A REVIEW OF THE USE OF INHALED NITRIC OXIDE IN THE PICU AT RED CROSS CHILDREN'S HOSPITAL, 2011-2015: A RETROSPECTIVE COHORT STUDY

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DECLARATION

I, Dr Sandhia Padayachee, hereby declare that the work on which this dissertation is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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I would like thank every patient that we have the privilege of treating at Red Cross Hospital, we are lucky to be able to learn from them. I would like to thank every member of staff that contributes to patient care, their documentation and note keeping make projects like this possible. Lastly I would like to thank my friends and family for their tireless encouragement.

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LIST OF ABBREVIATIONS

ARDS	-	Acute Respiratory Distress Syndrome
BPD	-	Bronchopulmonary Dysplasia
CDH	-	Congenital Diaphragmatic Hernia
CGMP	-	Cyclic Guanosine Monophosphate
CPAP	-	Continuous Positive Airway Pressure
FiO2	-	Fraction of Inhaled Oxygen
HFOV	-	High Frequency Oscillatory Ventilation
iNO	-	Inhaled Nitric Oxide
MPAP	-	Mean Pulmonary Artery Pressure
NHLS	-	National Health Laboratory System
NO	-	Nitric Oxide
NOS	-	Nitric Oxide Synthase
OI	-	Oxygenation Index
PaO2	-	Partial Pressure of Oxygen
PAP	-	Pulmonary Artery Pressure
PHT	-	Pulmonary Hypertension
PHTC	-	Pulmonary Hypertensive Crisis
PHTCs	-	pulmonary Hypertensive Crises
PICU	-	Paediatric ICU
PIM2 Score	-	Paediatric Index of Mortality Score
PPHN	-	Persistent Pulmonary Hypertension of the Newborn
PVRI	-	Pulmonary Vascular Vascular Resistance Index
RCTs	-	Randomised Controlled Trials
RCWMCH	-	Red Cross War Memorial Children's Hospital
SVRI	-	Systemic Vascular Resistance

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INTRODUCTION AND LITERATURE REVIEW

Background:

Nitric oxide (NO) is primarily a modulator of vascular tone and has many features of an ideal pulmonary vasodilator. When inhaled, it has a rapid onset of action, is delivered directly to the lungs thereby minimizing systemic side effects, and improves ventilation-perfusion mismatch. (1)

Inhaled Nitric Oxide (iNO) was first approved by the Food and Drug Administration in 1999 for use in neonates with Persistent Pulmonary Hypertension of the Newborn (PPHN). Since then there has been considerable interest in its possible role as a pulmonary vasodilator in other conditions. (2)

Although it has been validated for use in PPHN by numerous randomised controlled trials (RCTs), its use in other settings is not widely supported. (2, 3) Whilst there is often an improvement in oxygenation observed with its use, it is not known if this translates into an improvement in morbidity and mortality, or whether there are subgroups of patients that respond preferentially to treatment. In our resource limited setting, it is often employed in severe, refractory hypoxaemia secondary to acute respiratory distress syndrome (ARDS) and in pulmonary hypertension (PHT) following cardiac surgery. It is an expensive treatment that is used without a protocol to guide its use and weaning, and this is often left to the discretion of the attending physician.

NO is synthesized from the terminal nitrogen of L-arginine by the enzyme nitric oxide synthase (NOS) in vascular endothelial cells. NO then diffuses into vascular smooth muscle where it binds to soluble guanylate cyclase to convert guanosine triphosphate into cyclic guanosine monophosphate (CGMP). CGMP then mediates vascular smooth muscle relaxation thereby improving perfusion and in turn, oxygenation. Ventilation-perfusion mismatch is improved as iNO is preferentially delivered to well aerated lung segments. (1) Decreased pulmonary vascular pressures may also reduce right to left intra-cardiac shunting through a patent ductus arteriosus or patent foramen ovale if present.

Once in the bloodstream, iNO binds with iron in oxyhaemoglobin to form methaemoglobin and nitrate, and with deoxyhaemoglobin to form iron-nitrosyl-globin. It is rapidly inactivated which largely accounts for its low side effect profile. (3, 4)

Inhalation of low levels of NO appears to be safe. The major clinical toxic effects are due to the formation of nitrogen dioxide which may cause pulmonary oedema and methaemoglobinaemia which may result in hypoxia. These are however usually observed when high doses of iNO, usually more than 80ppm, are used. It is recommended that serum methaemoglobin be measured at 8hours and 24hours, and treatment weaned or discontinued if levels methaemoglobin levels rise above 5%. Other adverse effects may include bleeding due to impaired platelet adhesion and aggregation and renal dysfunction, although these are not usually observed in the paediatric population. iNO mediated lung injury may occur and results primarily from inactivation of surfactant protein A and decreased surfactant production. Prolonged iNO exposure is associated with a transient increase in markers of oxidative lung injury. (5)

In vitro, nitric oxide has been shown to have some bacteriostatic effect and some immune modulatory effects. This has however not been proven in vivo. (6, 7) Leukocyte activation is inhibited thereby inhibiting the generation of oxygen free radicals. (2, 8) In addition, immune function is affected by modified cytokine release from alveolar macrophages, and inhibition of active adhesion molecules and inhibition of the neutrophil oxidative burst involved in neutrophil migration. Attenuation of the inflammatory response, particularly in lung injury associated with sepsis, may therefore be an important factor in the success or failure of treatment with iNO. (9)

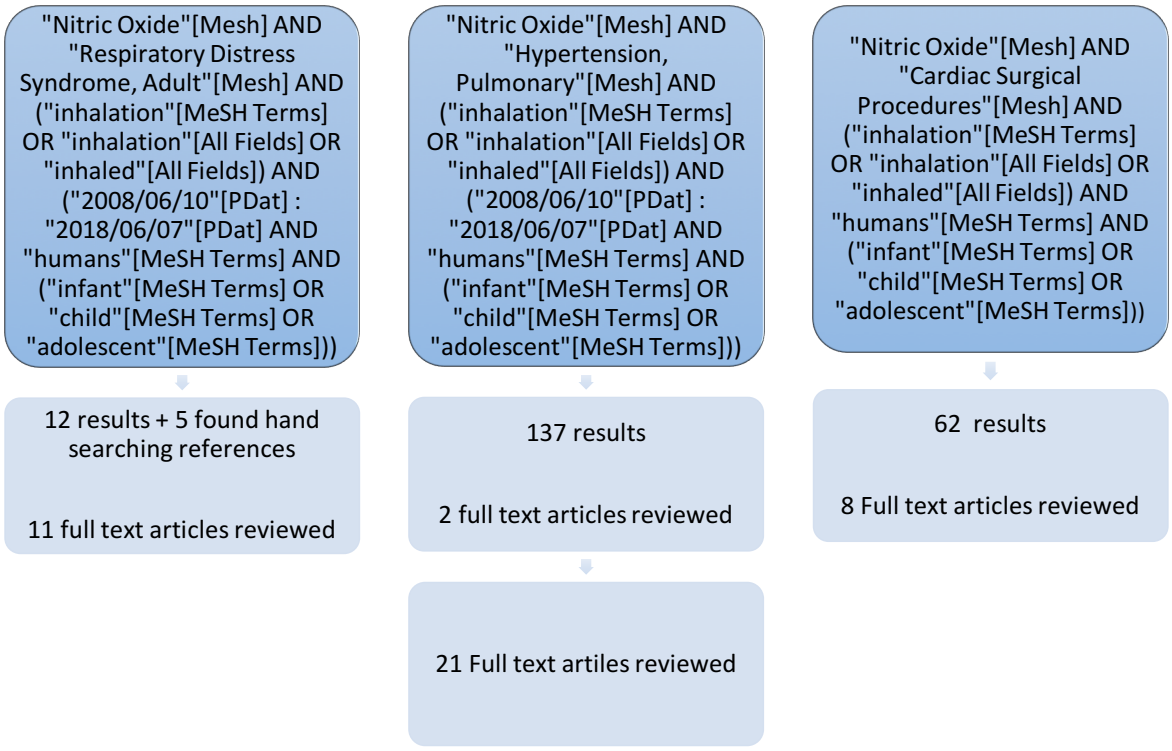
There is a lack of standardised guidelines for the dosage and weaning of iNO. A response to treatment is usually observed at doses of 20ppm. When iNO is stopped abruptly, rebound pulmonary hypertension sometimes develops. This can usually be averted by a slow weaning of iNO to 1ppm before discontinuation, increasing FiO2 during weaning, or the concomitant use of phosphodiesterase inhibitors. (5) Sildenafil is recommended by the American Heart Association to prevent rebound pulmonary hypertension in patients who have evidence of a sustained increase in pulmonary artery pressure on withdrawal of iNO or require retreatment with iNO despite gradually weaning the dosage. (10) This rebound phenomenon is not seen when treatment with iNO is limited to 30 minutes, and for this reason, treatment should be discontinued promptly in patients that have not responded to a short trial of treatment.

Objectives:

The objective of this literature review is to appraise the outcomes of patients treated with iNO for ARDS and pulmonary hypertension following cardiac surgery. Primary outcomes looked at will be response to treatment with improved oxygenation, haemodynamics and mortality. Secondarily we will try to ascertain whether there are subgroups of patients that respond preferentially to treatment. The aim is to gauge whether continued use of this expensive treatment modality without strict guidelines is in fact justified in our clinical setting.

Search strategy

Table 1. Literature Review Search Parameters



An electronic search of the Pubmed and Cocharane databases was undertaken in 2015 and again in December 2018. Medical Subject Headings (MeSH) were used in these searches. These headings included “Nitric oxide”, “Adult Respiratory Distress Syndrome”, “Pulmonary Hypertension” and “Cardiac Surgical Procedures”. Filters were applied to include only studies in humans, studies in children, and studies published after 1998, although key RCTs published before this time period were included due to the paucity of good quality evidence.

Results were screened based on relevance of the title and review of the abstract. All systematic reviews, meta-analyses, randomized controlled trials and recent large retrospective studies were included. References in meta-analyses were hand searched as some trials were published prior to the time frame used in this search. Studies comparing iNO to other therapies or to adjunctive maneuvers, those looking at dose response relationships, use in specific cardiac procedures, use in neonates, different methods of delivery and effects on long term disability were excluded. Only articles available in full text in English were included.

Results:

iNO in ARDS

Definitions and practice:

Paediatric ARDS is defined by the presence of respiratory distress, hypoxaemia and bilateral infiltrates on chest radiograph. (11) Stricter definitions have been applied for research purposes, however, in our setting any lung disease with hypoxaemia is commonly labelled ARDS, without differentiation based on underlying cause.
ARDS may be caused by a number of underlying conditions, and because of this, response to treatment may vary. In the literature, patients with ARDS are often analysed as a cohort irrespective of underlying cause. Given the heterogeneity in underlying pathology, it is not known whether there are subsets of patients with specific conditions that respond preferentially to treatment with iNO. (8)

In our unit iNO is administered to patients with refractory hypoxaemia on mechanical ventilation via a continuous delivery method, and not non invasively via face mask or Continuous Positive Airway Pressure (CPAP) as practiced elsewhere. In patients with ARDS, treatment is often initiated based on a clinical suspicion of PHT without echocardiographic confirmation, which is largely due to an overburdened cardiology service and difficulty in accessing routine echocardiography.
A response to treatment is subjectively determined by the attending physician, usually based on an improvement in oxygen saturation alone. In the literature, the standard for assessing response to treatment in most trials is an improvement in the oxygenation index (OI) of 20 percent from baseline (8) or an improvement in the ration of PaO2/FiO2 of more than 10 (12,

13). The OI is calculated by the formula (FiO2*Mean Airway Pressure)/PaO2. An assessment of clinical response based on oxygen saturation alone may be confounded by factors such as ventilator settings, adjunctive measures such as prone positioning, sodium bicarbonate or neuromuscular blockade.
The timing of initiation of treatment may also play a role as it is hypothesized that early initiation of treatment is associated with improved outcomes. (12)
Ventilation strategies in our unit are clinician driven rather than protocol driven and are guided by arterial blood gas measurements and pulse oximetry. In some studies, protocols including the use of regular 6 hourly radiographs are used to guide ventilation which may account for a slight variation between findings in the literature and findings in clinical practice. (12, 14)

Improvement in Oxygenation:

A systematic review by Afshari et al in 2011 that included 3 paediatric trials (Day, Dobyns, Ibrahim) showed that iNO effected only a transient improvement in oxygenation that did not extend beyond 24 hours. Dosing regimens however varied in the included trials and it is not known whether prolonged fixed dosing may result in tolerance which may have affected results. Furthermore, many trials were conducted more than 15 years ago and ventilation strategies have advanced since then with a greater focus being placed on lung protective ventilatory strategies. (15) An earlier systematic review by Adhikari et al in 2007 including two pediatric trials, (11) as well as the European Consensus Statement on the use of iNO in Neonates and Children concur that iNO provides only a short, non-sustained improvement in oxygenation. (16)

A small RCT by Day et al in 1997 looked at 12 patients treated with iNO and 12 controls. Patients were either treated with iNO at 10ppm for 24 hours or conventional treatment, after which the control group as well as the initial treatment group were treated with iNO for a further 24 hours. They found that whilst the OI in the initial treatment group was improved in the first hour following treatment, this was not maintained at 24 hours. Patients in the initial control group interestingly demonstrated a sustained improvement in oxygenation beyond 24hours of treatment. This was however a small study and the use of HFOV was not stratified for. (17)

A large multicenter RCT by Dobyns et al in 1999 assessed response to treatment with improved oxygenation. One hundred and eight patients with acute hypoxic respiratory failure were enrolled. Treatment with iNO was compared to conventional ventilation alone for 72hours. Crossover was allowed if patients failed to improve with mechanical ventilation alone. Although standardized ventilation protocols were used, the use of HFOV, neuromuscular blockade and prone positioning were not stratified for. It was found that at 12 hours there was a significant improvement in oxygenation in the treatment group, but this was not sustained beyond that. (18)

A recent prospective multicenter RCT performed in 2015 by Bronicki et al, including 24 patients treated with iNO and 29 controls, showed a significant improvement in OI at 12 hours in the treatment group that was again not sustained beyond 24 hours. (14)

Medjo et al in 2004 prospectively enrolled a treatment group of 16 patients and looked at a retrospective group of patients with ARDS that were treated with iNO. They found only a short term improvement in oxygenation that was not sustained beyond 24 hours. (13)

Fioretto et al in 2004 showed in a prospectively enrolled treatment group of 18 patients compared with a retrospective control group of 21 patients that early initiation of iNO within 1.5 hours of diagnosis of ARDS, irrespective of the severity of the clinical presentation at the time, resulted in an early and sustained improvement in oxygenation. This suggests that the timing of initiation of treatment may affect response. (12)

Mortality:

A Cochrane review of the literature, including pooled data from 4 paediatric trials, showed no improvement in mortality following treatment with iNO in paediatric patients with ARDS. The combined number of paediatric patients included in the review were too few to demonstrate any other benefits or harm in paediatric patients. (1)

Afshari et al reviewed 3 paediatric RCTs, only one of which did not allow for crossover and was hence suitable for assessment of mortality. No improvement in mortality was found. (15)

A review by Adhikari et al found a possible trend towards increased mortality, however this was based on trials in adults as the paediatric trials in this review both allowed crossover and could not provide information on mortality as an outcome. (11)

The European consensus statement on the use of iNO in ARDS states that iNO has not been shown to improve mortality and that further studies that stratify for underlying disease are needed. (16)

In a large retrospective study that included 160 patients treated at the Children's Hospital of Philadelphia, Dowell et al in 2017 looked at mortality by stratifying patients according to responders to iNO (those with an improvement in oxygenation index or an improvement in oxygenation saturation of >20%) and non-responders. No statistical difference in mortality was found between the two groups. (8)

Gupta et al in 2016 conducted a large multicenter retrospective study including 521 propensity score matched paediatric patients from 9 different centres across the United States. Patients were enrolled prospectively from an online critical care network that contained patient demographics, clinical information and costs of treatments. They also found no benefit in mortality. (19)

Medjo et al also reported on mortality with no benefit being conferred by treatment with iNO. (13)

Secondary Outcomes:

Dowell et al showed that patients with ARDS that responded to treatment with iNO were less likely to require HFOV and ECMO and that there was a significant decrease in ventilator days in responders. A standardized protocol for ventilation and the use of iNO was not used in this study and a non-invasive method of delivery of iNO was used. This meant that patients could be weaned off ventilation irrespective of a continued need for treatment with iNO. The authors suggest a trial of iNO in these patients due to the potential for decreased morbidity and costs from ECMO, HFOV and ventilator days. This is not relevant in our setting, firstly because ECMO was not available in our unit during the time period investigated and

secondly because iNO is usually used in patients with ARDS that are already failing treatment with HFOV. (8)

Bronicki et al also found that ventilator free days and ECMO free days were higher in the group treated with iNO. (14)

Fioretto et al found no appreciable difference in duration of mechanical ventilation and length of stay in ICU between treatment groups with early initiation of iNO and control groups. (12)

Medjo et al also reported a decrease in ventilator settings with the use of iNO which might result in fewer ventilator-associated complications. (13)

Gupta et al 2016 found significantly worse outcomes in terms of ventilator free days, mechanical ventilation and duration of hospital and ICU stay in treatment groups. They also showed an increase in costs in patients treated with iNO compared to control groups. This is the first study to show increased morbidity and higher costs in patients treated with iNO for ARDS. Possible factors contributing to these findings are a detrimental effect of discontinuing iNO because of the suppression of endogenous NO production, and longer duration of ventilation due to slow weaning of iNO. (19)

Dobyns et al found that patients with severe lung disease and high OI at initiation of treatment, as well as patients that were immunocompromised, showed a better response to treatment. (18) Dowel et al found that no other demographic or severity of illness variables were predictive of an improved response to iNO. (8)

iNO in PHT post cardiac surgery

Definitions and practice:

In the paediatric population PHT is defined as a pulmonary arterial pressure (PAP) >25mmHG or PAP greater than 50% of systemic arterial pressures. Acute pulmonary hypertensive crises (PHTCs) are defined as an acute increase in PAP with a resultant impairment of haemodynamics and oxygenation. The increase in pulmonary vascular resistance results in increased right ventricular afterload and eventually impaired cardiac

output. (20) It is theorized that the ability of the right ventricle to adapt to an increase in afterload rather than the absolute increase in PAP that determines the outcome in pulmonary hypertensive crises. (10)

PHTCs are a major contributor to morbidity and mortality post cardiac surgery. Life threatening pulmonary crises are experienced in 7% of these patients and is associated with a 29% mortality rate. (3) PHTCs may be triggered by pain, hypoxia and suctioning in the post-operative period.

The post-operative period, particularly if cardiopulmonary bypass was used, is associated with high pulmonary pressures secondary to hypoxia, an excess production of endothelin and thromboxane, an increased production of microemboli and ischaemia-reperfusion injury. In addition, endogenous production of nitric oxide is decreased in the immediate post operative period. (21)

INO is used in this setting for its desirable effect in improving oxygenation without impairment of systemic haemodynamics.

Impact on number of PHT crises:

A Cochrane review that was updated in 2014 including combined data from 4 RCTs (Day, Miller, Morris, Russel) and 210 patients found no difference in the number of pulmonary hypertensive crises in patients treated with iNO when compared to controls. The timing of initiation of treatment in these trials were however predetermined and treatment was administered prophylactically. Russel and Miller commenced treatment immediately post-operatively, Day, on arrival in ICU, and Morris at a median of 8.5 hours. Dosing also varied across trials ranging from 5-40ppm. (3)

A RCT by Day et al, 2000 assessing the impact of iNO on the number of PHTC post-operatively in 38 patients, showed no statistical difference in the number of PHTCs. Patients were recruited if their post-operative pulmonary pressures were more than 50% of systemic on cardiac catheterization, and the use of iNO was compared to conventional treatment which was determined by the attending physician and was not standardized between groups. (22)

A large RCT by Miller et al in 2000 enrolled 124 infants with preoperative PAP >50% of systemic and compared the number of post-operative PHTCs in patients treated with iNO

compared to placebo. This trial used continuous prophylactic iNO at a dose of 20ppm. They found a 30% reduction in the number of PHTCs in the treatment group. (6)

The American Heart Association recommends that iNO be used as the initial therapy for PHTCs and right heart failure following cardiac surgery and that sildenafil be utilized when withdrawing iNO, Class 1, Level of Evidence B (i.e. treatment recommended but based on single RCT or non-randomized trials). (10)

The European Consensus Statement on the management of pulmonary hypertension in the ICU suggests considering the early use of INO following bypass surgery for its benefit in reducing pulmonary vascular resistance and its possible role in reducing the number of pulmonary hypertensive crises and shortening the post-operative course. (10, 21, 23)

Impact on mortality:

The Cochrane review in 2014 including data from Day and Miller et al found no impact on in hospital mortality with the post-operative use of iNO in patients with congenital cardiac disease. Long term mortality was not commented on in any of the studies. (3) Most other studies either allowed crossover or did not comment on mortality.

Miller, 2000 also found no improvement in mortality conferred by treatment with iNO. (6)

Secondary outcomes:

The Cochrane review in 2014 found no decrease in mean pulmonary artery pressure (MPAP) following treatment with iNO combining data from Day and Morris. They also found an increase in methaemoglobin levels, but these did not reach toxic levels. They found no significant differences in subgroups comparing iNO to placebo or conventional management. (3)

It has been shown that patients with higher pulmonary vascular resistance (PVR) and lower partial pressure of oxygen (PaO2) generally respond better to iNO. It was also shown that patients with Down Syndrome, with an age of less than 1 year and pre-operative pulmonary

hypertension are more likely to require post-operative iNO in a large retrospective review of 457 patients by Laitenen et al 2000. (24)

Miller et al found a decrease in time to eligibility for extubation in patients treated with iNO. (6)

Day et al showed no difference in PaO2: fraction of inspired oxygen (FiO2) between treatment and control group. Day, Morris and Russel showed no statistical difference in mean arterial pressure and heart rate between treatment and control groups and also that patients with higher pulmonary pressures respond better to treatment. (3)

Russel et al 1998 published a randomised double blinded study including 40 patients with pre-operative PHT. MPAP was assessed post-surgery. Patients with PHT post operatively responded to treatment with iNO with a decrease in MPAP, whilst MPAP in patients with only pre-operative PHT and normal post-operative MPAP was unaffected. (25)

A small RCT by Morris et al 2000 including 12 patients looked at the use of iNO in patients with confirmed PHT post-operatively. Patients were randomized to receive either iNO or hyperventilation to a pH of 7.5 for 30 minutes followed by a washout period of 30minutes and then a combination of both treatment modalities for a further 30 minutes. They found a selective decrease in PAP and pulmonary vascular resistance index (PVRI) with the use of iNO but an additive increase in systemic vascular resistance index (SVRI) and decrease in cardiac index in patients treated with hyperventilation. (20)

Conclusions:

In patients with ARDS, iNO is shown to improve oxygenation only over a short period of time that does not extend beyond 24hours. Most studies however date back as far as 15 years, and there has since been a change to more lung protective ventilation strategies. Dosing regimens also differed between trials and it is not known if a sustained response was lacking due to tolerance associated with fixed dosing regimens. In addition, adjunctive maneuvers such as prone positioning, the use of neuromuscular blockade and HFOV were not always stratified for.

There has also been no demonstrated benefit in terms of mortality. Evidence however is poor and based on only a few trials in paediatrics. There is some evidence to show that early introduction of iNO following diagnosis of ARDS might result in a more sustained improvement in oxygenation however this has not been shown to translate to an improvement in mortality. There has been no evidence to show that subgroups of patients with different underlying pathology respond preferentially to treatment.
Most early trials have shown an increase in ventilator free, ECMO free and HFOV free days in patients treated with iNO, however a large retrospective trial published in 2016 was the first to show worsened outcomes in terms of morbidity and cost incurred due to prolonged treatment, ventilation and admission.

In patients with PHT following cardiac surgery, a Cochrane review showed no impact on mortality, MPAP, MAP, number of PHTCs and PaO2: FiO2. Notwithstanding, the American Heart Association and the European Consensus Guidelines suggest early use of iNO for its possible effect in decreasing the number of PHTCs and decreasing PVR. These guidelines are however established in resource rich settings. This likely indicates that whilst iNO may decrease PAP, there are other factors that contribute to mortality such as the right ventricle's ability to deal effectively with the increase in afterload caused by a raised PAP. In a resource poor setting there is a lack of evidence to support routine use of iNO in the post operative period.

Aims and Objectives of the Research Project:

The aim of this research project is to evaluate the use and outcomes of patients treated with iNO in our setting in order to judge its efficacy and whether continued use is justified.

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MANUSCRIPT IN PUBLICATION READY FORMAT:

A Review of the Use of Inhaled Nitric Oxide in the PICU at Red Cross Children's Hospital, 2011-2015: a Retrospective Cohort Study

Abstract:

Background:

Inhaled Nitric Oxide (iNO) functions as a selective pulmonary vasodilator. It is an expensive treatment that is often employed as rescue therapy for refractory hypoxaemia in acute respiratory distress syndrome (ARDS) and pulmonary hypertension (PHT) following cardiac surgery.

Objectives:

To describe the response to treatment with iNO. Secondary observations were deaths, co-morbidities of the patients treated, lengths of treatment and admission, and the cost of treatment.

Methods:

A retrospective descriptive study of all patients treated with iNO in the Paediatric Intensive Care Unit (PICU) at Red Cross War Memorial Children's Hospital (RCWMCH) from 2011-2015.

Results:

A total of 140 patients were treated with iNO during this time period, 82 were for PHT following cardiac surgery, 53 for ARDS and 5 for PPHN. A response to treatment was observed in 64% of the cohort as a whole, 80% of those with PPHN, 67% of those with PHT post-cardiac surgery, and 64% of those with ARDS. A longer duration of ICU and hospital admission, and higher in hospital mortality (53%) was seen in the group with ARDS, in particular those with adenoviral infection (63%), when compared to patients treated for PHT (18%) and for PPHN (20%).

There is no protocol in place guiding the use of iNO in our unit, and it was found that response to treatment was not being objectively measured and documented and that practise varied between clinicians.

Conclusions:
Considering the cost of treatment and lack of evidence to support beneficial effects of iNO therapy, its continued use in our resource poor setting should be guided by protocol.

Keywords: Nitric Oxide, iNO, Pulmonary Hypertension, Children, PICU

Introduction:

Nitric oxide (NO) has many features of an ideal pulmonary vasodilator. When inhaled, it has a rapid onset of action, is delivered directly to the lungs thereby minimizing systemic side effects, and improves ventilation-perfusion mismatch.[1]
It was first approved by the Food and Drug Administration (FDA) in 1999 for use in neonates with persistent pulmonary hypertension of the newborn (PPHN). Since then, there has been considerable interest in its potential role as a pulmonary vasodilator in other conditions, and it has been employed in severe, refractory hypoxaemia secondary to acute respiratory distress syndrome (ARDS) and in pulmonary hypertension (PHT) following cardiac surgery. [2] It is an expensive treatment, and whether or not it improves outcomes, remains controversial.

In patients with ARDS, inhaled nitric oxide (iNO) has been shown to only transiently improve oxygenation,[3-9] and no improvement in survival has been demonstrated.[1, 3, 4, 8-10] Most studies date back as far as 15 years and very few randomized controlled trials (RCTs) have been conducted in children.
In patients with PHT following cardiac surgery, an improvement in mortality following treatment with iNO has not been shown.[11, 12] Although some small studies have shown a decrease in the number of Pulmonary Hypertensive Crises (PHTCs) post-operatively,[12] pooled data shows otherwise. [11, 13] There has also been no significant impact on mean pulmonary artery pressure (MPAP), mean arterial pressure (MAP),[11] and oxygenation demonstrated.[11, 13] The American Heart Association and the European Consensus Guidelines suggest early use of iNO for its possible effect in decreasing the number of PHTCs and decreasing pulmonary vascular resistance (PVR).[9, 14, 15] These guidelines were, however, developed in well resourced settings.

Data published in resource limited settings such as ours is lacking. It is also not known whether there are subgroups of patients with different underlying diseases or co-morbidities that respond differently to treatment.
In our setting, there are no protocols in place guiding its use and the indications for use, dosage, weaning and discontinuation are usually left to the discretion of the attending physician.

Due to the paucity of evidence showing improved outcomes with the use of iNO and the difference in context between our setting and that of most of the published data, we aimed to review its use and the outcomes of patients treated at a tertiary paediatric hospital in the Western Cape.

Methods:

A retrospective, descriptive study was performed reviewing all patients treated with iNO in the PICU at Red Cross War Memorial Children's Hospital (RCWMCH) from 2011 - 2015. The 22 bed multi-disciplinary PICU admits approximately 1300 patients annually, including acute medical admissions, trauma patients and post-surgical patients. Approximately 60% of admissions are acute medical admissions and approximately 320 children are admitted electively post-cardiac surgery each year.
Approval was obtained from the RCWMCH Departmental Research Committee (Appendix C), as well as the Human Research Ethics Committee of the University of Cape Town (HREC Ref: 369/2016, Appendix B).
Patients that received treatment with iNO during the period being reviewed were identified using the electronic PICU database. All patients were included.
Data pertaining to response to treatment, duration of admission to ICU, underlying diagnoses, comorbidities and patient characteristics were extracted from the ICU electronic database and patient files. The duration of hospital admission and survival to discharge was obtained from the Clinicom database. Results of tests for retroviral disease, blood cultures and respiratory tract specimens were accessed via the National Health Laboratory System (NHLS). The presence of pulmonary hypertension was ascertained from the electronic database in the ICU as well as the department of cardiology's electronic database of echocardiograms.
Data relating to costs of using the treatment was obtained from the Pharmacy at RCWMH.

Data were entered into a standardized data collection sheet and transferred into a Microsoft Excel Spreadsheet. Names and folder numbers were removed to maintain confidentiality. Missing data were included and marked as unknown. Medians, proportions and interquartile ranges were determined using Stata 12.0 for Mac.

The number of patients that responded to treatment in the cohort as a whole as well as in subgroups with different underlying conditions was assessed as a primary outcome. A positive response to treatment was defined as any subjective improvement observed by the attending clinician.

Secondarily we looked at mortality, length of treatment, length of admission as well as co-morbidities present and their association with outcomes.

Results:

Study Population

A total of 140 patients received treatment with iNO from 2011 to 2015 at Red Cross War Memorial Children's Hospital. The demographics of these patients are shown in table 1.

Table 1. Patient Demographics

Males	72/140 (51)
Females	68/140 (49)
Age(months)	3 (1 - 9)
Weight(kilograms)	4.5 (3.2 - 8.2)
Premature at birth*	23/140 (16)
Underweight for age**	72/140 (51)
Pulmonary TB	4/140 (3)
HIV positive	5/140 (4)

Categorical data are presented as n (%) and continuous data as median(IQR).

*Gestational age <37weeks at birth

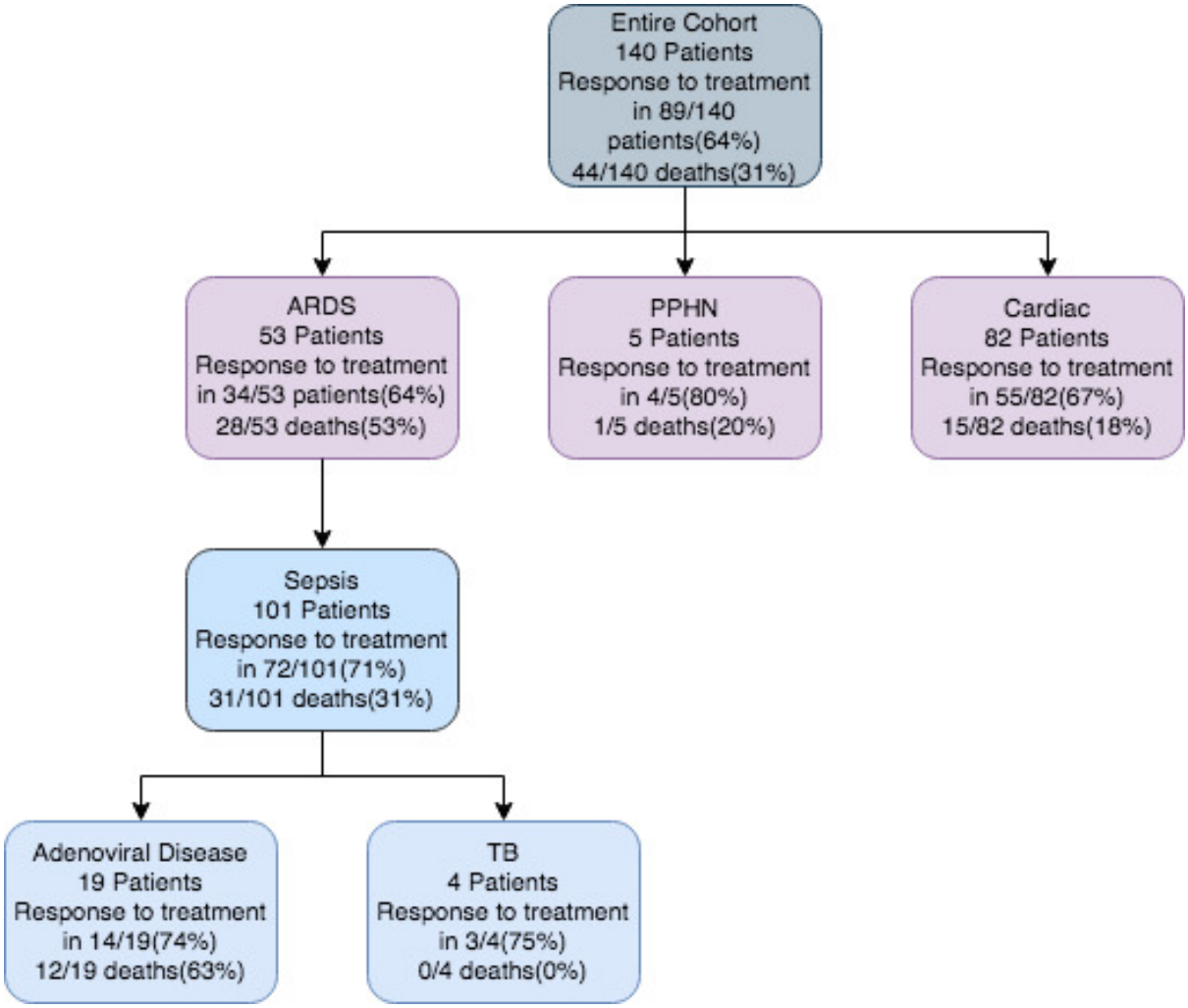
**Weight for age <-2 Z score on WHO growth chart

The reason for initiating iNO and response to treatment is shown in Figure 1.

The number of deaths in PICU compared with those at any point during hospital admission is shown in Table 2.

Reasons for Treatment

Figure 1. Reasons for Initiating Treatment with iNO



Of the cohort, 56% (n=78/140) received treatment with iNO as rescue therapy, either during an acute pulmonary hypertensive crisis following cardiac surgery or for refractory hypoxaemia thought to be due to related to raised pulmonary pressures in ARDS. Three percent (n=4/140) were treated prophylactically to prevent pulmonary hypertensive crises following cardiac surgery. The reason for initiation of treatment was not documented in 58 patients.

All patients that were treated for ARDS had either a positive blood culture, sputum culture or viral study on sputum. Of the children treated for ARDS, 8% (n=4/53) of these were admitted to the ICU for burns, 9% had abdominal surgery (n=5/53), and 47% had comorbid cardiac disease (n=25/53).

Oral sildenafil was used to facilitate weaning off iNO in 47% of patients (n=66/140).

Table 2. Deaths in ICU and Deaths in Hospital

	Deaths in ICU n(%)	Deaths in Hospital n(%)
Entire Cohort	36/140 (26)	44/140 (31)
PHT Post Cardiac Surgery	9/82 (11)	15/82 (18)
ARDS	26/53 (49)	28/53 (53)
PPHN	1/5 (20)	1/5 (20)
Rescue	29/115 (25)	34/115 (30)
Prophylaxis	0/8 (0)	2/8 (25)
WFA<-2*	19/72 (26)	25/72 (35)
WFA>-2**	16/63 (25)	18/63 (29)
HIV+	3/5 (60)	3/5 (60)
HIV-	33/134 (25)	41/134 (31)
Premature at Birth	8/23 (35)	9/23 (39)
Sepsis	24/101 (24)	31/101 (31)
TB	0/4 (0)	0/4 (0)
Adenovirus	11/19 (58)	12/19 (63)
Responders	22/93 (24)	26/93 (28)
Non-responders	5/20 (25)	6/20 (30)

*Weight for age <-2 z score on WHO growth chart

**Weight for age >-2 z score on WHO growth chart

The median PIM2 score was 0.09876 (IQR 0.0338 - 0.2827) in the cohort as a whole. In the group treated for ARDS, the median PIM2 score was 0.15966 (IQR 0.0269 – 0.3697) 0.2983 (IQR 0.25012 – 0.8993) in those treated for PPHN and 0.0796 (IQR 0.0336 – 0.2183) in those treated for PHT following cardiac surgery.

The duration of treatment with iNO and length of PICU and hospital stay is shown in Table 3.

The annual NO expenditure is shown in Table 4.

Table 3. Length of Treatment and Duration of Admission

	Length Treatment	ICU days	Hospital Days
	Median(IQR)	Median(IQR)	Median(IQR)
Cohort	3 (2 - 4)	15 (9 - 23)	29 (19 - 50)
PHT Post Cardiac Surgery	3 (2 - 4)	16 (9 - 22)	30 (20 - 51)
ARDS	3 (2 – 4)	13 (9 - 23)	28 (16 - 44)
Adenovirus	3 (2 - 6)	20 (11 - 26)	30 (21 - 52)
Adenovirus:Survivors	4 (2 - 6)	23 (20.5 - 28.5)	48 (29 - 60.5)
Adenovirus:Non-Survivors	3 (2 - 3)	11.5 (7 - 25.5)	25.5 (12 - 47)
PPHN	3.5 (2.3 - 4.8)	23 (6 - 50.5)	38 (13 - 61)
Underweight for age	3 (2 - 4)	16 (9 - 24.5)	33 (20 - 56.5)
HIV+	5 (2,7 - 5)	12 (4 - 17)	24 (13 - 33.5)
Premature at Birth	3 (2,3 – 3.75)	18 (10 - 26)	34 (18 - 52)
TB	4.5 (2 - 9)	23 (14.5 - 36.5)	38.5 (29 – 49.5)
Sepsis	3 (2 - 5)	18 (11 - 25)	32 (22 - 52)

Cost Per Annum:

Table 4. Annual Expenditure on iNO in South African Rands

Year	Cost
2011	**R345 563**
2012	**R229 824**
2013	**R178 558**
2014	**R352 676**
2015	**R334 755**
Total over 5 years:	**R1 441 376**

Discussion:

Our cohort compromised a young population with a median age of 3 months.

A positive response to treatment was seen in 64% of our cohort, and was similar in those treated for ARDS and those for PHT following cardiac surgery. This is similar to findings by Medjo[8] and Day[5] who reported positive responses in 69% and 58% of patients treated for ARDS respectively. Fioretto[16] reported a 94% response to treatment in patients with ARDS. This was however a small trial that likely may pre-dated the change to lung protective

ventilatory strategies. Our findings were limited as a standard definition of response to treatment was not used and a positive response was defined as any subjective improvement observed by the attending clinician.

We found that patients with sepsis and those with adenoviral disease demonstrated better responses to treatment than the rest of the cohort. The PIM 2 score in patients with adenoviral disease was higher than the rest of the cohort pointing to more severe disease in these patients. Dobyns[6] similarly reported that patients with more severe lung disease, those with a high OI on starting treatment, and those that are immunocompromised respond better to treatment. This may be related to the the role of iNO in modulating inflammation. iNO is used universally in our unit as rescue therapy in patients with ARDS that are failing treatment with ventilation alone. There is however some evidence to show that early initiation of treatment, irrespective of disease severity, improves outcomes.[16]
The literature shows that iNO effects only a transient improvement in oxygen saturation.[3-9] The rationale behind continued use, is that this temporary improvement in oxygenation may afford time for other therapies to be instituted or time for recovery of the underlying condition itself. Mortality however has not been shown to decrease with treatment with iNO. This is likely because these patients often have multi-organ dysfunction that is not improved by iNO, and because a response to treatment with improved oxygenation does not necessarily indicate an improvement in lung parenchymal disease.
In patients post-cardiac surgery, iNO therapy is employed on the premise PHTCs are the result of an increase in pulmonary vascular resistance and that reversing this would ameliorate the crisis. The lack of significant benefit with treatment however suggests that there are multiple factors contributing to the development of PHTCs, such as the ability of the right ventricle to handle an increase in PVR rather than the absolute increase in PVR itself.

Thirty-one percent of the the cohort demised in hospital. This value is higher than predicted by the Median Pim2 score (0.09876). Mortality in the ARDS group was 53%. This is higher than the reported mortality by Medjo,[8] Day[5], Dobyns[6] and Dowell[17] of 44%, 46%, 43% and 34%respectively. Mortality was 63% in those with adenoviral disease, despite the good response to treatment seen in this group. We found no difference in mortality in responders vs non-responders, in keeping with findings by Dowell.[17]

The cost of treating the cohort with iNO was R1 441 376 during the period being reviewed, which is a considerable strain on a resource limited setting. Gupta[10] was the first to show worse outcomes in terms of costs and morbidity in patients treated with iNO. We also report longer lengths of admission in patients with ARDS and those with TB. When the group with adenoviral infection is divided into those that survived to discharge and those that did not, we see markedly longer lengths of admission in the survivors, compounding the costs incurred in treating these patients.

It is difficult to draw any other conclusions from this study due to its limitations. It was a retrospective review without a control group, and many patient's files and data fields were missing. What we did find was that practice was not standardized in our unit due to a lack of protocols guiding the indications for use, dosage, weaning and discontinuation of treatment. Echocardiography, which is the standard non-invasive investigation of choice in diagnosing PHT recommended by the AHA and European Consensus Guidelines,[9, 14, 15] was not routinely used in our setting. The electronic cardiology database was accessed in an attempt to gather data on pulmonary pressures before and after treatment. This was abandoned to missing data in most patients.

A positive response to treatment was judged by the attending clinician and was usually based on an increase in oxygen saturation alone. There was no defined increment in saturation that was used to denote a response. Oxygenation indices were not calculated in any of the patients that were treated, and it was not possible to calculate these retrospectively due to missing patient records. Most studies defined a positive response as improvement in the oxygenation index (OI) of 20 percent from baseline[17] or an improvement in the ration of PaO2/FiO2 of more than 10[8,16]. Response to treatment as judged by an increase in oxygen saturation alone may have been confounded by adjunctive measures or therapies such as prone positioning, HFOV, neuromuscular blockade or changes in ventilator settings. Response to treatment, or lack thereof, was not well documented in patient files. In patients with PHT following cardiac surgery, iNO is often used in our unit as rescue therapy in patients with PHTCs. In all of the published literature, INO is used prophylactically in an attempt to prevent the onset of PHTCs.[12, 13, 18] We did not have access to data regarding the number of PHTCs in our cohort. Sildenafil is recommended for use when weaning treatment with iNO.[15] Only 47% of our cohort was treated concomitantly with Sildenafil when weaning treatment with iNO.

Conclusions:

We report that 64% of patients treated with iNO responded to treatment. Response to treatment was however poorly defined and not well documented in the clinical records. The use of iNO in the PICU was not standardized and the cost of treatment was high.
Despite this response to treatment with iNO, mortality in our cohort remained high, particularly in those with ARDS and adenoviral infection. Length of hospital and PICU admission were also longer in these patients. Further studies in patients with ARDS that stratify for underlying conditions are required. Further studies looking at long term outcomes and cost effectiveness in resource limited settings are also required to justify ongoing use of this expensive treatment.
In patients with PHT following cardiac surgery, the use of rescue vs prophylactic use needs to be further elucidated by good quality RCTs. It is also not clear whether the type of underlying cardiac condition is a predictor of response to iNO.
Overall, practice was not standardized in our unit and the cost of using this treatment is high.

The continued use of this treatment should be protocol driven, with clear criteria for indications for use, dosage and weaning, discontinuation, and determining a response to iNO. This should include the use of the oxygenation index and echocardiographic evidence of pulmonary hypertension.

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APPENDIX A: APPROVED STUDY PROTOCOL

A Review of the use of Inhaled Nitric Oxide in the PICU at Red Cross Children's Hospital

Investigator: Sandhia Padayachee

Supervisor: Shamiel Salie

Background:

Inhaled nitric oxide(iNO) has been approved by the Food and Drug Administration in the United States for the treatment of persistent pulmonary hypertension of the newborn(PPHN) in term/near term neonates since 1990. All other uses are considered off label and evidence to support its use in other settings is lacking(1).

Nitric oxide (NO) is primarily a modulator of vascular tone. It is synthesized from the terminal nitrogen of L-arginine by the enzyme nitric oxide synthase(NOS). There are three NOS isoforms that are expressed in the lung. NO activates guanyl cyclase, leading to the production of cyclic GMP which is a vascular smooth muscle relaxant (2). After inhalation, NO diffuses into the bloodstream and rapidly reacts with oxyhemoglobin to form methemoglobin and nitrate, and with deoxyhemoglobin to form iron-nitrosyl-haemoglobin(3). Inhaled NO(iNO) has many features of an ideal pulmonary vasodilator. It has a rapid onset of action, is delivered directly to the lungs thereby minimizing systemic effects, and also improves ventilation–perfusion mismatch since areas of the lung that are preferentially ventilated will receive more NO(2). It is also known to reduce right-to-left intra-cardiac shunting of blood through the foramen ovale and ductus arteriosus(4). Nitric oxide affects immune function by modifying the release of cytokines from alveolar macrophages, and causing inhibition of active adhesion molecules and the neutrophil oxidative burst involved in neutrophil migration. Attenuation of the inflammatory response, particularly in sepsis-induced lung injury, may therefore be an important factor in the success or failure of treatment with iNO(5). Inhaled nitric oxide has been demonstrated to exert platelet inhibitory effects resulting in prolonged bleeding time at both high and low doses. This has however been inconsistently reported in clinical trials(5).

Inhalation of low levels of NO appears to be safe. The major clinical toxic effects are due to the formation of Nitric Dioxide causing pulmonary edema and methemoglobinemia causing hypoxia, however this is only demonstrated at high doses >80ppm(3,4). It is recommended that serum methemoglobin be measured at approximately 8 hours and 24 hours after initiation of therapy, and

daily thereafter, and that INO should be weaned or discontinued if the methemoglobin level rises above 5%(4). INO-mediated lung injury results primarily from inactivation of surfactant protein A and decreased surfactant production. Prolonged INO exposure is also associated with a transient increase in markers of oxidative lung injury(4).

There is no standardized guideline for the dosage and weaning iNO. In the Neonatal Intensive Care Unit(NICU), a significant improvement in the ratio of pulmonary to systemic artery pressure is only seen when the iNO dose is at least 20 ppm. When iNO is stopped abruptly, rebound pulmonary hypertension sometimes develops. This can usually be overcome by slowly weaning iNO to 1ppm before discontinuation(2), increasing FiO2 by up to 20%(4), or the concomitant use of phosphodiesterase inhibitors(4). Sildenafil is recommended by the American Heart Association to prevent rebound pulmonary hypertension(PH) in patients who have evidence of a sustained increase in Pulmonary Artery Pressure(PAP) on withdrawal of iNO or require retreatment with iNO despite gradually weaning the dose(6). This rebound phenomenon is not seen when treatment with iNOis limited to 30 min. This supports prompt discontinuation of INO following a short trial in patients that don't respond(4).

The main use of iNO in the Paediatric Intensive Care Unit (PICU) at Red Cross War Memorial Children's Hospital (RCWMCH) has been for the management of pulmonary hypertension post cardiac surgery. A Cochrane review showed no difference in mortality, number of pulmonary hypertensive crises(PHC), changes in mean pulmonary artery pressure, mean arterial pressure or oxygenation with the use of iNO vs placebo or conventional management of pulmonary hypertensive crises. Conventional management includes hyperventilation, use of sodium bicarbonate, inotropic and vasodilatory agents, intravenous sedatives and neuromuscular blockade. A significant increase in the methaemoglobin level in patients treated with iNO was demonstrated, although they did not reach toxic levels(7). There are, however, trials that have shown lowered pulmonary vascular resistance, lower frequency of pulmonary hypertensive crises and shortened the time to extubation(8), and the American Heart Association recommends that in addition to conventional postoperative care, iNO should be used as the initial therapy for PHCs and right-sided heart failure(9). Although the frequency of PHC was reduced by the use of inhaled nitric oxide, they were not completely abolished. This implies that other pathogenic mechanisms in addition to a relative deficiency of nitric oxide are involved in postoperative pulmonary hypertension(8).

In our resource limited setting where extra corporeal membrane oxygenation(ECMO) is not available, rescue therapy with iNO is often employed as a last resort in children with refractory hypoxaemia from acute respiratory distress syndrome (ARDS). iNO is associated with a transient improvement in oxygenation in the first 72hours in older children and adults with ARDS, but there is no significant

effect on mortality(10,5,9). This is thought to be due to the fact that most patients dying from ARDS suffer from multiple organ system failure, therefore lung-selective therapy may not improve the overall survival rate(11). Limited data demonstrates a decrease in the duration of ventilation, length of stay in the intensive care unit and length of stay in hospital(10).
Although the evidence shows no benefit on mortality, most studies did not stratify for primary disease or take into account combined treatment modalities such as prone positioning or high Positive end expiratory pressure or low tidal volume protective lung ventilation(10).

iNO appears to increase the risk of renal impairment among adults but not the risk of bleeding or methaemoglobin or NO2 formation(10). A meta-analysis actually demonstrated a trend towards increased mortality in patients receiving nitric oxide(9). Possible reasons for non response to treatment are the prolonged fixed dosing regimens that were used in most trials may have attenuated benefit over time because of increased sensitisation, dampening the oxygenation benefit while continuing to expose patients to oxidative damage, or confounding by concurrent use of a harmful mechanical ventilation strategy(9). Although there has been a consistent lack of a mortality benefit across trials, the possibility of some subgroups of patients benefiting from nitric oxide has not been studied sufficiently. In an adult study, significant and sustained improvement in oxygenation in patients with ARDS due to H1N1 virus infection was demonstrated as opposed to the transient response that is usually seen(12). This raises the possibility that specific pulmonary infections, opposed to extra pulmonary causes of ARDS, behave differently in response to iNO. The use of nitric oxide as rescue therapy for patients with critically low oxygenation is also not well researched, and the short term improved oxygenation achieved may create a window for other strategies to improve lung function, such as treatment of the underlying cause of ARDS(9).

In term/near term infants with PPHN, response to iNO is not shown to be superior to that of high frequency oscillatory ventilation(HFOV) alone(13). If used it is recommended that INO therapy be instituted early in the disease course(4). Although iNO reduces the need for ECMO and improves oxygenation, mortality rates are not decreased. Echocardiographic evidence of PPHN is not shown to affect outcome. The incidence of disability and deafness is similar between tested survivors who received nitric oxide or not(1)and lung function during early infancy was not adversely affected(4). Sildenafil is a reasonable adjunctive therapy for infants with PPHN who are refractory to iNO, especially with an oxygenation index that exceeds 25(6).

In very ill preterm infants, although authors of a cochrane review concluded that iNO as rescue therapy does not appear to be effective(14) AHA guidelines support its use in severe hypoxemia that is due primarily to PPHN physiology rather than parenchymal lung disease, particularly if associated with prolonged rupture of membranes and oligohydramnios, as well as in infants with established

BPD and symptomatic PH(6). The outcome of infants with congenital diaphragmatic hernia(CDH) is not improved, possibly due to left ventricular dysfunction complicating CDH(6).

Aims:

To review the PICU use of nitric oxide at RCWMCH to better understand its effect on patient outcomes, in an effort to guide future use of this expensive intervention.

Objectives:

Primary:

1. To document the response of patients treated with iNO.

Secondary:

1. To describe the indications for starting treatment with iNo in the PICU.
2. To describe clinical characteristics of patients that responded to iNO.
3. To determine whether certain patient characteristics are associated with a response to iNo.
4. To describe the PICU and hospital mortality rates of children treated with iNo.
5. To document the cost per annum of this intervention.

Methods:

This is a retrospective cohort study reviewing all patients treated with nitric oxide in the PICU from 2011-2015. Data will be extracted retrospectively from patient files as well as the PICU database. All data will be captured using the data sheet attached and entered into an electronic database. After all required data has been captured, names and folder numbers will be removed and patients will be assigned random numbers to maintain confidentiality. This will then be submitted to a statistician for analysis.

Information regarding cost of treatment will be obtained from the Pharmacy at RCWMCH.

Study Setting:

This study is set in the PICU at RCWMCH. The 22 bed multi-disciplinary PICU admits approximately 1300 patients annually. Approximately 60% of admissions are acute medical and approximately 250 children are admitted electively post cardiac surgery.

Study Population:

We estimate that 40 patients per annum are treated with iNO at RCWMCH, which translates to approximately 200 patients over the 5year period studied. This includes patients post cardiac surgery, those with confirmed pulmonary hypertension, diaphragmatic hernias, and acute respiratory infections. Very few newborns with PPHN are treated at RXH PICU as they are managed predominantly at specialized neonatal units.
All patients that were treated with iNO from 2011-2015 will be included in the study with no exclusions.

Data Analysis:

Findings will be presented using tables, graphs and descriptive statistics (as appropriate).
Nominal categorical data will be generated for the primary outcome investigated. The data will be described as proportions and percentages. The hypothesis will be tested using contingency tables and either the Chi squared test for association or the Fisher Exact test. We will use the cochrane rule to decide which test to use. We will use the same analysis to test for associations between patient characteristics and outcomes.
Numerical data will be generated for no of days treated, highest dose of treatment used, no of days in ICU, PIM2 score on admission and oxygenation index before treatment. These will be described as means with standard deviations or medians with interquartile ranges if the data is skewed.
Trends in the number of patients treated over the 5 year period will be presented using raw data on a histogram.
A significance value of $P<0.05$ will be used for all analysis. Population estimates will be described using 95% confidence intervals.
Data analysis will be performed using Stata/IC(Statacorp) for Windows, version 12.1.
A statistician will be consulted to verify all calculations.

Dissemination of information:

The results of this study will be written up and reported in the form of a research report that meets the requirements of the MMed (Paediatrics) degree program.
Data will be presented to the Department of Paediatrics and submitted for publication in a peer reviewed journal.

Significance:

This review will help guide and rationalize the use of iNO in different patient groups.

Risks to study participants:

Since the study is a retrospective review, there are no risks to patients.

Schedule:

	May	Jun	Jul	Aug	Sep	Oct	Nov	Dec	2017 Jan	Feb	Mar	Apr	May	Jun	Jul
Completion of protocol	X														
Ethics approval			X												
Literature review					X										
Data collection									X						
Data analysis												X			
Final write up														X	
Research submission															X

Ethical considerations:

As this is a retrospective study, consent from each individual parent will not be sought. Ethical approval from the Human Research Ethics Committee of the University of Cape Town and RCWMCH Research Committee will be obtained prior to beginning the research project. The study will be developed and carried out in accordance with the Declaration of Helsinki, 2013.
Beneficence: Although the study does not directly benefit the patients being studied, we aim to improve patient care in the future by reviewing current practice.
Non-maleficence: No individual will be harmed as a result of this study.
Autonomy and consent: As this is a retrospective trial, consent from each individual parent will not be sought.
Confidentiality: Patient confidentiality will be strictly maintained. Identifying details of patients will be omitted once data capturing is completed by the investigator.
Actions related to gross abnormalities: If any gross adverse outcomes become evident during the study, clinical specialists will be consulted.

Strengths and limitations:

This study is limited in that it is a retrospective review and all required data may not have been adequately recorded . Furthermore there isn't a control population for comparison. It will however give a reasonable overview of outcomes achieved and possible predictors of outcomes to guide future management protocols in our setting.

Budget:

All data will be captured electronically and no costs will be involved. The cost of recruiting a statistician will be borne by the Registrar.

References:

1. Finer N, Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term. The Cochrane Library: 2006, Issue 4
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3. Ichinose F, Roberts JD Jr, Zapol WM. Inhaled Nitric Oxide: A Selective Pulmonary Vasodilator: Current Uses and Therapeutic Potential. Circulation: 2004; 109: 3106-3111
4. DiBlasi RM, Myers TR, Hess DR. Evidence-Based Clinical Practice Guideline: Inhaled Nitric Oxide for Neonate With Acute Hypoxic Respiratory Failure. Respiratory care journal 2010.

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7. Bizzarro M, Gross I, Barbosa FT. Inhaled nitric oxide for the postoperative management of pulmonary hypertension in infants and children with congenital heart disease. The Cochrane library: 2014, issue 7
8. Miller OI, Fong Tang S, Keech A, Pigott NB, Beller E, Celermajer DS. Inhaled nitric oxide and prevention of pulmonary hypertension after congenital heart surgery: a randomised double-blind study. The Lancet Vol 356 • October 28, 2000.
9. Adhikari NKJ, Burns KEA, O Friedrich J, Granton, Cook DJ, O Meade M. Effect of nitric oxide on oxygenation and mortality in acute lung injury: systematic review and meta-analysis. BMJ, doi:10.1136/bmj.39139.716794.55
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11. Steinhorn RH. Therapeutic approaches using nitric oxide in infants and children. Radic Biol Med: September 2011,March 2007
12. Funk DJ, Kumar A. Inhaled nitric oxide in patients with the acute respiratory distress syndrome secondary to the 2009 influenza A (H1N1) infection in Canada. Canadian Journal of Anesthesia: February 2013, Volume 60, Issue 2.
13. Kinsella JP, Truog WE, Walsh WF, Goldberg RN, Bancalari E, Clark RH, Mayock DE, Redding GJ, deLemos RA, Sardesai S, McCurnin DC, Yoder BA, Moreland SG,Cutter GR, Abman SH. Randomized, multicenter trial of inhaled nitric oxide and high frequency ventilation in severe persistent pulmonary hypertension of the newborn. Pediatric Research: 1996;39:222A.
14. Barrington KJ, Finer N. Inhaled nitric oxide for respiratory failure in preterm infants. Cochrane Neonatal Group. Published Online: 8 DEC 2010

APPENDIX B: ETHICS APPROVAL

UNIVERSITY OF CAPE TOWN

FACULTY

This serves as notification of annual approval, including any documentation described below.

☑ Approved	Annual progress report	Approved until/next renewal date	30/12/2019
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	/2/18

Comments to PI from the HREC
N/A

Date (PI submitting this form)	04 · 12 · 2018		
HREC REF Number	369/2016	Current Ethics Approval was granted until	01 12
Protocol title	A Review of the use of Nitric oxide the Paediatric ICU at Red Cross Hospital 2011 - 2015.		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes ☑ No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study	N/A		
Principal Investigator	Dr S Saule		
Department / Office Internal Mail Address	shamiel.saule@uct.ac.za		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

FHS016: Annual Progress Report / Renewal

HREC office use only (FWA00001637; IRB00001938) This serves as notification of annual approval, including any documentation described below.			
☐ Approved	Annual progress report	Approved until/next renewal date	30 / 11 / 18
☐ Not approved	See attached comments		
Signature Chairperson of the HREC		Date Signed	13/12/2017

Comments to PI from the HREC

Principal investigator to complete the following:

1. Protocol information

Date (when submitting this form)	11.12.2017		
HREC REF Number	369/2016	Current Ethics Approval was granted until	30th June 17
Protocol title	A review of the use of inhaled nitric oxide in the paediatric ICU at Red Cross Childrens Hospital		
Protocol number (if applicable)			
Are there any sub-studies linked to this study?	☐ Yes ☒ No		
If yes, could you please provide the HREC Ref's for all sub-studies? Note: A separate FHS016 must be submitted for each sub-study.	N/A		
Principal Investigator	Dr S Salie		
Department / Office Internal Mail Address	Shamiel.salie@uct.ac.za		

(Note: Please complete the Closure form (FHS010) if the study is completed within the approval period)

UNIVERSITY OF CAPE TOWN
Faculty of Health Sciences
Human Research Ethics Committee

Room E53-46 Old Main Building
Groote Schuur Hospital
Observatory 7925
Telephone [021] 406 6626
Email: shuretta.thomas@uct.ac.za
Website: www.health.uct.ac.za/fhs/research/humanethics/forms

09 June 2016

HREC REF: 369/2016

Dr S Salie
Paediatric Intensive Care Unit
Red Cross War Memorial Children's Hospital

Dear Dr Salie

PROJECT TITLE: A REVIEW OF THE USE OF INHALED NITRIC OXIDE IN THE PAEDIATRIC ICU AT RED CROSS CHILDREN'S HOSPITAL (MMed candidate- Dr S Padayachee)

Thank you for submitting your study to the Faculty of Health Sciences Human Research Ethics Committee.

It is a pleasure to inform you that the HREC has **formally approved** the above-mentioned study.

Approval is granted for one year until the 30th June 2017.

Please submit a progress form, using the standardised Annual Report Form if the study continues beyond the approval period. Please submit a Standard Closure form if the study is completed within the approval period.
(Forms can be found on our website: www.health.uct.ac.za/fhs/research/humanethics/forms)

Please quote the HREC REF in all your correspondence.

Please note that the ongoing ethical conduct of the study remains the responsibility of the principal investigator.

Please note that for all studies approved by the HREC, the principal investigator **must** obtain appropriate institutional approval before the research may occur.

The HREC acknowledge that the student, Dr Sandhia Padayachee will also be involved in this study.

Yours sincerely

PROFESSOR M BLOCKMAN
CHAIRPERSON, FHS HUMAN RESEARCH ETHICS COMMITTEE
Federal Wide Assurance Number: FWA00001637.
Institutional Review Board (IRB) number: IRB00001938
This serves to confirm that the University of Cape Town Human Research Ethics Committee complies to the Ethics Standards for Clinical Research with a new drug in patients, based on the Medical

APPENDIX C: Departmental Research Committee Approval

Western Cape Government
Health

Dr AS Booysen
Manager: Medical Services
Email: Tony.Booysen@Westerncape.gov.za
Tel: +27 21 658 5788 fax: +27 21 658 5166
RXH: RCC28

Dr S Salie
Red Cross War Memorial Children's Hospital

Dear Dr S Salie

APPROVAL OF RESEARCH

PROJECT TITLE: A REVIEW OF THE USE OF INHALED NITIC OXIDE IN THE PICU AT RED CROSS WAR MEMORIAL CHILDREN'S HOSPITAL

It is a pleasure to inform you that approval is hereby granted to conduct the above-mentioned study at Red Cross War Memorial Children's Hospital.

Yours sincerely

Dr AS Booysen
Manager: Medical Services
Date: 07.07.16

APPENDIX D: Data Collection Sheet

DATA COLLECTION SHEET

Name:	
Folder No:	
Date of hospital admission:	
Date of ICU admission:	
Sex:	
Age (months):	
Weight on admission (kilograms):	
Underlying Condition: (post cardiac surgery/ARDS/PPHN/diaphragmatic hernia):	
Co-morbidities: (RVD/TB/cardiac lesion):	
Pre-existing pulmonary hypertension(yes/no):	
Nutritional status: (Normal/Moderate acute malnutrition/severe acute malnutrition):	
PIM 2 score:	
RVD Status: (positive/negative)	
Reason for starting iNO: (prophylaxis/rescue)	
Oxygenation index before treatment:	
Oxygenation index after treatment:	
Increase in SpO2 with iNO:(yes/no)	
Length of treatment with iNO in days:	
Max iNO dose in ppm:	
Sildenafil: (yes/no)	
Death in ICU: (date if yes)	
Length of ICU admission (days):	
Death in Ward: (date if yes)	
Length of hospital admission (days):	
Survivial to discharge: (yes/no)	

APPENDIX E: AUTHOR GUIDELINES: SOUTH AFRICAN JOURNAL OF CRITICAL CARE

General article format/layout

General:

- Manuscripts must be written in UK English (this includes spelling).
- The manuscript must be in Microsoft Word or RTF document format. Text must be 1.5 line spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes). Pages and lines should be numbered consecutively.
- Please make your article concise, even if it is below the word limit.
- Qualifications, ***full*** affiliation (department, school/faculty, institution, city, country) and contact details of ALL authors must be provided in the manuscript and in the online submission process.
- Abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.
- Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160.
- Quotes should be placed in single quotation marks: i.e. The respondent stated: '...'
- Round brackets (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.
- Medical drugs should be referred to by their generic name although the trade name may be used in brackets in the text once if unique.

Research

Guideline word limit: 3 000 words (excluding abstract and bibliography)

Research articles describe the background, methods, results and conclusions of an original research study. The article should contain the following sections: introduction, methods, results, discussion and conclusion, and should include a structured abstract (see below). The title of the manuscript should concisely describe the study but should not include the outcome. The introduction should be concise – no more than three paragraphs – on the background to the research question, and must include references to other relevant published studies that clearly lay out the rationale for conducting the study. Some common reasons for

conducting a study are: to fill a gap in the literature, a logical extension of previous work, or to answer an important question. If other papers related to the same study have been published previously, please make sure to refer to them specifically. At the end of the introduction clearly state the aim or objective of the study. The primary and secondary outcomes should be specified.

In the Methods section describe in sufficient detail so that others would be able to replicate the study should they need to. Sections of the methods that have been described in previous publications need only be referenced. The statistical methods should be described. Where appropriate, sample size calculations should be included to demonstrate that the study is not underpowered.

Results should describe the study sample as well as the findings from the study itself, but all interpretation of findings must be kept in the discussion section. The conclusion should briefly summarise the main message of the paper and provide recommendations for further study.

The discussion should be confined to an interpretation of your results with respect to your stated aim and if applicable, a comparison to the results of similar studies. The strengths and weaknesses of your study should be discussed.

The conclusion should be confined to an interpretation of the results of the study and a recommendation if applicable.

- May include up to 6 illustrations or tables.
- References should only include the most recent and relevant articles. A maximum of 30 references is advised.

Structured abstract

- This should be no more than 250 words, with the following headings:
    - **Background:** why the study is being done and how it relates to other published work.
    - **Objectives:** what the study intends to find out

- **Methods:** must include study design, number of participants, description of the research tools/instruments, any specific analyses that were done on the data.
- **Results:** first sentence must be brief population and sample description; outline the results according to the methods described. Primary outcomes must be described first, even if they are not the most significant findings of the study.
- **Conclusion:** must be supported by the data, and be aligned with the conclusion in the main text.
- Please ensure that the structured abstract is complete, accurate and clear and has been approved by all authors. It should be able to be intelligible to the reader without referral to the main body of the article.
- Do not include any references in the abstracts.

References

NB: Only complete, correctly formatted reference lists in Vancouver style will be accepted. If reference manager software is used, the reference list and citations in text are to be unformatted to plain text before submitting.