Effectiveness of Glucocorticoids on acute respiratory distress syndrome: An umbrella review

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Abstract

Background

Management of Acute Respiratory Distress Syndrome is a very challenging critical illness in ICU with high morbidity and mortality worldwide.The review was intended to provide evidence on the effectiveness of Glucocorticoid treatment for acute respiratory distress syndrome

Method

A comprehensive search strategy was conducted on PubMed/Medline, Cochrane Library, Science direct, LILACS, and African Online Journal. Data extraction was carried out with two independent authors with customized checklist. The quality of each systemic review was assessed by two independent authors using AMSTAR tool and the overall quality of evidence was generated with online GRADEpro GDT software for primary and secondary outcomes.

Result

The umbrella review included nine systemic reviews and meta-analysis and one narrative review with eight thousand four hundred ninety one participants. The methodological quality of the included studies was moderate to high quality. The overall quality of evidence and recommendation varied form high to very low.

Conclusion

There is high to moderate quality evidence on the initiation of early low dose prolonged glucocorticoid for reduction of mortality for ARDS. However, randomized controlled trials with large sample sizes to address ventilator-free days, the incidence of infection and other glucocorticoid associated adverse events is required as the quality of evidence with these secondary outcomes were low to very low

Background

Acute respiratory distress syndrome (ARDS) is an acute inflammatory lung process associated with increased pulmonary vascular permeability, increased lung weight, and hypoxemic respiratory failure which results in significant morbidity and mortality worldwide[1 – 6]. The first clinical description of ARDS was traced back to 1967 by AShbaugh et al on 12 patients having refractory cyanosis due to hypoxemia respiratory failure requiring mechanical ventilation[5]. In 1994, The American European Consensus Conference (AECC) established a uniform definition and diagnostic criteria which comprises of acute onset, bilateral chest infiltration, and hypoxemia based on Pa02/FI02 without PEEP, and no evidence of left atrial hypertension with capillary wedge pressure which is greater than 18 cmH20[7]. However, this definition had a number of limitations and modified by the American Thoracic Society and the Society of Critical Care Medicine in Berlin to establish the Berlin definition.

The onset of respiratory symptoms within one week of a known insult, severity of hypoxemia as mild (200 mmHg > Pa02 ≤ 300mmHG), moderate (100 mmHg > Pa02 ≤ 200 mmHg) and severe (Pa02 ≤ 100), exclusion of acute lung injury, requirement of positive end-expiratory pressure (PEEP) of ≥ 5 cmH2O and an objective evaluation of cardiogenic pulmonary edema with echocardiography were the major recommendation of Berlin definition[2].

The Kigali modification defined ARDS without the PEEP, as the presence of bilateral opacities on the chest radiograph or lung ultrasound and hypoxia defined as SpO2/FIO2 less than or equal to 315[8–11]. A study by Riviello et al published on incidence of ARDS with a Kigali modification of the Berlin definition which is applicable in resource-limited set up where Arterial blood gas analysis is not available[11]. The Kigali modification defined ARDS as the presence of bilateral opacities on the chest radiograph or lung ultrasound, hypoxia defined as SpO2/FIO2 less than or equal to 315 and without the requirement of PEEP which is validated to be employed in resource-limited setup[8].

ARDS is a clinical syndrome associated with respiratory failure due to pulmonary and nonpulmonary insults[3,6,12]. A number of pulmonary risk factors of ARDS have mentioned in the literature and from which pneumonia accounted for more than fifty percent followed by aspiration of gastric content and pulmonary contusion whereas as sepsis, non-cardiogenic shock and massive blood transfusion are the most common nonpulmonary causes of ARDS[1,12].

Despite a number of observational and Randomized Clinical trials, the Incidence of ARDS is still very high. A large observational study (LUNG SAFE) with 50 high and middle-income countries including 459 Intensive Care Unit (ICU) centers revealed that the incidence of ARDS was 10.4% with patient mortality of around fifty percent in severe cases[4]. However, the incidence and mortality were very high in low and middle-income countries with resource-limited setups[6,13].

Management of Acute Respiratory Distress Syndrome is a very challenging critical illness in ICU with high morbidity and mortality. Recent studies revealed that low tidal volume ventilation (6 ml/kg ideal body weight), prone positioning (16-20hrs), airway recruiting maneuvers, Extra-corporeal Membrane Oxygenation (ECM) and lung stem cell provision decrease patient mortality, decrease ventilator-free days and ICU discharge. However, glucocorticoid administration for prevention and/or treatment didn't show conclusive evidence[14,15].

Three systemic reviews and meta-analysis of Randomized Controlled Trails(RCTs) revealed that early and prolonged administration of methylprednisolone reduced mortality and duration of mechanical ventilation [16–18]. On the other hand, five Meta-analyses of randomized trials failed to show conclusive evidence on mortality benefit of glucocorticoids in a patient with Acute Respiratory Distress Syndrome[19 – 23]. A systemic review by Curtis failed to show a significant benefit of glucocorticoids for the late stages of ARDS[24]. Therefore, this umbrella review is aimed to provide evidence on the efficacy of glucocorticoids on the treatment and prevention of acute respiratory distress syndrome.

Objectives And Research Question

Objectives

The objective of this umbrella review was to provide evidence on the effectiveness of Glucocorticoid treatment for acute respiratory distress syndrome.

Research question

- Do we have high-quality evidence on the effectiveness of glucocorticoids for acute respiratory distress syndrome?
- When should glucocorticoids be initiated for acute respiratory distress syndrome?
- Is low dose regimen of glucocorticoids more effective than high dose regimen glucocorticoids for acute respiratory distress syndrome?

Methods

Types of studies

All systemic reviews of Randomized Controlled Trials and Cohort study designs comparing the effects of glucocorticoids on acute respiratory syndrome without language and date restriction were included. This umbrella review was registered in Prospero international prospective register of systemic reviews (CRD42019130539).

Types of participants

All Systemic reviews incorporating adult ICU patient with ARDS receiving glucocorticoid and placebo were considered

Intervention

The intervention was any type of glucocorticoids administered to patients with acute respiratory distress syndrome.

Comparator

The control was patients who took a placebo or other form of treatment with the purpose of comparing it with glucocorticoids.

Types of outcomes

The primary outcomes were hospital mortality and the number of mechanical ventilator-free days. The secondary outcomes were duration of ICU stay and glucocorticoid related adverse effects including the incidence of infection, hyperglycemia, and neuromuscular dysfunction.

Eligibility criteria

Inclusion criteria

The umbrella review included all systemic reviews with or without meta-analysis comparing the effectiveness of glucocorticoids on acute respiratory disease syndrome either for treatment or prevention strategies.

Exclusion criteria

The overview view excluded systemic reviews assessing the effectiveness of glucocorticoid on pediatrics acute respiratory syndrome, a systemic review of cross-sectional studies and clinical reviews.

Search strategy

The search strategy was intended to explore all available published and unpublished systemic reviews on the effectiveness of glucocorticoids for treatment or prevention of acute respiratory distress syndrome. A three-phase search strategy was employed in this umbrella review. An initial search on PubMed/Medline, Cochrane Library, Science direct, LILACS, and African Online Journal was carried out followed by an analysis of the text words contained in Title/Abstract and indexed terms. A second search was undertaken by combining free text words and indexed terms with Boolean operators. The third search was conducted with the reference lists of all identified reports and articles for additional studies. Finally, an additional and grey literature search was conducted on Google scholars up to ten pages. The result of the search strategy was presented with the Prisma flow chart (figure-1). The search strategy conducted in PubMed was presented in appendix 1.

Methodological Quality Assessment

The methodological quality of each included systemic review was evaluated with the AMSTAR tool (Assessing the Methodological quality of systemic reviews) by two independent authors[25]. A score was given for each included systemic review from the sum of all positive points to the checklist items and the inconvenience between the two authors was resolved by the third author. The included systemic reviews were classified based on the AMSTAR scores as high quality 8-11, moderate quality 4-7 and low quality 0-3 score values (Table 1).

Table 1 Assessment of Methodological quality

Author/year	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Score
Menduri et al [16] 2018	√	X	√	X	√	√	X	√	√	X	√	7
Yang et al[21] 2017	√	√	√	√	√	√	√	X	X	√	X	8
Menduri et al[18] 2016	√	X	X	X	X	√	X	X	√	√	√	5
Horita et al[23] 2015	√	√	√	X	√	√	√	X	√	√	√	9
Ruan et al [19] 2014	√	√	√	√	√	√	√	X	X	X	√	9
Khilnani and colleague [22] 2011	√	√	√	√	X	X	X	√	X	X	X	5
Curtis and colleague[26] 2010	√	X	X	X	X	X	√	√	X	X	X	3
Benjamin et al[17] 2009	√	√	√	√	X	√	X	X	√	X	X	6
Peter et al[20] 2008	√	√	√	√	X	X	√	√	√	X	√	8
Marik et al	x	√	x	X	x	√	x	√	x	x	x	3

The AMSTAR tool (Assessing the Methodological quality of systemic reviews)

Q1: Was an 'a priori' design provided?

Q2: Was there duplicate study selection and data extraction?

Q3: Was a comprehensive literature search performed?

Q4: Was the status of publication (i.e. grey literature) used as an inclusion criterion?

Q5: Was a list of studies (included and excluded) provided?

Q6: Were the characteristics of the included studies provided?

Q7: Was the scientific quality of the included studies assessed and documented?
Q8: Was the scientific quality of the included studies used appropriately in formulating conclusions?

Q9: Were the methods used to combine the findings of studies appropriate?

Q10: Was the likelihood of publication bias assessed?

Q11: Was the conflict of interest included?

Data extraction

The data from each systemic review and meta-analysis was extracted with two independent authors for description of included studies and grading the overall quality of evidence of each systemic reviews and meta-analysis. The data extracted included author, year of publication, number of RCTs included, number of participants, methodological quality, outcome of interest, total events in treatment and control and effect sizes (Odds Ratio, Relative Risk, Mean difference and 95% confidence interval). The overall quality of evidence was graded with online GRADEpro GDT software. The umbrella review was presented based on the Preferred Reporting Items for Systemic Reviews and Meta-Analysis (PRISMA)[27] **(additional File).**

Grading the quality of evidence

The overall qualities of evidence for the studied outcome were evaluated using the GRADE system (Grading of Recommendations Assessment, Development, and Evaluation)[28,29]. The system incorporates study quality (risk of bias), inconsistency (comparison of effect estimates across studies), indirectness (applicability of the population, intervention, comparator and outcomes to the clinical decision), imprecision (certainty of confidence interval) and high probability of publication bias. The overall quality of evidence was categorized as follows by evaluating and combing the above five parameters for mortality, mechanical ventilator free days and incidence of infection.

- Effective interventions: indicated that the review found high-quality evidence of effectiveness for an intervention.
- Possibly effective interventions: indicated that the review found moderate-quality evidence of effectiveness for an intervention, but more evidence is needed.
- Ineffective interventions: indicated that the review found high-quality evidence of lack of effectiveness (or harm) for an intervention.
- Probably ineffective interventions: indicated that the review found moderate-quality evidence suggesting a lack of effectiveness (or harm) for an intervention, but more evidence is needed.
- No conclusions possible: indicated that the review found low or very low-quality evidence, or insufficient evidence to comment on the effectiveness or safety of an intervention.

Results

Description of included studies

The search strategy identified 272 systemic reviews and meta-analysis from different databases as described in the methodology section. Thirty systemic reviews and meta-analysis were selected for further evaluation after the successive screening. Finally, ten systemic reviews and meta-analysis with 8491 participants were included for the umbrella review (Table 2) and the rest were excluded with reasons (Table 3). The systemic reviews and meta-analysis included in the umbrella review were published from 2008 to 2018 with participant size varied from 567 to 1474. The methodological quality of included systemic reviews was ranged from low to high quality. Four systemic reviews were rated as high quality while another four were moderate quality. There was only one systemic review scored low with the methodological assessment.

Table 2
description of included studies

Author	year	Design/Participant(N)	Quality score	Primary outcome	Main findings
Menduri et al	2018	9RCTs(N = 766)	7	mortality	Glucocorticoid revealed mortality reduction for ARDS(RR = 0.68, 95% CI 0.57 to 0.82)
Yang et al	2017	14 RCTs(N = 772)	8	mortality	Subgroup analysis of low and high dose glucocorticoid revealed mortality reduction (RR = 68,95% CI 0.50 to 0.91)
Menduri et al	2016	8 RCTs(N = 569)	5	weaning	Glucocorticoids reduce MV free days
Horita et al	2015	11 RCTs(N = 949)	9	mortality	Glucocorticoid didn't show significant difference on mortality reduction (RR = 0.77, 0.58 to 1.03)
Ruan et al	2014	8 RCTS and 10 Cohort(N = 1474)	9	mortality	Subgroup analysis didn't show significant difference in mortality (RR = 1.14, 95% CI 0.79 to 1.65)
Khilnani and colleague	2011	9 RCTs(N = 1025)	5	mortality	Glucocorticoid failed to show significant difference in mortality
Marik et al	2011	8RCTs(N = 567)	3	mortality	Glucocorticoid revealed mortality reduction for ARDS(RR = 0.68, 95% CI 0.56 to 0.81)
Curtis and colleague	2010	4RCTs and 5 Cohort(N = 648)	3	mortality	Subgroup analysis showed that glucocorticoid mortality reduction(RR = 0.62, 95% CI 0.43 to 0.91)
Benjamin et al	2009	4RCTs and 5 Cohort(N = 648)	6	mortality	Subgroup analysis showed that glucocorticoid mortality reduction(RR = 0.62, 95% CI 0.43 to 0.91)
Peter et al	2008	9RCTs(1073)	8	mortality	preventive steroid didn't show significant benefit(OR = 1.55, 95% CI 0.58 to 4.05)
RCTs: Randomized controlled Trials; CI: Confidence interval; RR: Relative Risk; OR: Odds Ratio					

Table 3
description of excluded studies

Author	year of publication	reason for exclusion
Fernandesand colleague	2005	clinical review of glucocorticoid for ARDS
Freire and colleagues	2003	clinical review on biological efficacy of glucocorticoid
Rio de Janeiro et al	2009	glucocorticoid for septic shock
Meduri and colleagues	2016	mini review on ICU acquired weakness due to prolonged steroid
Meduri et al	2010	expert clinical review
schwingshak et al	2016	clinical review of prolonged glucocorticoid in pediatrics with ARDS
Yan et al	2016	efficacy of glucocorticoid for severe community acquired pneumonia
Alonso-Coello et al	2015	glucocorticoid for severe community acquired pneumonia
Delara et al	2018	glucocorticoid for preterm infant in ARDS

Nine of the included systemic reviews were systemic review and meta-analysis[16 – 21,23,26,30] whereas only one systemic review was narrative review[22]. The methodological quality assessment was reported only in three systemic reviews[18,20,21]. One study reported the GRADE pro summary table[18]. Publication bias was reported in two studies[21,23]. Three systemic reviews included both Cohort and randomized controlled trials[17,19,26] while the other seven systemic reviews included only randomized controlled trials[16,18,20–23].

Table 4
GRADE evidence summary table for effectiveness of glucocorticoids for mortality reduction

Certainty assessment								No. of participants		Effect	
Author	N0. Of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	glucocorticoid	control	Relative(95% CI)	Abs (95
Curtis et al 2010	3	RCT	serious	serious	not serious	serious	none	144	101	-	MD high (0.4 high 0.9 high
John et al 2008	3	RCT	not serious	not serious	not serious	serious	none	46/88 (52.3%)	36/66 (54.5%)	OR 1.50 (0.30 to 5.94)	97 r per 1,00 (fro 281 few 332 mor
Meduri et al	9	RCT	serious	not serious	not serious	not serious	none	112/397 (28.2%)	157/369 (42.5%)	RR 0.68 (0.57 to 0.82)	136 few per 1,00 (fro 183 few 77 few
Yang et al	9	RCT	not serious	not serious	not serious	not serious	none	158/584 (27.1%)	209/555 (37.7%)	RR 0.58 (0.44 to 0.75)	158 few per 1,00 (fro 211 few 94 few
Ruan et al 2014	8	RCT	serious	not serious	not serious	serious	none	173/391 (44.2%)	167/334 (50.0%)	RR 0.91 (0.71 to 1.18)	45 f per 1,00 (fro 145 few 90 mor

CI: confidence interval; RR: Relative Risk; OR: Odds Ratio; MD: Mean Difference

Table 5

GRADE evidence summary table for effectiveness of glucocorticoids on number of MV free days and infection rate

Certainty assessment								No. of participants		Effect	
Author	N0. Of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other consideration	glucocorticoid	control	Relative(95% CI)	Ab (9
Benjamin et al 2009	4	RCT	not serious	serious	not serious	serious	none	140	167	-	M lo (9 lo 0. lo
Meduri et al 2015	4	RCT	not serious	serious	not serious	serious	none	186	136	-	M hi (3 hi 11 hi
Yang et al 2017	4	RCT	not serious	serious	not serious	not serious	none	249	225	-	M 1. hi (4 hi 0
Incidence of infection											
Benjamin et al 2009	9	RCT	serious	not serious	not serious	not serious	none	84/304 (27.6%)	74/265 (27.9%)	RR 0.89 (0.65 to 1.23)	31 pe 1,((fr fe 64 m
Meduri et al 2015	8	RCT	not serious	not serious	not serious	serious	none	22/299 (7.4%)	27/270 (10.0%)	OR 0.77 (0.56 to 1.08)	21 pe 1,((fr fe 7 r
Yang et al 2017	7	RCT	not serious	serious [a]	not serious	not serious	none	102/361 (28.3%)	99/339 (29.2%)	OR 1.00 (0.44 to 2.25)	0 f pe 1,((fr 13 fe 18 m
Ruan et al 2014	5	RCT	serious	not serious	not serious	serious	none	79/303 (26.1%)	70/268 (26.1%)	RR 0.83 (0.65 to 1.06)	44 pe 1,((fr fe 16 m

CI: confidence interval; RR: Relative Risk; OR: Odds Ratio; MD: Mean Difference; MV: mechanical ventilator

List of tables

The majority of systemic reviews compared the efficacy of early low dose glucocorticoid while two studies compared the effectiveness of glucocorticoid for late and unresolving ARDS[17,26]. Five systemic reviews assessed the benefit of glucocorticoid treatment for ARDS for a longer duration (greater than seven days)[16–18,21,22] whereas one study compared short term(less than seven days) therapeutic benefit of glucocorticoid for ARDS[21]. All of the included studies assessed the therapeutic effectiveness of glucocorticoid on ARDS whereas four systemic reviews compared the preventive effectiveness of glucocorticoid in moderate and high-risk patients for ARDS as well[18 – 20,22].

Hospital or ICU mortality was the primary outcome in nine systemic reviews[16,17,19–23,26,31] while one systemic review reported a number of mechanical ventilator-free days as a primary outcome[32]. Incidence of infection was mentioned in five systemic reviews[17,19–21,32] and number of mechanical ventilator-free days was reported in three systemic reviews[16,21,26].

One systemic review reported neuromyopathy, lung injury score, multiorgan dysfunction syndrome score, and all major adverse events as a secondary outcome[17].

Data synthesis

The primary objective of this umbrella review was to provide quality evidence on the effectiveness of glucocorticoids on acute respiratory distress syndrome. The methodological quality of each systemic review was assessed with the AMSTAR tool and the overall quality evidence for the outcomes such as mortality, a number of mechanical ventilator-free days and incidence of infection were evaluated with online GRADEpro software. The primary outcome quality of evidence was provided with the GRADEpro summary table (Tables 4 and 5). The provision of glucocorticoids and its impact on patients with ARDS are themed as follows:

Early glucocorticoid therapy

There are discrepancies among systemic reviews on early initiation of glucocorticoids (less than 7 days) for the mortality benefit of patients with ARDS. One systemic review with high quality of evidence showed 67% reduction in mortality (OR = 0.37, 95% confidence interval (CI) 0.16 to 0.86, 8 studies, 501participants)[21]. Another moderate quality of evidence systemic review revealed that early glucocorticoid therapy reduced mortality by 32% (RR = 0.68, 95% confidence interval (CI) 0.57 to 0.82, 9 studies, 766 participants)[16]. One low quality systemic review showed 38% mortality reduction (RR = 0.62, 95% confidence interval (CI) 0.43 to 0.91, 5 cohort and 4 RCTs, 648 participants)[17]. However, two low-quality systemic reviews and one very low-quality systemic review didn't show any significant difference in mortality between glucocorticoid and control[23,32,33].

Low to moderate quality of evidence showed that low incidence of infection and longer duration of mechanical ventilator-free days was observed in a patient with early low dose glucocorticoid when compared with controls[16,20,21,23,26,32,33].

Late glucocorticoid

The benefit of initiating glucocorticoid in late and unresolving phases of ARDS (after seven days) didn't show a significant difference in mortality, mechanical ventilator-free days and rates of infection. A moderate quality of evidence systemic review by Yang et al didn't show a significant difference in mortality (RR = 0.59, 95% confidence interval (CI) 0.34 to 1.03, two RCTs, 271participants)[21]. Another moderate quality of evidence review by Menduri et al failed to show a significant benefit of late initiation of glucocorticoid for ARDS(RR = 0.67, 95% confidence interval (CI) 0.44 to 1.04, 314 participants)[16].

Prolonged glucocorticoids

Prolonged low dose glucocorticoid initiated at least one week revealed certain mortality reduction in low to moderate quality evidence systemic reviews[16,18]. Moderate quality evidence from Yuan et al systemic review showed a 56% reduction in mortality (OR = 0.44, 95% confidence interval (CI) 0.30 to 0.64, 6 RCTs, 551 participants)[19]. Another two moderate-quality evidence systemic review by Menduri et al in 2015 and 2018 revealed a significant mortality reduction by 44% and 32% respectively[16,18]. Another two low-quality evidence systemic reviews by Yuan et al and Curtis et al showed a significant reduction in mortality and mechanical ventilator-free days[26,33].

Short term glucocorticoid

The initiation of high dose glucocorticoids for ARDS in for less than a week didn't show a significant difference in the reduction of mortality, mechanical ventilator-free days and rates of infection[21]. Moderate quality evidence from Yuan et al systemic review failed to show a significant difference in mortality (OR = 0.77, 95% confidence interval (CI) 0.52 to 1.13, 6 RCT, 588 participants)[19].

Glucocorticoid for prevention of ARDS

The provision of glucocorticoid for high-risk patients to prevent acute respiratory distress syndrome didn't show a significant difference in survival and incidences of infection. Low-quality evidence from John et al systemic review showed an insignificant difference in mortality (OR = 1.52, 95% confidence interval (CI) 0.30 to 5.94), 3 RCTs, 154 participants)[20]. Low-quality evidence from Yuan et al systemic review also failed to show a significant difference in mortality (RR = 1.24, 95% confidence interval (CI), 0.57 to 2.72, 3RCTs, 154 participants)[19].

Discussion

Acute respiratory distress syndrome is the most challenging critical illness in the Intensive Care Unit with significant mortality and morbidity. Glucocorticoid has been employed for the management of ARDS in different dosage, duration and timing. Despite plenty of randomized controlled trials and systemic reviews, there is no conclusive evidence on the effectiveness of glucocorticoids for ARDS. The aim of this umbrella review is to assess the quality of evidence of available systemic reviews and meta-analysis on the effectiveness of glucocorticoids for ARDS.

High-quality evidence of effectiveness

High-quality evidence showed a reduction in mortality and prolonged numbers of mechanical ventilator-free days in a patient with acute respiratory distress syndrome taking early low dose prolonged glucocorticoid therapy[21].

Moderate quality evidence of effectiveness

Moderate quality of evidence showed early low dose glucocorticoid reduced mortality[16,20]. Moderate quality of evidence also revealed that early low dose glucocorticoid decreased incidence of infection and prolonged numbers of mechanical ventilator-free days[17,20,21]. Moderate quality of evidence failed to show mortality benefit in late phase ARDS initiation of glucocorticoids[26]. A prolonged administration of glucocorticoids showed a reduction in mortality as depicted with moderate quality of evidence systemic reviews[16,18,21]. Moderate quality of evidence failed to show a significant difference in mortality in patients taking high dose short term glucocorticoid treatment[21].

Low to a very low quality of evidence

Low to a very low quality of evidence didn't show a significant difference in mortality in a patient who was on early low dose glucocorticoid when compared to control[17,19,23,26]. Low quality of evidence showed that prolonged glucocorticoid reduced mortality and prolonged number of mechanical ventilator-free days[26]. Low quality of evidence failed to show a significant difference in mortality and incidence of infection in a patient who was on preventive glucocorticoids[20].

Limitation of the overview

The umbrella review incorporated ten systemic reviews with high to a very low quality of evidence. The majority of systemic reviews had moderate to a very low quality of evidence and strong recommendation on the effectiveness of glucocorticoids which is indeed affected with time to initiation, duration of therapy and dosage could be a challenge. Besides, some of the systemic reviews didn't report the relevant information for the GRADE evidence profile.

Conclusion

This umbrella review summaries the evidence from systemic review and meta-analysis of randomized controlled trials and cohort studies to address the effects of glucocorticoids for acute respiratory distress syndrome. The finding of this review is valuable for clinicians, researchers, and policy-makers for decision making and evidence translation.

There is high-quality evidence from one systemic review and meta-analysis of randomized controlled trials regarding the mortality benefit of early and low dose glucocorticoid for greater than one week for acute respiratory distress syndrome. Moderate to low-quality evidence showed early low dose glucocorticoids decrease mortality; prolong a number of mechanical ventilator days and incidence of infection. However, moderate-quality evidence failed to show a significant benefit of the administration of glucocorticoid in the late phase of acute respiratory distress.

Low to a very low quality of evidence from systemic reviews failed to show a significant benefit of glucocorticoid initiated in the late phase of acute respiratory distress syndrome. Low to a very low quality of evidence also didn't show mortality reduction, prolonged number of mechanical ventilator-free days and rates of infection with preventive glucocorticoid for severe and unresolved acute respiratory distress syndrome.

Despite strong recommendation on the initiation of early low dose prolonged glucocorticoid for reduction of mortality for ARDS, randomized controlled trials with large sample sizes to address ventilator-free days, the incidence of infection and other glucocorticoid associated adverse events as the quality of evidence with these secondary outcomes were low to very low.

Abbreviations

AECC American European consensus conference

AMSTAR Assessing the Methodological quality of systemic reviews

ARDS Acute Respiratory Distress Syndrome

CI Confidence Interval

ECOM Extra-Corporeal Membrane Oxygenation

GDT Guideline Development Tool

ICU Intensive Care Unit

MD Mean Difference

OR Odds Ratio

RCT Randomized Controlled Trials

RR Relative Risk

PEEP Positive End Expiratory Pressure

PRISMA Preferred reporting Items for Systemic Review and Meta -Analysis

Declarations

Ethics approval and consent to participate

Ethical clearance and approval were obtained from the ethical review board of the College of Health Science and Medicine.

Consent for publication

Not applicable

Registration

This umbrella review was registered in Prospero international prospective register of systemic reviews (CRD42019130539).

Availability of data and materials

Data and material can be available where appropriate.

Competing interests

The authors declare that there are no competing interests

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Authors' contributions

SA and HK conceived the idea and design the study. SA, HK and VB involved in searching strategy, data extraction, quality assessment, analysis and manuscript preparation. All authors have read and approved the manuscript.

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References

1. Pham, T. and Rubenfeld, G. D. Fifty years of research in ards the epidemiology of acute respiratory distress syndrome a 50th birthday review. Am. J. Respir. Crit. Care Med. **195**, 860–870 (2017).
2. Ranieri V. M. et al. Acute respiratory distress syndrome: The Berlin definition. JAMA **307**, 2526–2533 (2012).
3. Confalonieri, M., Salton, F. and Fabiano, F. Acute respiratory distress syndrome. Eur. Respir. Rev. **26**, (2017).
4. Bellani G, Laffey G, Pham T et al. Epidemiology, patterns of care, and mortality for patients with acute respiratory distress syndrome in intensive care units in 50 countries. JAMA - J. Am. Med. Assoc. **315**, 788–800 (2016).
5. Rezoagli, E., Fumagalli, R. & Bellani, G. Definition and epidemiology of acute respiratory distress syndrome. Ann. Transl. Med. **5**, 1–12 (2017).
6. Buregeya, E, Riviello D and Twagirumugabe T. Acute respiratory distress syndrome in the global context. Glob. Heart **9**, 289–295 (2014).
7. Bernard, G. R, Artigas A, Birgham K et al. Report of the American-European consensus conference on ARDS: Definitions, mechanisms, relevant outcomes and clinical trial coordination. Intensive Care Med. **20**, 225–232 (1994).
8. Rawal, G., Yadav, S. & Kumar, R. The ARDS Kigali definition : do we need a new definition for low-income The ARDS Kigali definition : do we need a new definition for low-income countries ? (2016).
9. Riviello, E. D., Buregeya, E. & Twagirumugabe, T. Diagnosing acute respiratory distress syndrome in resource limited settings: The Kigali modification of the Berlin definition. Curr. Opin. Crit. Care **23**, 18–23 (2017).
10. Lazzeri, C. & Peris, A. The Kigali modification of the berlin definition: A new epidemiological tool for ARDS? J. Thorac. Dis. **8**, E443–E445 (2016).
11. Riviello, E. D. Kirviri W, Mueller A et al. Hospital incidence and outcomes of the acute respiratory distress syndrome using the Kigali modification of the Berlin definition. Am. J. Respir. Crit. Care Med. **193**, 52–59 (2016).
12. Rae, J. Acute Respiratory Distress Syndrome. anesthesia Tutorial Of the week, 6–11 (2019).
13. Afshar, M. & Netzer, G. The international epidemiology of acute respiratory distress syndrome: How can we think locally and measure globally? Crit. Care Med. **42**, 739–740 (2014).
14. Reddy, V. G. New therapies for acute respiratory distress syndrome (ARDS):–a review. Med. J. Malaysia **54**, 132–145 (1999).
15. Aronson, K. & Rajwani, K. The acute respiratory distress syndrome: a clinical review. J. Emerg. Crit. Care Med. **1**, 25–25 (2017).
16. Meduri, G. U., Siemieniuk, R. A. C., Ness, R. A. & Seyler, S. J. Prolonged low-dose methylprednisolone treatment is highly effective in reducing duration of mechanical ventilation and mortality in patients with ARDS. J. Intensive Care **6**, 1–7 (2018).
17. Tang, B. M. P., Craig, J. C., Eslick, G. D., Seppelt, I. & McLean, A. S. Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: A systematic review and meta-analysis. Crit. Care Med. **37**, 1594–1603 (2009).
18. Meduri, G. U. Marik E, Lisa B. et al. Prolonged glucocorticoid treatment is associated with improved ARDS outcomes: analysis of individual patients' data from four randomized trials and trial-level meta-analysis of the updated literature. Intensive Care Med. **42**, 829–840 (2016).

19. Ruan, S. Y, Lin HO, Huang C. et al. Exploring the heterogeneity of effects of corticosteroids on acute respiratory distress syndrome: A systematic review and meta-analysis. Crit. Care **18**, 1–9 (2014).
20. Peter, J. V. PeetaJ, Grham L. et al. Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: Meta-analysis. Bmj **336**, 1006–1009 (2008).
21. Yang, Z. G., Lei, X. L. & Li, X. L. Early application of low-dose glucocorticoid improves acute respiratory distress syndrome: A meta-analysis of randomized controlled trials. Exp. Ther. Med. **13**, 1215–1224 (2017).
22. Khilnani, G. C. & Hadda, V. Corticosteroids and ARDS: A review of treatment and prevention evidence. Lung India **28**, 114–119 (2011).
23. Horita, N. et al. Impact of corticosteroids on mortality in patients with acute respiratory distress syndrome: A systematic review and meta-analysis. Intern. Med. **54**, 1473–1479 (2015).
24. Lakew, A., Tariku, B., Deyessa, N. & Reta, Y. Prevalence of <i>Catha edulis</i> (Khat) Chewing and Its Associated Factors among Ataye Secondary School Students in Northern Shoa, Ethiopia. Adv. Appl. Sociol. **04**, 225–233 (2014).
25. Shea, B. J. et al. Development of AMSTAR: A measurement tool to assess the methodological quality of systematic reviews. BMC Med. Res. Methodol. **7**, (2007).
26. Sessler, C. N. & Gay, P. C. Are corticosteroids useful in late-stage acute respiratory distress syndrome? Respir. Care **55**, 43–52 (2010).
27. Moher, D., Liberati, A., Tetzlaff, J. & Altman, D. G. PRISMA flow diagram PDF version. Ann. Intern. Med. **151**, 264–269 (2014).
28. Guyatt, G. H, Oxman D, Kunz R et al. GRADE guidelines 6. Rating the quality of evidence - Imprecision. J. Clin. Epidemiol. **64**, 1283–1293 (2011).
29. Atkins. DGrading quality of evidence and strength of recommendations. The GRADE Working Group. Br. Med. J. (Clin. Res. Ed). **328**, 328(7454):1490. (2004).
30. Fernandes, A. B. S., Zin, W. A. & Rocco, P. R. M. Corticosteroids in acute respiratory distress syndrome. Brazilian J. Med. Biol. Res. **38**, 147–159 (2005).
31. Bi, J. et al. Efficacy and safety of adjunctive corticosteroids therapy for severe community-acquired pneumonia in adults: An updated systematic review and meta-analysis. PLoS One **11**, 1–15 (2016).
32. Meduri, G. U., Schwingshackl, A. & Hermans, G. Prolonged glucocorticoid treatment in ARDS: Impact on intensive care unit-acquired weakness. Front. Pediatr. **4**, 1–5 (2016).

Appendix 1: Pubmed Search Result

Search (((((("Respiratory Distress Syndrome, Adult/complications"[Mesh] OR "Respiratory Distress Syndrome, Adult/mortality"[Mesh])) OR ((("Respiratory Distress Syndrome, Adult" [Mesh]) OR ((((((Respiratory Distress Syndrome, Acute) OR Acute Shock Lung) OR ARDS, Human) OR Adult Respiratory Distress Syndrome) OR Acute Respiratory Distress Syndrome) AND Review[ptyp])) AND Review[ptyp])) AND Review[ptyp])) AND ((("Glucocorticoids"[Mesh]) OR ((((Glucocorticoid) OR Glucocorticoid Effect) OR Glucorticoid Effects) AND Review[ptyp])) AND Review[ptyp]) Filters: Review

Figures

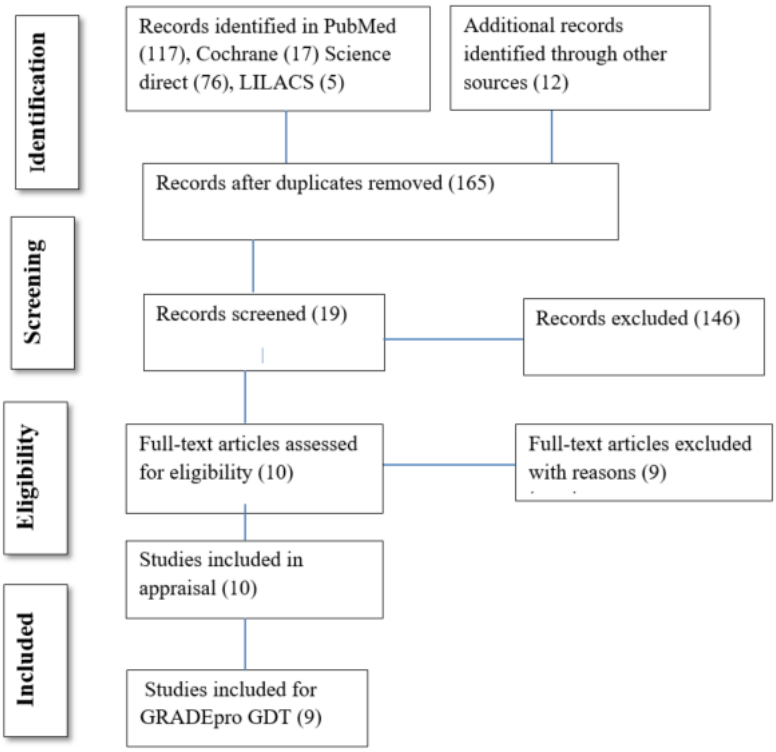

Figure 1

Prisma flow chart

Supplementary Files

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- prismachecklists.doc