CHEST

The Use of Inhaled Prostaglandins in Patients With ARDS

A Systematic Review and Meta-analysis

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OBJECTIVE: This study aimed to determine whether inhaled prostaglandins are associated with improvement in pulmonary physiology or mortality in patients with ARDS and assess adverse effects.

METHODS: The following data sources were used: PubMed, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, reference lists, conference proceedings, and ClinicalTrials.gov. Studies selected included randomized controlled trials and nonrandomized studies. For data extraction, two reviewers independently screened titles and abstracts for eligibility. With regard to data synthesis, 25 studies (two RCTs) published over 21 years (1993-2014) were included. The PROSPERO registration number was CRD42014013180.

RESULTS: One randomized controlled trial showed no difference in the change in mean Pao_2 to Fio_2 ratio when comparing inhaled alprostadil to placebo: 141.2 (95% CI, 120.8-161.5) to 161.5 (95% CI, 134.6-188.3) vs 163.4 (95% CI, 140.8-186.0) to 186.8 (95% CI, 162.9-210.7), $P = .21$. Meta-analysis of the remaining studies demonstrated that inhaled prostaglandins were associated with improvement in Pao_2 to Fio_2 ratio (16 studies; 39.0% higher; 95% CI, 26.7%-51.3%), and Pao_2 (eight studies; 21.4% higher; 95% CI, 12.2%-30.6%), and a decrease in pulmonary artery pressure (−4.8 mm Hg; 95% CI, −6.8 mm Hg to −2.8 mm Hg). Risk of bias and heterogeneity were high. Meta-regression found no association with publication year ($P = .862$), baseline oxygenation ($P = .106$), and ARDS etiology ($P = .816$) with the treatment effect. Hypotension occurred in 17.4% of patients in observational studies.

CONCLUSIONS: In ARDS, inhaled prostaglandins improve oxygenation and decrease pulmonary artery pressures and may be associated with harm. Data are limited both in terms of methodologic quality and demonstration of clinical benefit. The use of inhaled prostaglandins in ARDS needs further study. CHEST 2015; 147(6):1510-1522

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ABBREVIATIONS: iNO = inhaled nitric oxide; mPAP = mean pulmonary artery pressure; PGE_1 = prostaglandin E_1; PGI_2 = prostaglandin I_2; RCT = randomized controlled trial

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In terms of mortality and survivor morbidity, ARDS exacts a significant toll on patients and the health-care system.[1] Shunt physiology drives hypoxemia; pulmonary hypertension is common and may have adverse prognostic significance.[2-5] The use of inhaled pulmonary vasodilators, which could improve oxygenation by preferentially improving perfusion to well-ventilated lung regions and reduce pulmonary pressures, therefore, has physiologic rationale. Inhaled nitric oxide (iNO) continues to be used for a significant minority of patients with ARDS.[6,7] While shown to improve oxygenation, meta-analyses of randomized trials demonstrate no mortality benefit with iNO, and an association with harm.[8,9] It is unknown whether other inhaled pulmonary vasodilators are associated with similar physiologic or clinical outcomes.

The inhaled prostaglandins epoprostenol (prostaglandin I_2 [PGI_2]; Flolan) and alprostadil (prostaglandin E_1 [PGE_1]) promote pulmonary vasodilation via a cyclic adenosine monophosphate-mediated decrease in intracellular calcium.[10] They also have antiinflammatory and antiplatelet aggregation properties, providing further potential mechanistic benefit in ARDS.[10-15] One observational study demonstrated the use of inhaled epoprostenol in 22% of patients with severe ARDS treated with extracorporeal support.[16] A systematic review that included only one randomized controlled trial (RCT) of 14 pediatric patients concluded that enough evidence did not exist to support or refute the use of inhaled epoprostenol in ARDS.[17] However, other clinical studies have been completed since this review was published. As such, it is unknown whether the use of inhaled prostaglandins in ARDS provides any benefit.

Therefore, the objectives of this study were to perform a systematic review of the literature, including RCTs and observational studies, to determine whether the inhaled prostaglandins epoprostenol and alprostadil are associated with an improvement in pulmonary physiology (eg, oxygenation, pulmonary artery pressures) or mortality in postneonatal children and adults with ARDS. An assessment of the adverse effects associated with this therapy was also an aim of interest. Based on the existing data regarding iNO, the primary hypothesis was that the use of inhaled prostaglandins would be associated with an improvement in oxygenation and pulmonary artery pressures, but would not confer any mortality benefit.

Materials and Methods

This systematic review was designed, conducted, and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (e-Appendix 1) and Meta-analysis of Observational Studies in Epidemiology (MOOSE) (e-Appendix 2) guidelines.[18,19] It was registered with PROSPERO (registration number CRD42014013180). Ethical approval from the Human Research Protection Office at the principal investigator's institution was not required.

Search and Identification of Studies

A written protocol (e-Appendix 3) that was finalized prior to beginning the search was followed. The timeline was from 1976 (discovery of PGI_2) through 2014, and searched PubMed, EMBASE, Cumulative Index of Nursing and Allied Health Literature (CINAHL), the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Database of Systematic Reviews. Searches were completed in May 2014. A trained medical librarian (S. F.) experienced in systematic reviews assisted in designing the search strategy and in conducting the electronic search. Two authors (B. M. F. and N. M. M.) also manually screened reference lists of articles selected for inclusion to identify additional studies. To identify potential unpublished data, B. M. F. also (1) searched abstracts from the Society of Critical Care Medicine, European Society of Intensive Care Medicine, American Thoracic Society, CHEST, International Symposium on Intensive Care and Emergency Medicine, and Pharmacotherapy from 1999 to 2014 and (2) searched online for clinical trials registration (ClinicalTrials.gov). B. M. F. also contacted principal investigators of published and unpublished studies as needed.

Inclusion Criteria

RCTs were included, as well as nonrandomized studies (prospective interventional studies, prospective and retrospective cohort analyses, case series). The inclusion of nonrandomized studies was decided a priori for the following reasons: (1) high likelihood the question of interest could not be investigated strictly with RCTs secondary to lack of existing randomized trials; (2) to provide an explicit evaluation of strengths and weaknesses of the current literature; (3) to assess evidence of effects (benefit and harm); and (4) to provide evidence for the undertaking of randomized trials.[20] The intervention was inhaled epoprostenol or inhaled alprostadil; the comparison was placebo or no intervention/usual care, as well as iNO, provided that all crossover studies reported data transparently. Studies of hypoxemic patients that did not explicitly state the population was ARDS were excluded. Studies that did not report preintervention and postintervention data, such as the effect on oxygenation, were excluded. Papers that were reviews, correspondences, editorials, and nonhuman studies were also excluded. The reference list of all review articles was screened to identify additional studies for inclusion.

Study Selection and Data Abstraction

Two reviewers (B. M. F. and N. M. M.) independently screened titles and abstracts of identified studies for eligibility. After this relevance screen, full text articles were assessed for eligibility, and the two reviewers compared their exclusion logs to determine whether there was disagreement. All studies deemed potentially relevant after the screen were obtained and the full manuscripts were reviewed (B. M. F., N. M. M., and L. S.). In cases of disagreement, a consensus was reached among the three reviewers.

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Assessment of Study Quality

The quality of clinical trials selected for inclusion was assessed by using the Cochrane Collaboration Tool for assessing the risk of bias in clinical trials.[21] High quality was defined as a grade of "A" in at least three of the four methodology domains. For studies of observational design, quality was assessed with the Newcastle-Ottawa Scale, assigning a maximum of nine points.[22,23] Five or fewer points indicated a high risk of bias.

Assessment of Publication Bias

A graphic display (funnel plot) of the size of the treatment effect against the precision of the trial was used to evaluate for potential publication bias.[24]

Data Analysis

During the conduct of the systematic review, a scoping review of the literature revealed a lack of controls from which to compare mortality or adverse events.[25] Therefore, the decision was made to assess physiologic end points as the primary outcomes, including oxygenation parameters (Pao_2 to FIO_2 ratio and Pao_2), and mean pulmonary artery pressure (mPAP). Secondary outcomes included mortality and adverse effects.

Meta-analysis: Review Manager (RevMan, Version 5.1; The Nordic Cochrane Centre, The Cochrane Collaboration) was used to conduct the meta-analysis. A generic inverse variance, random effects model was used. Continuous data are reported as mean difference (measure of absolute change). Overall effect estimates were generated using a Z test and presented as mean differences (measures of absolute change). A P value of $\leq .05$ was considered statistically significant. The decision to combine the data on epoprostenol and alprostadil was made a priori. The decision to not combine evidence from randomized trials and nonrandomized studies was also made a priori, as per expert recommendation.[20] Stratified subgroup analyses were performed, as were sensitivity analyses, which excluded the study with the largest mean difference in Pao_2 to FIO_2 ratio and the largest number of patients.[26,27]

Heterogeneity between studies was assessed using the I^2 statistic, with suggested thresholds for low (25%-49%), moderate (50%-74%), and high ($\geq$75%) values.[28,29] During the systematic review, it was evident that the secondary outcomes (mortality and adverse effects) could not be assessed quantitatively. A post hoc decision was, therefore, made to report overall mortality and reported adverse effects in a descriptive, qualitative fashion. A post hoc decision to use a χ^2 test to compare differences in the rate of hypotension between the observational cohort studies (longer exposure to inhaled prostaglandins) and the prospective studies (very brief exposure to inhaled prostaglandins) was also made.

Meta-Regression: The I^2 statistic indicated significant heterogeneity among the entire collection of data. Subgroup analysis and meta-regression were performed to explain some of the heterogeneous effect sizes between studies. Possible sources of heterogeneity tested included baseline oxygenation, pulmonary vasodilator dosing, source of ARDS (pulmonary vs nonpulmonary), and study year. A linear meta-regression model weighted to reflect the variance of the individual studies was used to model the data. OpenMeta [Analyst] (Center for Evidence-Based Medicine, Brown School of Public Health) was used for regression with continuous covariates.[30]

Results

Search and Selection

The comprehensive search yielded a total of 380 potentially relevant publications. Details regarding the search, study selection, and reason for exclusion are shown in Figure 1.

Inclusion

After the relevance search, a complete manuscript review was performed on the remaining 47 articles. Twenty-five studies were included in the final analysis.

Study Characteristics and Outcomes Reporting

The characteristics of the included studies are shown in Tables 1 and 2.[26,27,31-53] Two studies were RCTs, six were prospective, nonrandomized interventional studies, 10 were observational studies, and seven were case series. The total number of patients across studies was 606 (n = 497 epoprostenol, n = 109 alprostadil, median 11 patients per study).

The RCTs were rated as high quality by the Cochrane Collaboration Tool for assessing the risk of bias in clinical trials. On the nine-point Newcastle-Ottawa Scale, the median risk of bias score was 5, indicating a high risk of bias. The main risk of bias was selection bias (eg, lack of a nonexposed cohort) and information bias (eg, lack of description in outcome assessment).

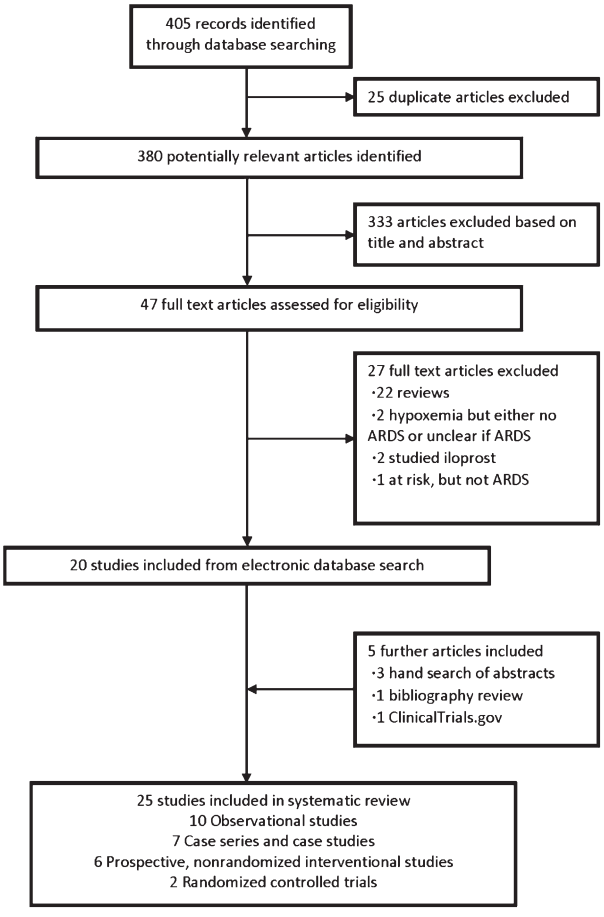

Figure 1 – *Search, inclusion, and exclusion flow diagram.*

TABLE 1] Study Characteristics of Randomized Controlled Trials

Study/Year	N	Therapy	Duration of Therapy	Timing of Therapy[a]	High-Quality RCT?[b]	Primary Outcome[c]	Secondary Outcomes[c]	Comments
Dahlem et al[34]/2004	14	PGI_2	≈ 125 min	ICU day 3	Yes	OI	Hemodynamics, ventilator settings	Crossover with normal saline placebo
Siddiqui et al[43]/2013	67	PGE_1	30 min	Within 24 h	Yes	Diastolic dysfunction, LVEDP	Pao_2:FIO_2	Double-blind, with normal saline placebo control

Continuous data are presented as mean (SD) unless otherwise noted. LVEDP = left ventricular end-diastolic pressure; PGE_1 = alprostadil; PGI_2 = epoprostenol; RCT = randomized controlled trial.

[a]Timing of therapy reported variably across studies and is referenced either to onset of ARDS, respiratory failure, or ICU day.

[b]As assessed by the Cochrane Collaboration Tool for assessing risk of bias in clinical trials. Four domains were assessed: random sequence generation, concealment of allocation, blinding, and selective outcome reporting. High quality was defined as a grade of "A" in at least three-fourths of the methodology domains. To explain, for trials where blinding is not feasible at the point of intervention, a grade of "A" would be assigned if the investigator collecting the primary outcome was blinded to the treatment allocation.

[c]Some outcomes were not explicitly stated or defined in the manuscript as primary or secondary outcomes, but reported as such in the table.

The primary outcome was physiologic in 24 of 25 studies (ie, oxygenation, pulmonary artery pressures) and clinical (ie, lengths of stay, mortality) in four of 25 studies. There was a wide range of delivered doses (e-Table 1).

Effect of Inhaled Prostaglandins on Physiologic Outcomes

The results of the two RCTs are reported separately and qualitatively.[20,34,43] One crossover randomized trial, using nebulized normal saline placebo, assessed the effect of epoprostenol on oxygenation index [(FIO_2 × mean airway pressure)/Pao_2] in 14 children. Preintervention oxygenation index was 10.0 (95% CI, 7.8-14.5), which decreased to 7.4 (95% CI, 6.5-9.7) after epoprostenol therapy was titrated to 30 ng/kg/min ($P = .001$). The effect on oxygenation was not reported. The other randomized trial assessed the effect of alprostadil vs placebo on 67 adults. Alprostadil was associated with an increase in mean Pao_2 to FIO_2 ratio from 141.2 (95% CI, 120.8-161.5) to 161.5 (95% CI, 134.6-188.3); this was not significant when compared with the increase in mean Pao_2 to FIO_2 ratio that occurred in the placebo (163.4 [95% CI, 140.8-186.0] to 186.8 [95% CI, 162.9-210.7]) ($P = .21$).

Meta-analysis: Aggregate meta-analysis of the remaining datasets (excluding the two RCTs) is presented in Table 3 and Figure 2. This analysis demonstrated that inhaled prostaglandins were associated with improved Pao_2 to FIO_2 ratio (16 studies, 497 patients, 994 measurements; 39.0% higher; 95% CI, 26.7%-51.3%), and Pao_2 (eight studies, 108 patients, 216 measurements; 21.4% higher; 95% CI, 12.2%-30.6%), and decrease in mPAP (seven studies, 76 patients, 152 measurements; −4.8 mm Hg; 95% CI, −6.8 mm Hg to −2.8 mm Hg). Funnel plot analysis (Fig 3) revealed possible reporting bias with asymmetric skew to the left.[54] There was significant statistical heterogeneity for each outcome.

To examine sources of heterogeneity in the aggregate meta-analysis and sources of variation in individual study results, additional stratified meta-analyses were performed. For these subgroups, analyses were restricted to (1) type of inhaled pulmonary vasodilator (epoprostenol or alprostadil), (2) publication year, (3) study type, (4) risk of bias, and (5) exclusion of case series. Meta-analysis of the data from the prospective, nonrandomized interventional studies was conducted separately from the observational studies and case series, in accordance with guideline recommendations of meta-analyses of nonrandomized studies.[20] This was done to decrease heterogeneity across study types, as the interventional

TABLE 2] Study Characteristics of Nonrandomized Studies

Study/Year	N	Therapy	Duration of Therapy	Timing of Therapy[a]	Risk of Bias (NOS Score)[b]	Primary Outcome[c]	Secondary Outcomes[c]	Comments
Prospective, nonrandomized interventional studies								
Walmrath et al[52]/1996	16	PGI_2	< 70 min	1-4 d	High (5)	Pao_2:FIo_2, Pao_2, shunt	mPAP PVR	Crossover study with iNO
Van Heerden et al[48]/1996	5	PGI_2	30 min	Not reported	High (4)	Pao_2, mPAP	None stated	Crossover study with iNO
Zwissler et al[53]/1996	8	PGI_2	45 min	10.3 d	High (5)	Pao_2, mPAP, PVR, shunt	Establish dose-response curve and optimal safe dose	...
Putensen et al[39]/1998	10	PGE_1	100 min	16 (1)	High (5)	Pao_2	mPAP PVR RVEF	Crossover with iNO and IV PGE_1
van Heerden et al[50]/2000	9	PGI_2	150 min	5.8 d	High (5)	Pao_2:FIo_2, A-a gradient	6-keto PGF1α, platelet aggregation	...
Domenighetti et al[35]/2001	15	PGI_2	75 min	32 (2) h	High (5)	Pao_2:FIo_2, Pao_2	mPAP, PVR	Examined difference between pulmonary and nonpulmonary ARDS
Observational cohort studies								
Meyer et al[26]/1998	15	PGE_1	103 (17) h, range 1-7 d	42 (8) h	High (5)	Pao_2, Pao_2:FIo_2	None stated	...
Siobal et al[45]/2003	11	PGI_2	Mean 41 h, range 9-116 h	3.9 (3.4) d	High (5)	Pao_2:FIo_2, Spo_2	None stated	...
Rovira et al[42]/2004	5	PGI_2	1-3 d	1-2 d	High (4)	Pao_2:FIo_2	None stated	Abstract only
Camamo et al[33]/2005	27	PGI_2 (n = 10), PGE_1 (n = 17)	5.9 (7.6) d, 4.6 (3.1) d	Not reported	High (4)	Pao_2:FIo_2, Pao_2	Differences between the two drugs on clinical outcomes	...
Raheem[40]/2009	15	PGI_2	23 (1-46) h	Not reported	High (4)	Pao_2:FIo_2	None stated	Abstract only

(Continued)

TABLE 2] *(continued)*

Study/Year	N	Therapy	Duration of Therapy	Timing of Therapy[a]	Risk of Bias (NOS Score)[b]	Primary Outcome[c]	Secondary Outcomes[c]	Comments
Ross et al[41]/2012	12	PGI_2	4.2 (2.5) d, range < 1-9 d	Not reported	High (4)	Pao_2:FIo_2, Spo_2, A-a gradient	Not stated	Abstract only Compared with iNO
Dunkley et al[36]/2013	16	PGI_2	4.8 (6.0) d	Not reported	High (3)	Pao_2:FIo_2 at 4 h, medication errors	Dose response, therapy duration, adverse events, mortality	…
Pacheo et al[27]/2014	216	PGI_2	Survivors 118.5 (85.1) h; nonsurvivors 99.1 (108.7) h	Survivors 55.2 (76.8) h; nonsurvivors 69.6 (93.8) h	Low (7)	Hospital mortality, 90-d mortality	Not stated	…
Torbic et al[46]/2013	32	PGI_2	3.2 (2.6) d	Not reported	Low (6)	Pao_2:FIo_2 at 1 h	ICU LOS, HLOS, Duration of therapy, MV duration, adverse events, cost	Compared PGI_2 to iNO
Singh et al[44]/2014	98	PGI_2	Not reported	Not reported	High (5)	Pao_2:FIo_2	Not stated	Abstract only
Case series and case studies								
Walmrath et al[51]/1993	3	PGI_2	≈90 min	2-3 d	N/A	Pao_2:FIo_2, mPAP	Shunt	…
Bein et al[32]/1994	1	PGI_2	30 min	Not reported	N/A	Pao_2, mPAP	Not stated	…
Pappert et al[38]/1995	3	PGI_2	Not reported	Day 15-55	N/A	Pao_2:FIo_2	Not stated	Studied children
Van Heerden et al[49]/1996	2	PGI_2	≈48 h	Not reported	N/A	Pao_2:FIo_2	Not stated	…
van Heerden et al[47]/1997	1	PGI_2	≈5 d	Not reported	N/A	Pao_2	6-keto PGF1α, platelet aggregation	…
Allan et al[31]/2010	1	PGI_2	≈31 h	≈1.5 d	N/A	Pao_2:FIo_2, Pao_2	…	…
McMillen et al[37]/2011	4	PGI_2	72.5 (58.8-99.8) h	Day 1-8	N/A	Pao_2:FIo_2	…	…

Continuous data are presented as mean (SD) unless otherwise noted. A-a = alveolar-arterial oxygenation; HLOS = hospital length of stay; iNO = inhaled nitric oxide; LOS = length of stay; mPAP = mean pulmonary artery pressure; MV = mechanical ventilation; N/A = not applicable; NOS = Newcastle-Ottawa Scale; OI = oxygenation index [(FIo_2 × mean airway pressure)/Pao_2]; PGF1α = prostaglandin F1α; PVR = pulmonary vascular resistance; RVEF = right ventricular ejection fraction; Spo_2 = peripheral oxygen saturation. See Table 1 legend for expansion of other abbreviations.

[a] Timing of therapy reported variably across studies and is referenced either to onset of ARDS, respiratory failure, or ICU day.

[b] As assessed by the Newcastle-Ottawa Quality Assessment Scale.

[c] Some outcomes were not explicitly stated or defined in the manuscript as primary or secondary outcomes, but reported as such in the table.

TABLE 3] Stratified Summary Values for Meta-analyses

Stratification	No. of Studies (Patients), Meta-analysis	Mean Difference [95% CI]	*P* Value	I^2 %
All datasets				
Pao_2:Fio_2	16 (497)	39.00 [26.68, 51.31]	<.0001	92
Pao_2	8 (108)	21.41 [12.19, 30.62]	<.0001	97
mPAP	7 (76)	−4.79 [-6.75, −2.83]	<.0001	95
Epoprostenol				
Pao_2:Fio_2	15 (465)	35.68 [23.67, 47.69]	<.0001	92
Pao_2	6 (66)	20.72 [9.15, 32.29]	.0004	97
mPAP	5 (51)	−3.75 [−5.71, −1.78]	.0002	95
Alprostadil				
Pao_2:Fio_2	2 (32)	77.45 [−42.67, 197.57]	.21	92
Pao_2	3 (42)	16.79 [4.27, 29.32]	.009	92
mPAP	2 (25)	−7.14 [−9.08, −5.20]	<.0001	54
Prospective, interventional studies				
Pao_2:Fio_2	3 (40)	13.07 [2.78, 23.35]	.01	78
Pao_2	5 (54)	19.17 [9.26, 29.07]	.0002	98
mPAP	5 (58)	−4.35 [−6.52, −2.19]	<.0001	97
Cohort studies				
Pao_2:Fio_2	13 (457)	46.91 [31.33, 62.49]	<.0001	91
Pao_2	3 (54)	25.89 [−5.23, 57.01]	.10	96
mPAP	2 (18)	−6.19 [−8.25, −4.12]	<.0001	0
Publication y, 1993-2000				
Pao_2:Fio_2	6 (50)	32.30 [17.12, 47.47]	<.0001	89
Pao_2	5 (54)	24.59 [17.98, 31.19]	<.0001	91
mPAP	4 (43)	−4.75 [−8.17, −1.34]	.006	97
Publication y, 2001-2014				
Pao_2:Fio_2	11 (451)	40.24 [22.01, 58.46]	<.0001	93
Pao_2	3 (54)	15.66 [−14.38, 45.71]	.31	96
mPAP	N/A	…	…	…
High risk of bias				
Pao_2:Fio_2	11 (239)	33.73 [21.64,45.83]	<.0001	87
Pao_2	8 (108)	21.41 [12.19, 30.62]	<.0001	97
mPAP	6 (73)	−4.60 [−6.61, −2.59]	<.0001	96
Low risk of bias		65.41 [2.30, 128.52]	.04	97
Pao_2:Fio_2	2 (248)	…	…	…
Pao_2	N/A	…	…	…
mPAP	N/A	…	…	…
Exclusion of case series				
Pao_2:Fio_2	13 (487)	41.16 [26.60, 55.73]	<.0001	93
Pao_2	8 (108)	21.41 [12.19, 30.62]	<.0001	97
mPAP	6 (73)	−4.60 [−6.61, −2.59]	<.0001	96

See Table 2 legend for expansion of abbreviations.

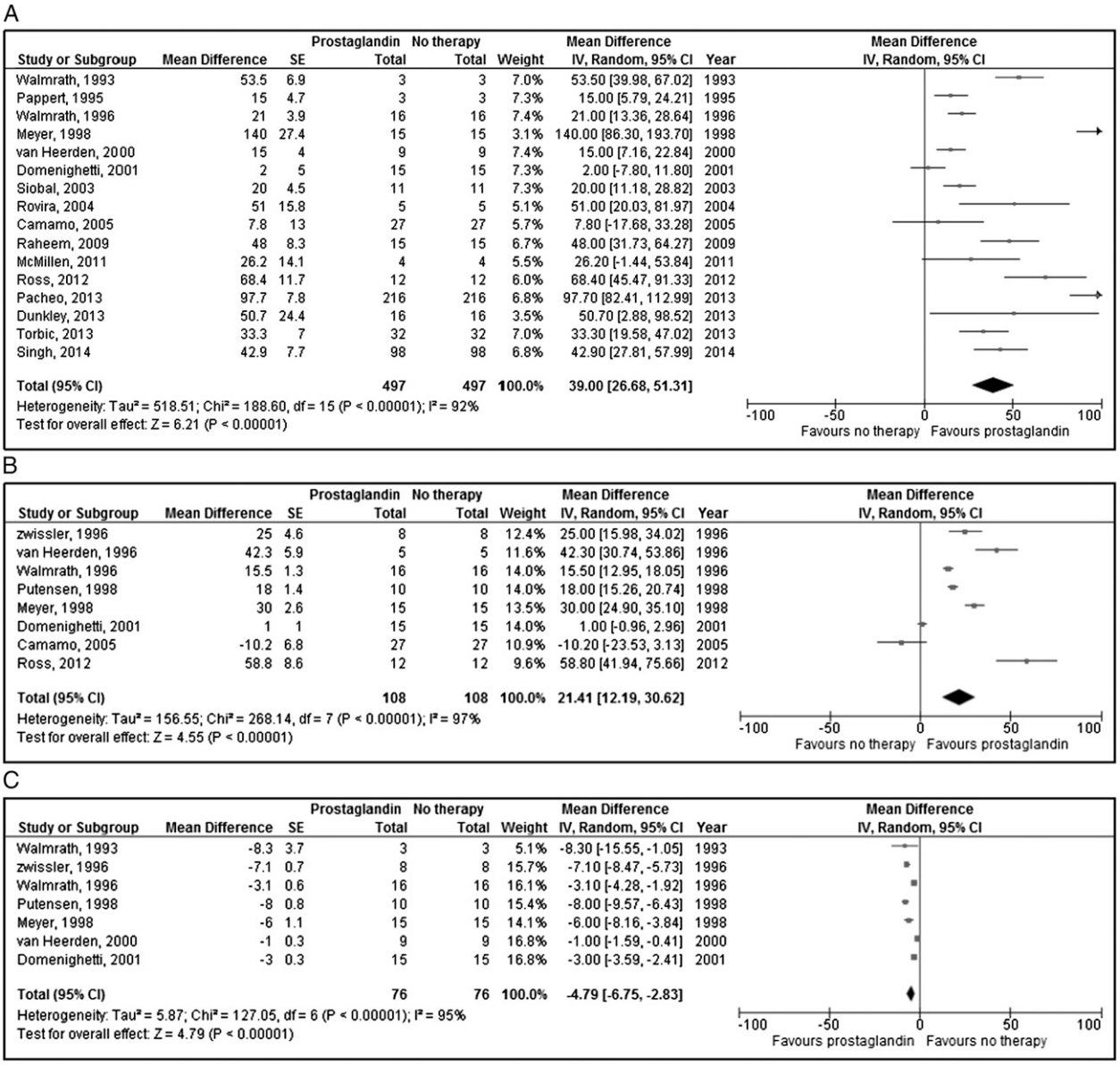

Figure 2 – *A-C, Effect of inhaled prostaglandins on Pa_{O_2} to Fi_{O_2} ratio (A), Pa_{O_2} (B), and mean pulmonary artery pressure (C). These parameters were assessed in a before-after fashion with respect to prostaglandin therapy. Therefore, the term "Total" refers to the number of measurements taken, which is exactly double the number of total patients in the each study.* df = *degrees of freedom.*

studies were more homogeneous with respect to size (n = 5-16 patients) and duration of intervention (very brief exposure to inhaled prostacyclins). The subgroup analyses are presented in Table 3. A similar effect on physiology was seen in the subgroup analyses. After exclusion of the study with the largest mean difference in Pa_{O_2}:Fi_{O_2} ratio, analysis demonstrated that inhaled prostaglandins were associated with improved Pa_{O_2} to Fi_{O_2} ratio (15 studies, 482 patients, 964 measurements; 35.7% higher, 95% CI, 23.7%-47.7%).[26] A similar result was obtained when excluding the study with the largest number of patients (15 studies, 281 patients, 562 measurements; 33.0% higher, 95% CI, 23.2%-42.9%).[27]

Meta-regression: Linear meta-regression was used to assess the impact of continuous covariates on treatment effect. Year of publication ($P = .862$), baseline Pa_{O_2} to Fi_{O_2} ratio ($P = .106$), and proportion of nonpulmonary ARDS ($P = .816$) were not associated with the treatment effect. A dose-response relationship was tested among studies that reported data separately for cohorts with a defined dose, and higher doses of inhaled prostaglandins increased Pa_{O_2} to Fi_{O_2} ratio linearly (Fig 4).

Adverse effects

Adverse events were variably reported overall. Twenty studies mentioned adverse events, or a lack of adverse

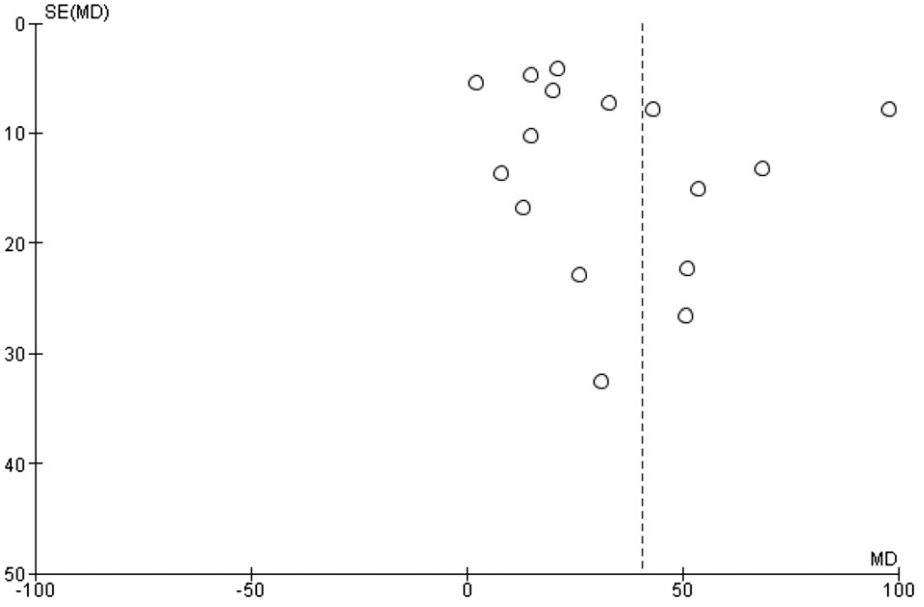

Figure 3 – *Funnel plot for outcome of Pa_{O_2} to Fi_{O_2} ratio in studies of inhaled prostaglandins for ARDS. MD = mean difference.*

effects (eg, "no effect on blood pressure"), somewhere in the manuscript (e-Table 2). Eleven studies reported no effect on systemic hemodynamics, while five studies reported hypotension, ranging from an incidence of 12.5% to 33.3%. There was a statistically significant difference in the rate of hypotension between the prospective studies vs the observational studies, 0.69% (1 of 144) vs 27 of 155 (17.4%) ($P < .001$). Three studies reported thrombocytopenia, anemia, or transfusion requirement.

Mortality

Mortality was reported in 17 of 25 studies (e-Table 3). Due to lack of controls, an investigation into an association of inhaled prostaglandin with mortality could not be ascertained. The overall reported mortality in patients with ARDS receiving inhaled prostaglandins was 295 of 522 (56.5%).

Discussion

In patients with ARDS, the traditional inhaled pulmonary vasodilator of choice has been iNO, with little data on inhaled prostaglandins. This systematic review and meta-analysis was, therefore, undertaken to assess outcomes associated with inhaled prostaglandins. The first finding is that inhaled prostaglandins appear to be used with some frequency in ARDS. This is demonstrated by the 25 publications included in the analysis, as well as the discovery of several other studies not meeting the inclusion criteria.[55-62] The data would also suggest that use is increasing in frequency, as approximately 75% of the patients were from studies published in the last 3 years. This is an interesting phenomenon when put into context of other findings in this analysis: (1) a lack of clinical outcome data demonstrating benefit, (2) overall low quality for the

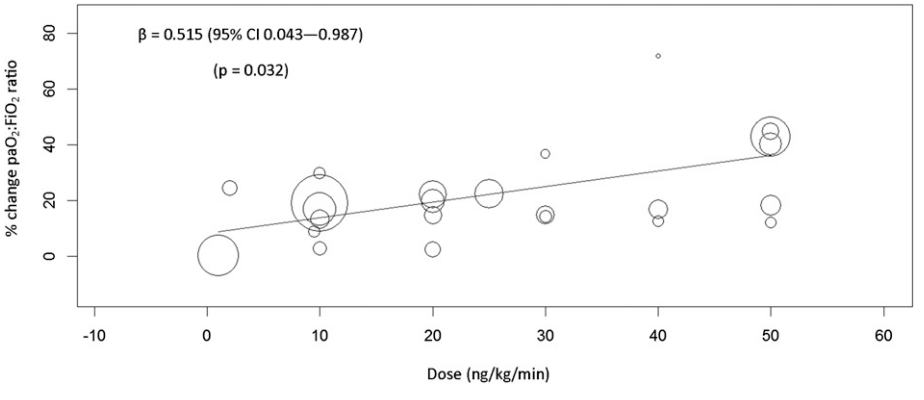

Figure 4 – *Meta-regression analysis demonstrating a dose-response relationship between oxygenation and increasing dose of inhaled pulmonary vasodilator.*

majority of data, and (3) significant heterogeneity in the data that does exist.

Only one study, to our knowledge, reported a clinical outcome as a primary analysis of interest. The two RCTs that exist had very brief exposure to study drug and did not study patient-centered outcomes. Furthermore, one RCT included only children, a potentially unique population with respect to ARDS incidence, outcome, and response to therapy.[63,64] The majority of observational studies were low quality. This suggests a lack of transparency and significant potential for bias in the published literature. Heterogeneity was demonstrated not only statistically, but also in a clinical overview of the reported data with respect to dosing, duration of exposure, and timing of therapy.

Aggregate meta-analysis and stratified subgroup analyses show improved oxygenation in ARDS. Similar results have been demonstrated with iNO, yet there is a lack of correlation between changes in oxygenation and outcome benefit in ARDS.[8,9,65,66] Furthermore, the majority of studies measured oxygenation changes in a before-after fashion, suggesting that the oxygenation benefit should be interpreted with caution. Without a placebo, it is impossible to assess whether oxygenation benefit was secondary to the use of inhaled prostaglandins. Consistency across data suggests this, but in a dose-finding study of iNO, 24% of the placebo group had an increase in Pao_2 of $\geq 20\%$.[67] Similar placebo effects were seen in one RCT included in this review.[43] Furthermore, some of the cohort studies specifically excluded patients whose oxygenation did not respond to therapy, and although averaged measures of oxygenation were found to improve for the group overall, multiple studies report that a significant percentage of patients were nonresponders.[34-36,39,44] So, it is possible that inhaled prostaglandins confer no oxygenation benefit, and these results reflect improved oxygenation secondary to a change in Fio_2 or other concomitant therapies that were not reported (eg, prone positioning, positive end-expiratory pressure setting).

Descriptive analysis of cohort studies suggests that patients dosed with inhaled prostaglandins experience adverse events that are serious and fairly common. Specifically, hypotension was reported in 17.4% of patients in the cohort studies. This is in contrast to the prospective interventional studies, which reported adverse events with less frequency. This may be secondary to the difference in drug exposure between the two study types, as the treatment duration in the cohort studies was significantly longer. There is biologic plausibility, as a prostaglandin metabolite, of 6-keto PGF1α, has been measured in the systemic circulation and demonstrates that the effect of inhaled prostaglandins is not isolated to the lung.[50] The lack of a control group in these studies also makes it difficult to conclude that the reported adverse events were related to inhaled prostaglandin therapy. Little data were provided on other ARDS treatments, such as adherence to lung-protective ventilation, and selective reporting of adverse events was common. However, the reported rate of hypotension in the cohort studies suggests that inhaled prostaglandins may be associated with possible harm and raises concern about prolonged exposure in the routine setting of ARDS treatment.

iNO does not reduce mortality in patients with ARDS.[9] Inasmuch as inhaled prostaglandins may have a similar effect on hypoxemia and pulmonary hypertension as iNO, if the only effect of inhaled prostaglandins is on this physiology, then it is unlikely that they will improve long-term clinical outcome either. However, there is also biologic plausibility that a potential effect of inhaled prostaglandins could be derived from their antiplatelet and antiinflammatory properties.[10-15] This may be more impactful as far as meaningful clinical outcome is concerned, but needs to be studied further. Reported ARDS mortality rate was 56.5% in patients treated with inhaled prostaglandins. While no inference on causation can be drawn, with this mortality rate exceeding that in reported ARDS literature, it is unclear that any benefit is derived.

There are important limitations in this systematic review. Due to a lack of RCTs, unpublished and nonrandomized studies were included in the analysis.[68,69] This decision has several implications. By including nonrandomized trials, biases in the primary data are likely to be greater.[20] An attempt to control for this was done by systematically grading each study for bias and reporting these results transparently. Nonrandomized trials often lead to increased heterogeneity, which was demonstrated in a clinical overview of the data reported, as well as statistically. Stratified subgroup meta-analyses were conducted in an attempt to control for this, and these gave similar results as the aggregate data. Meta-regression analysis was also performed. Confounding is also an issue with nonrandomized studies. It is possible that clinicians dosed patients with ARDS with inhaled prostaglandins based on a higher likelihood of clinical response or survival (ie, confounding by indication). A mortality rate of 56.5% speaks against this. On the

other hand, it is also possible that clinicians chose to dose patients with the most severe ARDS with inhaled prostaglandins, and the high mortality rate is a reflection of ARDS severity and a lower chance of survival. It is also possible that the search did not uncover all of the published literature in this domain, as nonrandomized studies are indexed poorly and have a lack of study registries. The search was exhaustive, rigorous, and reproducible, giving confidence that the largest amount of data on this topic to date was uncovered. Finally, while ARDS was an explicit inclusion criterion for this systematic review, not every individual study stated how ARDS was defined. An assumption would be that consensus definitional criteria for ARDS were used, but without an explicit statement to this fact in each publication, we are unsure.[70,71] It is recognized that these limitations make drawing conclusions on the use of inhaled prostaglandins for ARDS difficult. It, therefore, must be emphasized that due to the paucity of quality data, this analysis cannot discern whether there is truly any benefit or harm. However, this analysis provides an explicit evaluation of the strengths and weaknesses of the current literature to date, and by demonstrating a signal in the data for both benefit (ie, physiologic effects) and harm (ie, rate of hypotension), evidence for the need for randomized trials in this area has been provided.

Conclusions

The data regarding the use of inhaled prostaglandins for ARDS are limited both in terms of methodologic quality and demonstration of clinical benefit. Meta-analysis demonstrates that inhaled prostaglandins improve oxygenation and decrease pulmonary artery pressures and may be associated with adverse events. The use of inhaled prostaglandins in ARDS is in need of further study.

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Additional information: The e-Appendixes and e-Tables can be found in the Supplemental Materials section of the online article.

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