Original Article

Nitric Oxide in Cardiac Surgery: A Meta-Analysis of Randomized Controlled Trials

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Objectives: To investigate the efficacy and safety of perioperative administration of nitric oxide in cardiac surgery.
Design: Meta-analysis of randomized controlled trials (RCTs).
Participants: Cardiac surgery patients.
Interventions: A search of Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and MEDLINE for RCTs that compared nitric oxide with placebo or other comparators.
Measurements and Main Results: The primary outcome was intensive care unit (ICU) stay, and secondary outcomes were mortality, duration of mechanical ventilation, and reduction of mean pulmonary artery pressure. The study included 18 RCTs comprising 958 patients. The authors calculated the pooled odds ratio (OR) and the mean difference (MD) with random-effects model. Quantitative synthesis of data demonstrated a clinically negligible reduction in the length of ICU stay (MD –0.38 days, confidence interval CI [–0.65 to –0.11]; p = 0.005) and mechanical ventilation duration (MD –4.81 hours, CI [–7.79 to –1.83]; p = 0.002) compared with all control interventions with no benefit on mortality.
Conclusions: Perioperative delivery of inhaled nitric oxide resulted to be of no or minimal benefit in patients with pulmonary hypertension undergoing cardiac surgery. Large, randomized trials are needed to further assess its effect on major clinical outcomes and its cost-effectiveness.

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Key Words: nitric oxide; cardiac; pulmonary hypertension; meta-analysis; vasodilator; cardiopulmonary bypass

PULMONARY HYPERTENSION (PH) is defined by a mean pulmonary artery pressure ≥ 25 mmHg at rest, measured through right heart catheterization.1,2 PH is a recognized risk factor for increased morbidity and mortality after cardiac surgery.3,4 It is classified according to pathophysiologic mechanisms into the following 5 groups: pulmonary arterial hypertension (PAH, group 1), PH due to left heart disease (group 2), PH due to chronic lung disease and/or

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hypoxemia (group 3), PH due to chronic thromboembolic pulmonary hypertension (group 4), and PH due to unclear multifactorial mechanism (group 5). \(^5\)

The perioperative care of these patients is challenging, and selective pulmonary vasodilators are frequently administered to prevent or reverse right ventricular failure and cardiogenic shock. Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator whose potential benefits include pulmonary pressure reduction without systemic arterial hypotension, vasodilation in the adequately ventilated areas of the lungs, rapid onset and offset, a very low incidence of adverse effects in the usual range of dosage, and replacement of endogenous nitric oxide depletion due to cardiopulmonary bypass.\(^6\)-\(^12\)

The aim of this systematic review and meta-analysis was to assess and quantify the effect of intraoperative and/or postoperative delivery of iNO in a clinical population of cardiac surgery patients with known PH related to congenital heart disease or left heart disease.

**Materials and Methods**

**Study Type and Registration**

The authors conducted a systematic review of randomized, controlled, parallel-group trials in accordance with a previously registered protocol (International Prospective Register of Systematic Reviews, registration No. PROSPERO 2016: CRD42016032702) based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.\(^13\)

**Identification of Relevant Studies**

Two trained investigators independently searched pertinent studies in the Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and MEDLINE (updated up to January 25, 2018). They employed backward snowballing (ie, scanning of references of retrieved articles and pertinent reviews) and contacted international experts for retrieving additional studies. No language restriction was enforced, and non–English-language articles were translated before further analysis in order to include any indexed, peer-reviewed relevant publications and consequently prevent a "language bias." Detailed search strings and reference lists are given in the Supplemental Material. Two investigators independently examined the title and abstract of the references obtained from database and literature searches with divergences resolved by consensus and, if potentially pertinent, retrieved complete articles.

**Eligibility Criteria**

The authors included randomized, controlled, parallel-group trials with all the following criteria: cardiac surgery setting (adult or pediatric); patients receiving iNO versus any comparator such as placebo, no intervention, other inhalation therapies (eg, prostacyclin), or intravenous medications (eg, milrinone, nitroglycerin, sodium nitroprusside); and reporting at least one relevant outcome among length of stay in the intensive care unit (ICU) primary endpoint, duration of mechanical ventilation, mortality at longest follow-up, and reduction of mean pulmonary artery pressure.

**Trial Selection and Data Extraction**

Two authors independently extracted data, with disagreements resolved by discussion and, if needed, via a third author, who acted as an adjudicator. An attempt was made twice to contact authors to request any missing outcome data.

**Risk of Bias Assessment and Strength of Evidence**

Two authors independently examined the reported methodology for each article and assessed the risk of bias of included trials using the Cochrane Collaboration tool. The following domains were evaluated individually and graded as "low risk," "high risk," or "unclear risk": random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other bias. The item "selective outcome reporting" was assessed as "unclear" risk if the study protocol was not published or registered previously.

**Data Synthesis**

The authors used Review Manager (The Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) for performing the statistical analysis and drawing the related plots.\(^14\) They computed standard deviations from standard error of the mean according to the Cochrane Handbook for Systematic Reviews of Interventions.\(^15\) If continuous variables were expressed as median and interquartile range, the median was entered as mean and standard deviation was computed as the difference between third- and first-quartile values.\(^16\)

When nitric oxide was compared with multiple control interventions, the authors managed continuous variables combining groups to create a single pair-wise comparison according to the Cochrane Handbook for Systematic Reviews of Interventions recommended formula.\(^17\)

They calculated the pooled odds ratio and 95% confidence interval (CI) for binary outcomes using the Mantel-Haenszel method with random-effects model, and estimated the mean difference (MD) and 95% CI for continuous outcomes using the inverse variance method with random-effects model.

Heterogeneity was managed using the random-effects model and by performing subanalysis for age groups (ie, adult and pediatric patients). The hypothesis of statistical heterogeneity was tested using the Cochran Q test, with statistical significance set at the two-tailed 0.10 level, whereas extent of statistical consistency was measured with I\(^2\), defined as 100% \times (Q – df)/Q, where Q is Cochran’s heterogeneity statistic and df the degrees of freedom.\(^18\) Inconsistency across the studies was evaluated using the I\(^2\) test and was considered

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significant at $I^2 > 40\%$. Publication bias was evaluated by visualization of funnel plots.

Results

After excluding nonpertinent or noneligible studies (major exclusions listed in the Supplemental Material) the authors identified 18 studies (Table 1) randomizing 958 patients (Fig 1).

When the pooled data of all comparators were analyzed, iNO minimally decreased the length of ICU stay (MD $-0.38$ days, CI $[-0.65$ to $-0.11]$, $I^2 = 11\%$, $z = 2.79$, $p = 0.005$, with 9 studies reporting these data and 560 patients included) with no small publication bias (Figs 2 and 3). Nitric oxide also marginally reduced mechanical ventilation duration (MD $-4.81$ hours, CI $[-7.79$ to $-1.83]$, $I^2 = 31\%$, $z = 3.17$, $p = 0.002$, with 11 studies and 596 patients included (Fig 4) compared with all the studied control interventions.

Nitric oxide did not significantly reduce mean pulmonary artery pressure (MD $-1.37$, CI $[-4.40$ to $1.67]$, $I^2 = 74\%$, $z = 0.88$, $p = 0.38$, with 8 studies and 303 patients included) compared with all interventions (Fig 5).

No difference in survival was noted (absolute number of events 10/272 [3.67%] in the iNO group v 10/297 [3.37%] in the control group, OR 1.33, CI [0.52-3.39], $I^2 = 0\%$, $z = 0.6$, $p = 0.55$, with 8 studies and 569 patients included (Fig 6).

Compared with iloprost, prostacyclin, or prostaglandin E1, no differences between nitric oxide and comparators were found (Supplemental Figs 12-15). Compared with standard care or placebo, a significant reduction in mechanical ventilation duration in the nitric oxide group was found (MD $-7.9$ hours, CI $[-11.22$ to $-4.58]$, $I^2 = 0\%$, $z = 4.67$, $p < 0.00001$, Supplemental Fig 18).

Adult Patients

The authors performed a subanalysis for adult patients, mostly undergoing valve repair or valve replacement surgery (see Table 1), to compare nitric oxide with all comparators. The subanalyses confirmed a small reduction of ICU stay (MD $-0.31$ days, CI $[-0.61$ to $-0.01]$, $I^2 = 19\%$, $z = 2.01$, $p = 0.04$ [Fig 3 and Supplemental Fig 21]) and mechanical ventilation (MD $-5.76$ hours, CI $[-8.53$ to $-2.99]$, $I^2 = 11\%$, $z = 4.07$, $p < 0.0001$ v MD $-3.19$ hours, CI $[-9.3$ to $2.92]$, $I^2 = 34\%$, $z = 1.02$, $p = 0.31$ [see Fig 4 and Supplemental Fig 22]) in the iNO group, with a nonsignificant trend versus higher mortality in the intervention group (see Fig 6 and Supplemental Fig 21).

Pediatric Patients

The subanalysis on congenital heart disease pediatric patients showed a slightly inferior ICU stay in the nitric oxide treatment group (MD $-1.00$ days, CI $[-1.76$ to $-0.25]$, $I^2 = 0\%$, $z = 2.6$, $p = 0.009$ [see Fig 3 and Supplemental Fig 23]). No significant differences were found in mechanical ventilation duration and mortality between nitric oxide and all comparators (Figs 4 and 6; Supplemental Figs 24 and 25).

Risk of Bias

Most studies were unblinded, and the full Cochrane risk of bias analysis is illustrated in Supplemental Figures 26 and 27 and Supplemental Table 1. The small study publication bias
was absent, as depicted in the funnel plots (see Fig 2 and Supplemental Figs 1-11).

Discussion

The authors conducted a systematic review of 18 randomized controlled trials (RCTs) in cardiac surgery patients to evaluate the effect of perioperative delivery of nitric oxide on clinical outcomes. Most studies had a high or unclear risk of bias, and studies were highly heterogenous regarding the dosage, initiation, and duration of iNO delivery; the comparators; and the underlying cardiac defect or pathology. Considering these limitations, the quantitative synthesis showed that the perioperative use of nitric oxide minimally reduced the duration of length of ICU stay (MD $-0.38$ days, CI $[-0.65$ to $-0.11])$ and mechanical ventilation (MD $-4.81$ hours, CI $[-7.79$ to $-1.83])$, with no benefit on mortality rate compared with all comparators (including other vasodilator therapies). The small effect on mechanical ventilation is confirmed in the analysis of nitric oxide versus standard care or placebo (MD $-7.90$, CI $[-11.22$ to $-4.58])$. Surprisingly, no significant reduction of pulmonary artery pressure was found.

Although the authors recognize the “statistical strength” of these results, they should be interpreted with caution. Despite a significant association between iNO and a decrease in mechanical ventilation and ICU stay duration, the effect size seems small and clinically negligible. Furthermore, if those effects are real, they do not seem to relate with the degree of pulmonary artery pressure relief, so other mechanisms should be sought.

No previous reviews addressing the effects of iNO on major clinical outcomes in patients undergoing cardiothoracic procedures were found. One systematic review involved RCTs...
comparing the efficacy of the use of inhaled aerosolized vasodilators in the treatment of PH during cardiac surgery.\textsuperscript{36} That review found that aerosolized agents were associated with longer ICU stay compared with placebo, with no differences in hemodynamic profile and mortality. However, most of the studies had a moderate to high risk of bias, and the effect size for length of ICU stay outcome was pooled from 3 studies. Moreover, different drugs with variable pulmonary vasodilatory potency and distinct systemic vasodilation effects were included in the intervention group.

Some systematic reviews with greater data robustness evaluated the role of iNO in other intensive care settings. A Cochrane review of 14 trials in patients with hypoxic respiratory failure demonstrated improvement in the oxygenation index but no benefit in survival.\textsuperscript{37} Nevertheless, cardiac surgical patients with underlying PH face additional issues other than hypoxemia, including right ventricular failure and increased pulmonary vascular resistance on the background of surgical stress injury. In this context, some components of cardiopulmonary bypass inflammatory activation such as metabolic acidosis and systemic hypotension may act as contributors for PH exacerbation.

In infants born at or near term, a review demonstrated that iNO reduced the incidence of the combined endpoint of death and use of extracorporeal membrane oxygenation (ECMO).\textsuperscript{38} Due to favorable outcomes and the high quality of trials, neonates currently are the only population for which iNO holds Food and Drug Administration approval. In this analysis, the evidence of PH did not seem to affect the response to nitric oxide. In contrast to cardiac surgery patients, neonatal hypoxemia may result from a degree of pulmonary shunting and parenchymal lung disease.\textsuperscript{39} Similarly to the systematic review presented here, the studies conducted in neonatal patients were heterogenous in regard to the implementation of adjunctive therapies, which may limit the internal validity and generalizability of the results.

In patients with PH, cardiac surgery may constitute the only therapeutic alternative to treat the causal underlying condition. After surgical trauma, a number of mechanisms take place and may spark a PH crisis, including ischemia-reperfusion injury,
In such a proinflammatory milieu, perioperative administration of iNO may provide support against pulmonary vasculature constriction. In the present systematic review, the timing of delivery was variable, with the majority of studies initiating the intervention in the operating room. The effect of a pre-emptive iNO delivery from anesthetic induction in carefully selected patients at risk of PH exacerbation might be an interesting topic of investigation.

Nitric oxide delivery carries non-negligible risks and costs. iNO is inactivated rapidly in the circulation by hemoglobin iron oxidation, resulting in a dose-related methemoglobinemia. According to the published evidence, it seems that a clinically significant methemoglobinemia (> 5%) may develop not only in patients exposed to a high dose, but also in patients treated with conventional doses with specific risks. For example, a standard dose may cause this adverse event in patients affected by a methemoglobin reductase deficiency (ie, the enzyme involved in converting methemoglobin to hemoglobin) or in cases of technical mishaps (eg, pooling of nitric oxide in the breathing circuit or monitoring dysfunction).

Nitric oxide may be oxidized further to nitrogen dioxide, which may cause airway inflammation, bronchospasm, and pulmonary edema. Unfortunately, most included studies did not report sufficient data to quantitatively assess iNO-related organ toxicity. The administration of iNO also may increase the burden of tasks for medical and nursing staff due to cumbersome equipment and the need for more intensive monitoring. It also poses a safety risk of environmental pollution. Moreover, the mean cost of iNO delivery is estimated to be significantly more compared with aerosolized prostacyclin ($3,000/d v $200/d, respectively). However, nitric oxide has been used extensively worldwide over the last few decades as an off-label treatment in cardiac surgery. Nevertheless, the real cost-effectiveness of iNO therapy in cardiac surgical patients can be answered only by large, multicenter, randomized and adequately powered RCTs.

This systematic review was conducted to provide a qualitative and quantitative synthesis of the published literature regarding the use of iNO in cardiac surgery. The study question and rationale seem to be relevant because this therapy is available in many centers, despite its off-label use. The authors believe that the chosen outcomes are more relevant than instrumental indices of organ function because they relate better to the quality and costs of health care. Methodologic guidelines were strictly followed, the protocol was registered, and a comprehensive and inclusive search strategy was performed. To the authors’ knowledge, this is the first systematic review addressing the isolated effect of iNO in cardiac surgery. Any study on the combination of nitric oxide with other selective pulmonary vasodilator was carefully excluded, so its effect as add-on therapy cannot be assessed. Other aerosolized vasodilators were not considered in the inclusion criteria because they may have distinct pulmonary vasodilatory potency, pharmacokinetic properties, and variable safety profile.

**Fig 5.** Forest plot for change of mean pulmonary artery difference between nitric oxide and all comparison interventions. CI, confidence interval; IV, inverse variance; SD, standard deviation.

**Fig 6.** Forest plot for mortality odds ratio between nitric oxide and all comparison interventions. CI, confidence interval; IV, inverse variance; SD, standard deviation.
This systematic review has limitations. First, the number of studies included was limited, and most of them were small and single-centered. Second, most studies included had a high or unclear risk of bias. Blinding of personnel and outcome assessment were highly biased in the majority of trials, so a spurious inflation of intervention effects cannot be excluded. Third, a large variability of dose, timing of the initiation, duration of the intervention, and comparators was found (see Table 1). Fourth, the authors acknowledge the complexity of PH syndrome and its multiple pathophysiologic mechanisms in cardiac surgery patients undergoing different surgical procedures. Despite this, the authors considered that even in the setting of postcapillary PH, such as mitral stenosis, endothelium-dependent dysregulation of vascular tone still could affect both pulmonary vascular resistance and right ventricle afterload.48

These expected differences in treatment responses were addressed using a statistical model of random effects and performing subgroup analysis, but the scarcity of RCTs limited the efficacy of the latter strategy. Fifth, the authors cannot account for all undisclosed confounding factors, such as different mechanical ventilation strategies (eg, ventilator settings, inspired fraction of oxygen, weaning and extubation criteria) or vasopressor therapy, but believe that center- and study-related differences may be balanced.

This systematic review showed that perioperative delivery of iNO exerted minimal or null effects on major outcomes; therefore, new recommendations for practicing anesthesiologists and intensivists who face the challenging management of PH in cardiac surgery patients cannot be provided. Given the heterogeneity and limitations of the studies included, and the ongoing widespread use of iNO in this setting, the authors support the conduct of well-designed, adequately powered, multicenter randomized trials to investigate the appropriateness of iNO in this surgical population.

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Appendix A. Supporting Material

Supplementary data associated with this article can be found in the online version at https://doi.org/10.1053/j.jvca.2018.02.003

References


