist and placebo groups. A higher heart rate at day 4 was observed in the salbutamol group (103 $\pm$ 22 beats/min vs 88 $\pm$ 16 beats/min in the placebo group) in the BALTI study ($P = .06$). In addition, 5 patients on salbutamol had new-onset of supraventricular tachycardia requiring dose adjustment, compared to the 2 patients in the control group ($P = .20$).[18]

ALTA was a randomized, double-blinded, placebo-controlled, multicenter trial, wherein nebulized albuterol was compared to placebo in patients with ALI, and ventilator-free days was the primary outcome.[17] The aerosolized route was used in ALTA[17] because aerosolized β_2 agonist had been shown to reduce pulmonary edema.[5] The other potential benefits of this route are improved mucociliary clearance, improved respiratory mechanics, and decreased work of breathing.[5] The ALTA trial aimed to include 1,000 patients, but the data safety and monitoring board terminated the study after recruiting only 282 patients, because of futility: the ventilator-free days difference was unfavorable and above the futility limit (-0.4 d) in the albuterol group (-2.2 d). The other variables in the ALTA trial[17] were mortality and organ-failure-free days among the ALI patients, which showed no significant benefits. The only benefit that albuterol showed in ALTA was in ICU-free days (-2.7 d, 95% CI -4.9 to -0.4). The authors of this RCT[17] suggested that β_2 agonist does not improve clinical outcomes and therefore should not be used in mechanically ventilated patients with ALI.

Following the ALTA trial,[17] another trial, BALTI-2,[16] was conducted by the BALTI-1 investigators. The BALTI-2 trial was a randomized, double-blind, placebo-controlled, multicenter (46 centers) trial assessing 28-day mortality in ARDS patients.[16] The BALTI-2 trial was an extension of BALTI-1, which used intravenous salbutamol (15 μg/kg/h). The target sample size for BALTI-2 was 1,334, but the data monitoring and ethics committee stopped recruitment after the second interim analysis due to adverse effect of salbutamol on 28-day mortality (relative risk 1.55, 95% CI 1.07–2.24). For every 9 (95% CI 5–101) patients with ARDS that were treated with salbutamol, one additional death was observed. This led to the early termination of the BALTI-2 study. Furthermore, the treatment with intravenous salbutamol was poorly tolerated among the ARDS patients, thus worsening the outcomes. Patients had to be ventilated longer (-2.7 d, 95% CI -4.7 to -0.7) in the salbutamol group than in the placebo group. The incidence of tachycardia sufficient to stop treatment in the study group was almost 12 times higher in the salbutamol group than in the placebo group.[16] There was also a higher incidence of new-onset arrhythmias (relative risk 4.75, 95% CI 1.4–16.2) in the salbutamol group than in the placebo group.

Both BALTI and BALTI-2 should attract the attention of treating physicians toward the potential side effects of salbutamol, and should not be blinded toward the use of salbutamol with an aim of hypothetical benefit. The results of the present meta-analysis further consolidates the conclusion that β_2 agonist should not be used in patients with ALI or ARDS, because it provides no benefit and worsens mortality and other outcomes. The safety profile of β_2 agonists in patients with ALI or ARDS makes this medication unsafe, so further studies cannot be recommended.

Strengths

The main strength of our systematic review and meta-analysis is the comprehensive search of all major databases. To find all the possible studies and reduce publication bias, we hand-searched the abstracts and proceedings of the major pulmonary and critical care conferences. We contacted the corresponding authors of the studies to identify the missing data. We performed a post hoc subgroup analysis to explain the between-study heterogeneity, based on the severity of ALI, by which we explained the heterogeneity of the results.

Limitations

First, due to the small numbers of studies (only 3 RCTs), we could not assess the publication bias.[44] Even after detailed searching, we could not find any more articles. However, 2 of the 3 trials were multicenter studies, thus, strengthening the external validity of the study findings. Second, there are the inherent limitations of the definition of ARDS, due to the variability in chest radiograph interpretation, the difficulty of excluding left atrial hypertension, the lack of defining "acute," and the sensitivity of P_{aO_2}/F_{IO_2} to different ventilator settings. Thus, the new consensus Berlin definition of ARDS was developed to address some of these concerns.[45] The Berlin definition of ARDS[45] may serve as a better model for designing new trials, to differentiate the categories of ARDS according to severity, to create uniformity among the trials, and to help in better healthcare services planning. Third, using ventilator-free days as an outcome has its own limitation. Weaning strategies differ across institutions, and per physicians' or intensivists' preferences. There is variability among the weaning practices across the globe; recent trials have focused on using noninvasive ventilation for weaning, but there is still no consensus on that.[46] Thus, as an outcome, ventilator-free days may reflect more on the effectiveness of ICU care than on the patient's underlying disease or prognosis. Nevertheless, it provides important information, especially when the severity of disease is high, such as in ARDS, and can still be used as a reliable outcome. Lastly, our results are not applicable to patients under age 13, because we did not include any studies with subjects $<$ 13 years old.

Conclusions

In patients with ALI/ARDS, β_2 agonist did not improve hospital or 28-day mortality. Patients who received β_2 agonists had to be ventilated longer and had fewer organ-failure-free days than subjects who received placebo. The current evidence discourages the use of β_2 agonist in ALI/ARDS patients.

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