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.

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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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