World Journal of Pharmaceutical and Life Sciences
WJPLS
www.wjpls.org
SJIF Impact Factor: 5.088

EXOGENOUS SURFACTANT USE IN ACUTE LUNG INJURY AND ARDS; MORE CLEAR OR CLOUDIER-AN UPDATED META-ANALYSIS

***Mohammed Naeem, MD, FAAP, FCCP[1,2,3,4], Muhannad Abu-Abthan[1,3,5], Jude Almasoud[1,3,5], Hala Alkwai[1,3,5] and Mazen Ferwana, MD Phd[1,2,3,6]**

[1]Ministry of National Guard Health Affairs. Al Hars Al Watani, Ar Rimayah, Riyadh, Saudi Arabia.
[2]King Saud Bin Abdulaziz University and Health Sciences Center, Al Hars Al Watani, Ar Rimayah, Riyadh, Saudi Arabia 11481.
[3]King Abdullah International Medical Research Center, Al Arini Road, Ar Rimayah, Riyadh, Saudi Arabia 11481.
[4]Pediatric Intensivist. Department of Pediatrics, King Abdullah Specialized Children Hospital (KASCH), Ar Rimayah, Riyadh, Saudi Arabia 14611.
[5]Residents, Department of Pediatrics, KASC, Ar Rimayah, Riyadh, Saudi Arabia 14611
[6]Director, National Gulf Center for Evidence Based Medicine, Ar Rimayah, Riyadh, Saudi Arabia 14611.

***Corresponding Author: Dr. Mohammed Naeem**
Ministry of National Guard Health Affairs . Al Hars Al Watani, Ar Rimayah, Riyadh, Saudi Arabia.
DOI: 10.20959/wjpls201912-2545

Article Received on 15/10/2019 **Article Revised on 04/11/2019** **Article Accepted on 25/11/2019**

ABSTRACT

Objectives: Surfactant role in the management of pediatric ALI and ARDS is still unclear despite numerous clinical trials (CTs). This meta-analysis aims to analyze randomized and quasi randomized clinical trials in DerSimonian-Laird (Random-effect) model to ascertain the role of surfactant therapy. **Data Sources:** We searched PubMed, CINAHL, Cochrane, EMBASE, citations and conference proceedings (1980 to August 2018) plus manual search. **Study Selection:** We identified and extracted randomized controlled trials that evaluated intervention treatment effects of exogenous surfactant in ALI/ ARDS in pediatric age group and analyzed various outcomes including duration of mechanical ventilation, length of stay (LOS) in PICU and mortality. Inclusion criteria for studies was: Randomized and quasi randomized human clinical trials related to pediatric population who had ALI/ ARDS. We excluded neonatal trials and patients with congenital heart diseases. **Data Extraction:** We screened 1248 citations. 13 full-text articles were retrieved. After exclusion of three RCTs (2 no controls and I predominantly adult), ten studies included in meta-analysis. Three investigators (MA, JM, HA) independently extracted data. Ambiguities were resolved through discussions and amendments were done consulting third investigator (MN) when required. Data collected from each study included setting, patient demographics, surfactant characteristics and patient primary and secondary diagnoses. Duration of mechanical ventilation, the primary outcome, was defined as the total number of days the patient had been breathing via endo-tracheal tube and mechanical ventilator and calculated from day 1 of intubation to the day of successful extubation. **Data Synthesis:** Total ten Studies (N= Total 637, Intervention 322, Control 315) were included in the meta-analysis. Three clinical trials that enrolled 82 subjects provided detailed information about our primary outcome of duration of mechanical ventilation. Pooled data from these trials showed a statistically significant decrease in total duration of mechanical ventilation (Weighted Mean Difference -5.44 days, 95%CI -7.57 to -3.31, $p < 0.00001$). Regarding duration of hospital stay this study shows a statistically significant difference between the groups (WMD -3.57 days, 95% CI -6.21 to -0.92, $P<0.008$). The decrease LOS-PICU and increase in adverse effects was not significant. **Conclusion:** Exogenous surfactant administration in ALI/ ARDS decreases the total duration of mechanical ventilation and length of hospital stay. Mortality outcome could not be analyzed in context of multi-organ dysfunction/ failure. Further scientific evidence in future trials required for this promising intervention in appropriately qualified patients. **Abbreviations.** PICU; Pediatric Intensive Care Unit, ALI; Acute lung injury, CT; Clinical Trials, RCT; Randomized Clinical Trial, ARDS; Acute respiratory Distress Syndrome, PARDS; Pediatric Acute Respiratory Distress Syndrome, MOD; Multi organ dysfunction, MOF; Multi-organ failure.

KEYWORDS: Pediatric, ALI, ARDS, Surfactant, Respiratory Failure.

BACKGROUND

Despite the fact that there had been advancements in the management of Pediatric ALI and ARDS over last several decades, still critical care teams in pediatric intensive care units admitting patients who respond poorly to the standard management. In these patients the adjunctive therapies are required along with standard management.[1,2]

Exogenous surfactant had been used as adjunctive therapy for decades yet its definitive role is not clear. The physiological effects of endogenous surfactant in healthy and diseased pulmonary mechanics is well delineated[3]. In brief, these physiologic effects of endogenous Surfactant are predominantly relevant to decreasing alveolar surfaces tension and maintaining alveolar spaces. These are hampered due to qualitative or quantitative abnormalities. Existence of the potential clinical advantage of administration of exogenous surfactant has been reported encompassing improvement of respiratory indices.[3] The disadvantages are cost and side effects such as air leak syndromes.[4]

Multiple randomized clinical trials[5-14] had been conducted to evaluate the role of surfactant with no clear and definitive consensus and at times conflicting conclusions. Duffet et al included 6 clinical randomized clinical trials to do pooled analysis. They concluded that exogenous surfactant decreases the mortality and duration of mechanical ventilation.[15] However, later a large scale RCT did not confirm the results.[16] However, another recently conducted RCT reported positive association of survival and duration of ventilation when compared to alveolar surfactant with recruitment versus alveolar recruitment alone.[17] Considering the fact of newly published RCTs[11-14] in pediatric population since the meta-analysis by Duffet et al[15], we decided this updated meta-analysis. This study aims to pool the results from well conducted trials and analyze through DerSimonian-Laird (Random-effect) model.[18]

METHODS

The study was carried out in teaching hospital affiliated with Research center, College of medicine, College of Epidemiology and College of Pharmacy. An approval granted by Institutional Review Board. We Followed the recommendations of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) statement.[19] We followed basic steps of PICO.

Study Definitions

Duration of Mechanical Ventilation was defined as the total number of days the patient had been breathing via endo-tracheal tube and mechanical ventilator and calculated from day 1 of intubation to the day of successful extubation. *Duration of Hospital stay:* Number of days starting day I of admission until discharge from the hospital. *Duration of PICU stay:* Starting from Day1 until successful transfer from PICU.

Clinical outcomes and Data Source Search

The primary outcome was the duration of mechanical ventilation (d) while secondary outcomes included mortality, LOS in hospital (d) and LOS in PICU (d). We searched available literature utilizing PubMed, Cumulative Index to Nursing and Allied Heal Literature (CINAHL), Ovid Cochrane Central register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, Ovid EMBASE, non-indexed citations, and conference proceedings (1980 to August 2018) using keywords; acute lung injury (ALI) acute respiratory syndrome (ARDS), critical care, pediatrics, child, surfactant, pediatric intensive care, mechanical ventilation therapy, systematic reviews, meta-analysis. During literature search, we kept no initial time limit, final time limit of August 2018 and no language restriction. Strategies included using Medical Subject Headings (MeSH) and text words terms (keywords) as well as ‘‘AND and OR’’. Full articles were extracted. The most recent and/or completed were chosen when there were duplicated reports of any particular trial. The final search identified 10 RCTs that fulfilled the inclusion criteria. The first search completed in July 2018. We considered various synonyms found in literature such as surfactant (survanta, calfactant), Acute respiratory distress syndrome (ARDS, Pediatric ARDS, acute lung injury), RCT (randomized clinical trial, randomized controlled trials).

Study Selection, Study quality and Risk of Biased Assessment

Our literature search criteria and formulation of the inclusion criteria was to include Clinical Trials with following characteristics: 1) randomized and quasi randomized human clinical trials 2) Pediatric age group 3) subjects studied had ALI and or ARDS 4) Studied role of exogenous surfactant as intervention 5) Conducted according to Good Clinical Practice (GCP) guidelines.[20] Exclusion criteria included 1) CTs in preterm neonates, neonatal hyaline membrane disease, adults population 2) Primary diagnosis was Congenital Heart Defects. Researchers (MN,JM,HK) reviewed all eligible studies independently to be assured that study selection is compliant to the objectives.

Two reviewers (JM, MA) assessed proper methodological quality using Cochrane Criteria for Risk of Bias Tool.

Data Extraction: Three reviewers (JM, MA, HA) independently extracted data and recorded on study collection data form. This form underwent due procedure of generation, consensus and testing. The characteristics of the form included study size, study location and year of publication, patient population and age. Numerous corresponding authors were sent queries for deficient information and/or more clarifications.

Statistical Analysis

We used Review manager 5.0.0 (RevMan) for statistical analysis. We used random effect model because assumption was that there is no harmonized true effect size in the extracted clinical trials and there was true heterogeneity in order to get conservative estimates of intervention effect.[21] Duration of mechanical ventilation, LOS in hospital and PICU, being continuous outcomes were assessed utilizing Weigted Mean Differences (WMD) with 95% CI while Risk Ratio (RR)with 95% CI was calculated for Mortality (categorical outcome). Mantel-Haenszel method was used in order to adjust for confounding. All statistical tests were interpreted as statistically significant if $p \leq 0.05$. We measured heterogeneity via Q test and also Higgins I^2 for better accuracy[22] to describe heterogeneity due to between study variation and not due to chance. We used suggested thresholds of low, moderate and high (I^2= 25%, 50%, 75% respectively).[23] We were unable to perform meta regression to explore variations in treatment effects due to small number of studies.

RESULTS

Upon extensive literature search involving databases and manual searching, we identified 1490 citations utilizing "AND"/ "OR" of our search criteria Mesh words. Then, we excluded 242 because the citations were duplicated. Upon initial screening of 1248 citations by studying the titles and abstracts, we had to exclude 1235 citations because these did not meet our inclusion established criteria (adults 20, neonates without ARDS 36, Animal 176, incompatible design, 1003). Thirteen full text articles were accessed and reviewed. Among these, two were clinical trials without control and one had some subjects 18-21 years, so these three studies were also excluded (Figure 1).

CHARACTERISTICS OF ELIGIBLE STUDIES: We included 10 eligible studies in meta-analysis. As in Table 1, among 10 RCTs, two were from USA, two had patient population from USA and other countries, three from Italy, one from Germany and one from Cuba. Six out of 10 were specified multicenter studies. These studies enrolled total of 637 pediatric patients, 1-18 years. Accumulatively 322 in intervention group and 315 in control group. Although all the study population had diagnosed ARDS according to established criteria[24] however the underlying diagnosis was variable in terms of pulmonary etiologies with or without extra pulmonary involvement. Only 3 out of ten trials had enrolled patients with no extra pulmonary primary cause of PARDS while 7 out of ten had multi organ involvement as the causative factor. All patients in ten included trials received surfactant via intra tracheal route. Only one used synthetic surfactant (Table 2).

Primary outcome: The results show that primary outcome of duration of mechanical ventilation was significantly different in intervention and control groups (MWD-5.44 days, 95% CI -7.57 to -3.31, Overall effect P<0.00001, three trials, N=82; Fig 2. Secondary outcomes: Pooled data showed that the secondary outcome of mortality (RR 0.70, CI 0.41 y At present exogenous surfactant should not be routinely recommended in patients with P- ARDS to 1.19, overall effect P=0.19, six trials, N= 438) was not statistically different between the groups; Fig 3. Regarding duration of hospital stay this study shows a statistically significant difference between the groups (MWD -3.57 days, 95% CI -6.21 to -0.92, Overall effect P<0.008, three trials, N=304; Fig 4. However duration of PICU stay was reduced in intervention group though not statistically significant (MWD-2.45 days, 95% CI -5.14 to 0.25, Overall effect P<0.08, five trials, N=; Fig 5. The results showed a statistically non-significant increase in incidence of side effects in intervention group (OR 1.53, CI 0.58 to 4.03, overall effect P=0.39, four trials, N= 469); Fig 1 In Figure 2a we analyzed risk of potential biases. High risk bias was considerable in categories of Blinding and other bias (predominantly funding). Figure 2b describes the another analysis through Risk bias tool. In this study all the trials except two had been interpreted as low risk selection bias attributed to proper random sequence generation. Similarly, allocation concealment, completion of data and reporting parameters stayed in low risk of bias categories. Results reveals high risk blinding in number of tials[1,4,5,7, 9] while unclear information in two.[3,5]

LEGENDS (WITH FIGURES AND TABLES FOR REFERENCE)

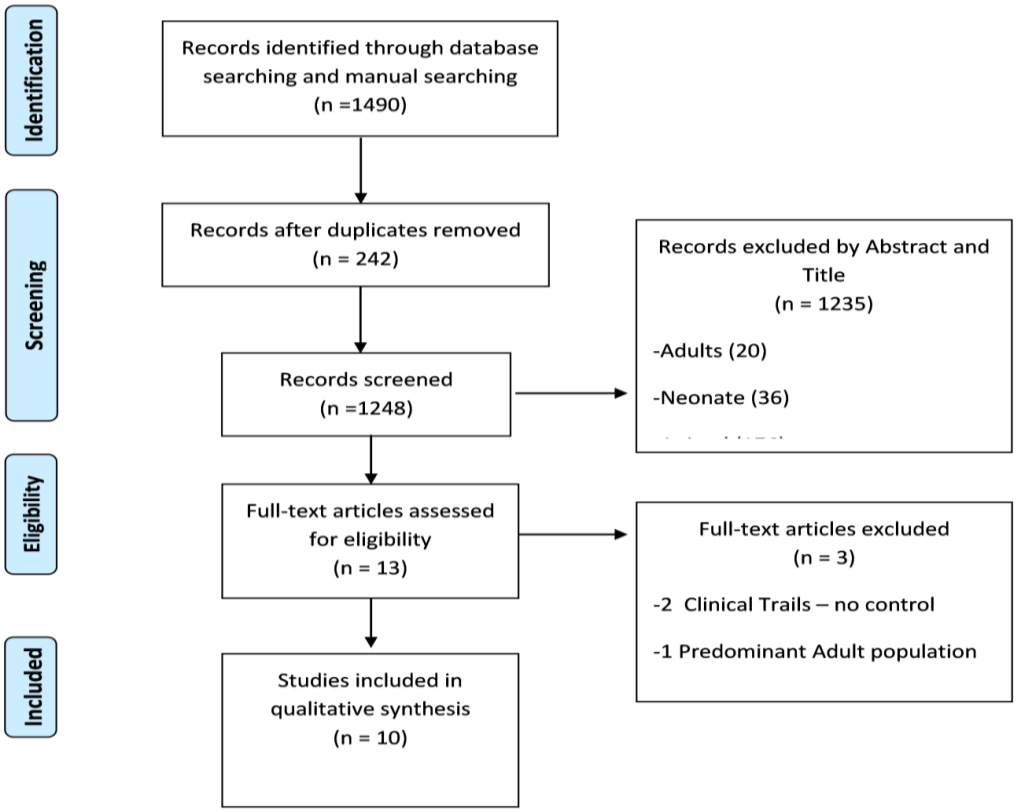

Fig 1. PRISMA Flow Chart

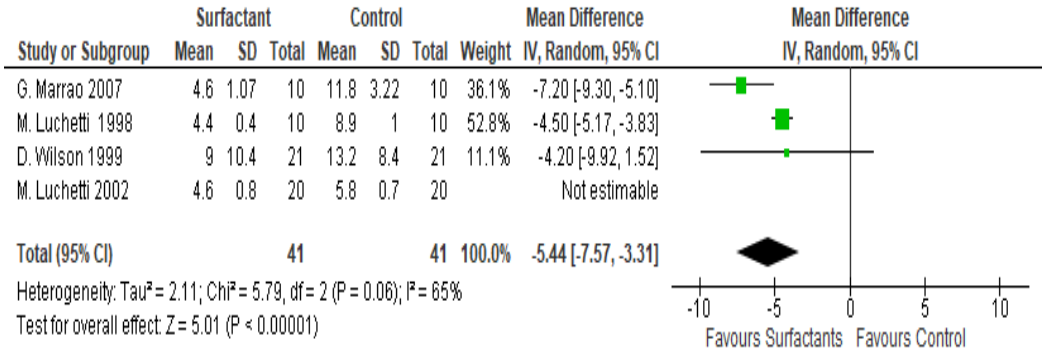

Figure 2: Effect of Exogenous surfactant administration in the Meta-analysis of surfactant trials in pediatric patients with ARDS on Duration of Mechanical Ventilation. *CI*, Confidence Interval. Contribution by each study is denoted by percentage weight.

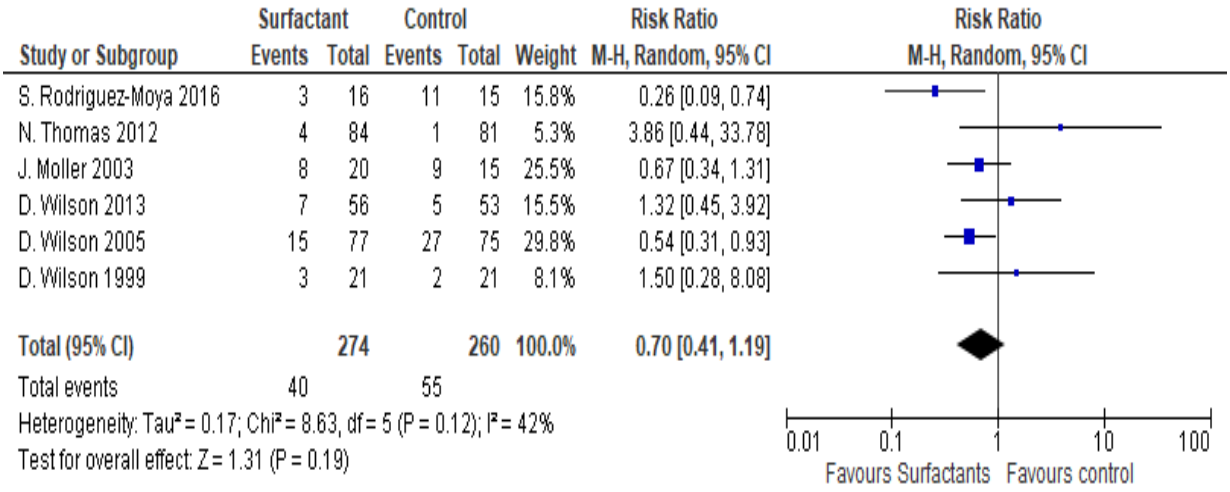

Figure 3: Effect of Exogenous surfactant administration in the Meta-analysis of surfactant trials in pediatric patients with ARDS on Mortality. *CI*, Confidence Interval. Contribution by each study is denoted by percentage weight.

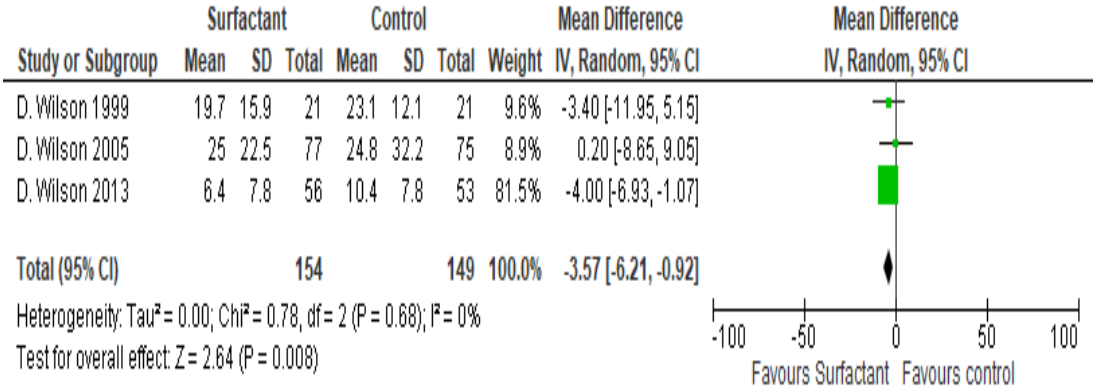

Fig 4: Effect of Exogenous surfactant administration in the Meta-analysis of surfactant trials in pediatric patients with ARDS on Duration of Hospital Stay. *CI*, Confidence Interval. Contribution by each study is denoted by percentage weight.

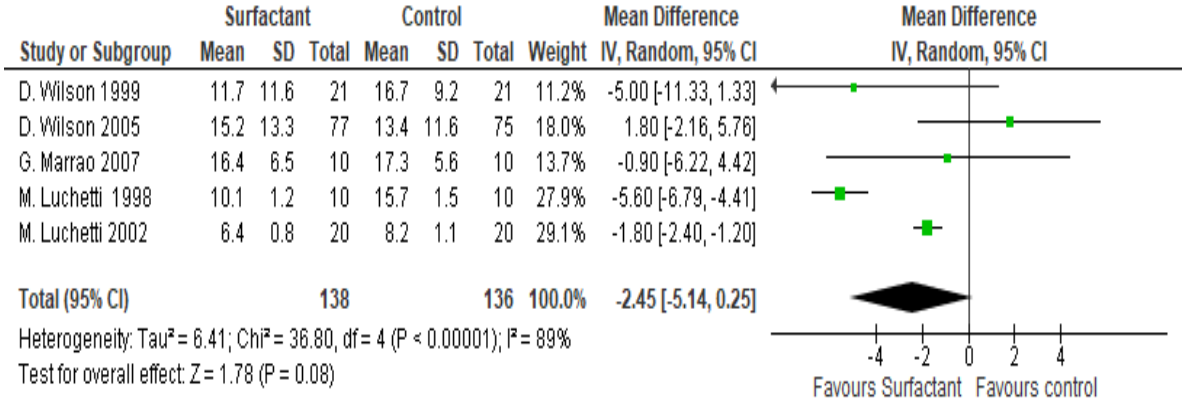

Fig 5: Effect of Exogenous surfactant administration in the Meta-analysis of surfactant trials in pediatric patients with ARDS on Duration of PICU Stay. *CI*, Confidence Interval Contribution by each study is denoted by percentage weight.

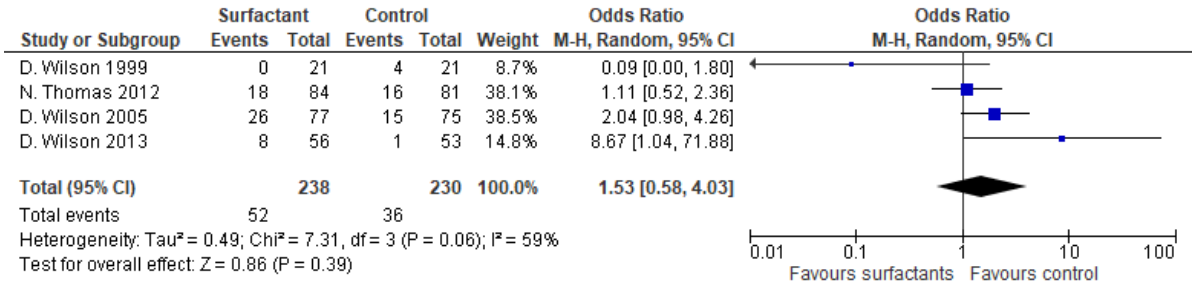

Fig 6: Effect of Exogenous surfactant administration in the Meta-analysis of surfactant trials in pediatric patients with ARDS on incidence of side effects. *CI*, Confidence Interval. Contribution by each study is denoted by percentage weight.

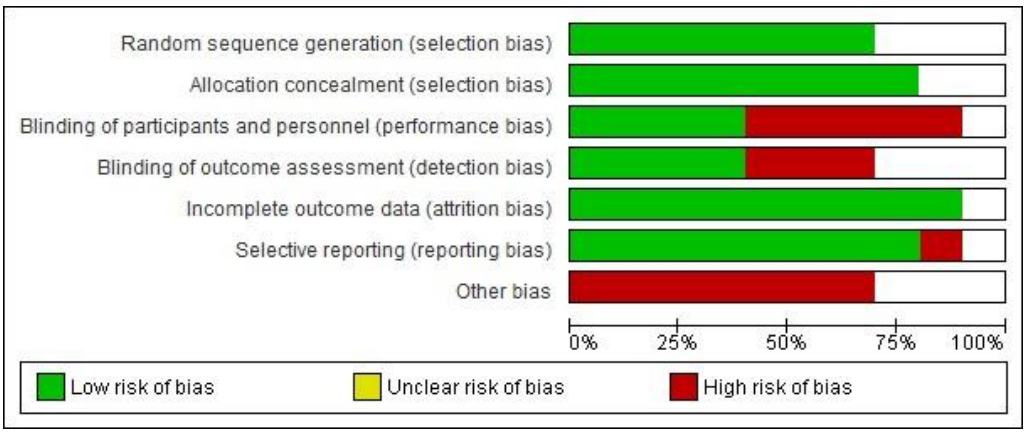

Fig 7a: Analysis of Risk of Bias. Percentage of risks in each category of potential bias.

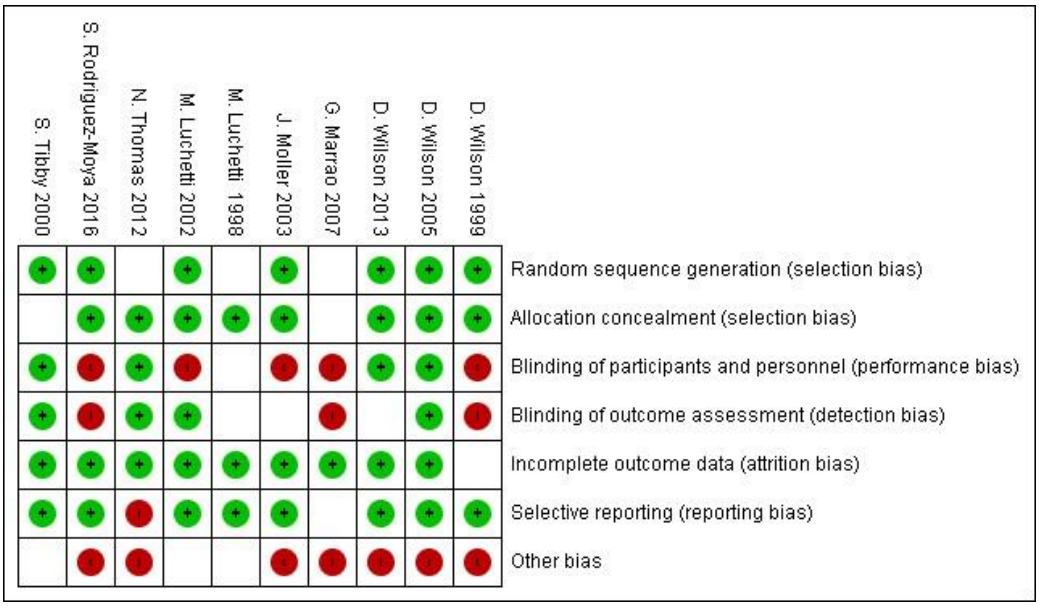

Fig. 7b: Risk of Bias Assessment according to in-depth reviews by the researchers.

DISCUSSION

This study identified clinically significant reduction in days of ventilation for pediatric patients with ALI/ ARDS when exogenous surfactant was administered. In the pooled data from the trials, we noticed a statistically significant decrease in total duration of mechanical ventilation (Weighted Mean Difference -5.44 days, 95%CI -7.57 to -3.31, overall effect: Z 5.01, p < 0.00001). Yet again like many previous reported studies related to surfactant use in ARDS patients, in this study we did not find any significant reduction in mortality outcome (RR 0.70, 95%CI -0.41 to -1.19, overall effect: Z 0.31, p = 0.19).

There are many plausible reasons for having lower duration of ventilation until extubated successfully and yet not the significant reduction in mortality. ALI/ ARDS patients may or may not be associated with multi organ

dysfunction (MOD) or multi organ failure (MOF). Upon searching literature relevant to presence of MOD/ MOF in ALI/ ARDS patients and its effect on mortality, we found numerous previous studies.[25-29] Scientific evidence explains that in patients with ALI/ ARDS strategy to attenuate systemic inflammatory response, that leads to multi organ dysfunction, is beneficial.[25] Wong et al[26] reported that among pediatric patient with ARDS survival was significantly higher in patients with multiple organ dysfunction (62% versus 91%, p=0.008). Similarly, In ALIEN study[27], Villar et al studying 255 patients with ARDS found Multiple organ failure as the predominant cause of death (45.8%, p,0.00001). Similarly, Erickson et al[28] evaluated 2451 patients with ARDS and reported pneumonia, a primary lung disease as a primary conditions, to be only 8 %. While in pediatric population, Flori et al found pneumonia to be associated with only 35% of ARDS patients.[29] On the other hand surfactant has no direct role in the management of MOD/MOF. All these data reiterates the importance of assessing MOD/MOF when assessing the mortality outcome relevant of any therapy including exogenous surfactant administration. We could not analyze the effect of MOD/MOF upon mortality in pooled analysis due to scarcity of data in the included trials.

Previously, meta-analyses involving surfactant trials in ARDS have also reported results that are partially similar to our trials. In a previous meta-analysis, Duffet et al[15], included 6 prospective randomized controlled trials in their systematic review. They excluded studies related to neonates. Their primary outcome was 28-day mortality. They reported a decrease in mortality (RR=0.7, 95% CI= 0.4-0.97), decrease in duration of ventilation and resultant increase in ventilator free days. Their meta-analysis had different reported mortality outcome primarily due to more homogenous protocols and study populations. More recently, Meng et al[30] reported a meta-analysis of 9 adult population studies. They concluded that exogenous surfactant may improve oxygenation but not mortality in ARDS patients. Their conclusion reflects direct beneficial effect on pulmonary mechanics yet no improvement in mortality.

Unfortunately, there is substantial variability directly related to exogenous surfactant administration and formulations in the conducted trials. For example, Marraro et al[11], instilled surfactant intratracheally followed by bronchoalveolar lavage. This variability contributed to overall heterogeneity.

There are several limitations of our study. We tried to minimize issues of internal validity and external validity through adequate evaluation for randomization, drop outs etc. However, in this regard, we could not assess three trials[5,11,12] due to unclear reporting. Regarding our primary outcome, the small-study effect may had contributed to the results, however, it did not reflect when we utilized fixed-random effect. Increased heterogeneity is noticed in our results and it may be due to multiple reasons related to intra as well as inter trials factors including heterogeneous multinational set-ups & protocols of management, variable severity of illness, variability of surfactant products & dosing, undetectable/ unreported/ unclear co-interventions, variability of modes of mechanical ventilation especially with advent of high frequency ventilation. Our attempts to evaluate numerous variables in depth in order to decrease the heterogeneity is not successful mostly due to missing data in the studies and inability to get reply from the authors of the trials.

Conclusion. This meta-analysis depicts that use of surfactant may be plausible as adjunctive therapy to standard recommendations in refractory pediatric ALI/ ARDS population. Its cost effective benefits may be considered related to decreasing the total length of stay in PICU and hospital.

Key Messages

1. Surfactant decreases the total duration of ventilation in pediatric ALI/ ARDS patients.
2. Mortality outcome may be affected by MOD/ MOF.
3. Future randomized trials are required to assess specific effect of surfactant on mortality by excluding MOD/MOF.

Conflict of Interest

There is no conflict of interest among authors
All authors endorse the data and conclusion

ACKNOWLEDGEMENTS

Ministry of National Guard Health Affairs
King Abdulaziz Bin Saud University for Health Sciences
King Abdullah International Medical Research Center
MN, MA, JA, HA equally contributed

Disclaimer: The manuscript is not under consideration for publication elsewhere. The authors have no commercial associations or sources of support.

REFERENCES

1. Khemani RG, Smith LS, Zimmerman JJ, et al. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: definition, incidence, and epidemiology: proceedings from the Pediatric Acute Lung Injury Consensus Conference. *Pediatr Crit Care Med, 2015; 16(5 Suppl 1): S23–S40.*
2. Mok YH, Lee JH, Rehder KJ, et al. Adjunctive treatments in pediatric acute respiratory distress syndrome. *Expert Review Of Respiratory Medicine*, 2014; 8(6): 703-16.
3. Bernhard W. Lung surfactant: Function and composition in the context of development and respiratory physiology. *Annals of Anatomy-Anatomischer Anzeiger*, 2016; 208: 146-50.

4. Meng H, Sun Y, Lu J, et al. Exogenous surfactant may improve oxygenation but not mortality in adult patients with acute lung injury/acute respiratory distress syndrome: a meta-analysis of 9 clinical trials. *Journal Of Cardiothoracic And Vascular Anesthesia*, 2012; 26(5): 849-56.
5. Luchetti M, Casiraghi G, Valsecchi R, et al. Porcine-derived surfactant treatment of severe bronchiolitis. *Acta Anaesthesiologica Scandinavica*, 1998; 42(7): 805-10.
6. Willson DF, Zaritsky A, Bauman LA, et al. Instillation of calf lung surfactant extract (calfactant) is beneficial in pediatric acute hypoxemic respiratory failure. *Critical Care Medicine*, 1999; 27(1): 188-95.
7. Tibby SM, Hatherill M, Wright SM, et al. Exogenous surfactant supplementation in infants with respiratory syncytial virus bronchiolitis. *American Journal Of Respiratory And Critical Care Medicine*, 2000; 162(4): 1251-6.
8. Luchetti M, Ferrero F, Gallini C, et al. Multicenter, randomized, controlled study of porcine surfactant in severe respiratory syncytial virus-induced respiratory failure. *Pediatric Critical Care Medicine*, 2002; 3(3): 261-8.
9. Möller JC, Schaible T, Roll C, et al. Treatment with bovine surfactant in severe acute respiratory distress syndrome in children: a randomized multicenter study. *Intensive care medicine*, 2003; 29(3): 437-46.
10. Willson DF, Thomas NJ, Markovitz BP, et al. Effect of exogenous surfactant (calfactant) in pediatric acute lung injury: a randomized controlled trial. *JAMA*, *200*5; 293(4): 470-6.
11. Marraro GA, Luchetti M, Spada C, et al. Selective medicated (normal saline and exogenous surfactant) bronchoalveolar lavage in severe aspiration syndrome in children. *Pediatric Critical Care Medicine*, 2007; 8(5): 476-81.
12. Thomas NJ, Guardia CG, Moya FR, et al. A pilot, randomized, controlled clinical trial of lucinactant, a peptide-containing synthetic surfactant, in infants with acute hypoxemic respiratory failure. *Pediatric Critical Care Medicine*, 2012; 13(6): 646-53.
13. Willson DF, Thomas NJ, Tamburro R, et al. Pediatric calfactant in acute respiratory distress syndrome trial. *Pediatric Critical Care Medicine*, 2013; 14(7): 657-65.
14. Rodríguez-Moya VS, Gallo-Borrero CM, Santos-Áreas D, et al. Exogenous surfactant and alveolar recruitment in the treatment of the acute respiratory distress syndrome. *The clinical respiratory journal*, 2017; 11(6): 1032-9.
15. Duffett M, Choong K, Ng V, et al. Surfactant therapy for acute respiratory failure in children: a systematic review and meta-analysis. *Critical Care*, 2007 Jun; 11(3): R66.
16. Willson DF, Thomas NJ, Tamburro R, et al. Pediatric calfactant in acute respiratory distress syndrome trial. *Pediatric Critical Care Medicine*, 2013; 14(7): 657-65.
17. Rodríguez-Moya VS, Gallo-Borrero CM, Santos-Áreas D, et al. Exogenous surfactant and alveolar recruitment in the treatment of the acute respiratory distress syndrome. *The Clinical Respiratory Journal*, 2017; 11(6): 1032-9.
18. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: an update. *Contemporary Clinical Trials*, 2007; 28(2): 105-14.
19. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals Of Internal Medicine*, 2009; 151(4): 264-9.
20. Bhatt A. Quality of clinical trials: A moving target. *Perspectives In Clinical Research*, 2011; 2(4): 124.
21. Borenstein M, Hedges LV, Higgins JP, et al. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Research Synthesis Methods*, 2010; 1(2): 97-111.
22. Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. *BMJ*, 2003; 327(7414): 557.
23. Sedgwick P. Meta-analyses: what is heterogeneity? *BMJ*, 2015; 350: h1435.
24. Pediatric Acute Lung Injury Consensus Conference Group. Pediatric acute respiratory distress syndrome: consensus recommendations from the Pediatric Acute Lung Injury Consensus Conference. *Pediatric Critical Care Medicine*, 2015 Jun; 16(5): 428.
25. Walkey AJ, Summer R, Ho V, et al. Acute respiratory distress syndrome: epidemiology and management approaches. *Clinical Epidemiology*, 2012; 4: 159.
26. Wong JJ, Loh TF, Testoni D, et al. Epidemiology of pediatric acute respiratory distress syndrome in singapore: risk factors and predictive respiratory indices for mortality. *Frontiers In Pediatrics*, 2014; 2: 78.
27. Villar J, Blanco J, Anon JM, et al. The ALIEN study: incidence and outcome of acute respiratory distress syndrome in the era of lung protective ventilation. *Intensive Care Med*, 2011; 37(12): 1932–1941.
28. Erickson SE, Martin GS, Davis JL, et al. *Crit Care Med*, 2009 May; 37(5): 1574-9.
29. Flori HR, Glidden DV, Rutherford GW, et al. Pediatric acute lung injury: prospective evaluation of risk factors associated with mortality. *Am J Respir Crit Care Med, 2005; 171(9): 995–1001.*
30. Meng H, Sun Y, Lu J, et al. Exogenous surfactant may improve oxygenation but not mortality in adult patients with acute lung injury/acute respiratory distress syndrome: a meta-analysis of 9 clinical trials. *Journal Of Cardiothoracic And Vascular Anesthesia*, 2012; 26(5): 849-56.