Use Of Inhaled Nitric Oxide In ICU – When Is A Therapy Trial Enough?

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Introduction

Inhaled nitric oxide (iNO) can be utilized as a rescue treatment option in critically ill patients with refractory hypoxaemia. Its use also extends to the potential reversal of pulmonary vascular resistance by pulmonary vasodilation.[1]

Despite anecdotal reports of increased use of iNO amidst the COVID-19 pandemic, its use remains controversial due to limited evidence regarding efficacy and potential side effects.[2] Furthermore, it requires additional equipment and consumables and its relatively infrequent use means staff may be unfamiliar with the treatment.

iNO requires careful assessment and monitoring of potential therapeutic benefit as well as side effects. Complications implicate include methemoglobinemia, NO_2 production and renal failure.[1]

Objectives

1) **To investigate use of iNO within our adult critical care unit in order to identify potential quality improvements that could be made to the delivery of this therapy.**
2) **To clarify the proportion of patients who demonstrated a favourable PaO2/FiO2 (PF) response to iNO.**

Methodology

We conducted a single-centre retrospective analysis of consecutive patients treated with iNO on the General & Cardiac Intensive Care Unit at Manchester Royal Infirmary between 01/01/2018 and 25/06/2021.

Data was extracted from electronic patient records on patient characteristics, indication for iNO, starting dose, ventilatory characteristics, change in PF ratio and ICU outcome. Results were recorded at iNO initiation, 2, 6, 12 and 24 hours. Comparable assessments in the final analysis were made between patients who had a complete data set across consecutive time intervals.

A responder was defined by improvement in the PF ratio of ≥20% relative to the ABG at initiation of iNO at any point up to 6 hours after initiation.

T-tests were performed to determine statistical significance.

Results

Variable	Response
Age, (years), mean, (SD), (n=37)	51, (14)
Sex, n, (%), (n=37)	
Female	6, (16%)
Male	31, (84%)
Diagnosis, n, (%), (n=37)	
COVID-19	27, (73%)
Non-COVID ARDS	4, (11%)
Primary pulmonary arterial hypertension	1, (3%)
Other	5, (14%)
Primary indication for iNO, n, (%), (n=37)	
Acute Respiratory Failure	32, (86%)
Right Ventricular Failure	5, (14%)
ICU Length of Stay pre iNO, days, mean, (SD), (n=37)	11, (11)
Invasive Ventilation pre iNO, hours, mean, (SD), (n=37)	163, (188)
Baseline Characteristics of Patients Treated with iNO	

By 6 hours, 14/37 patients (37%) had achieved a positive response.

There was a significant increase in PF ratios at 6 hours compared to baseline in responders (15.9kPa vs 12.0kPa, p=0.04) but no significant difference at any other time point.

At 24 hours, one patient showed a positive response who had not previously shown a response.

There was no difference in the duration of therapy in responders vs non responders (76 vs 85 hours, p=0.72).

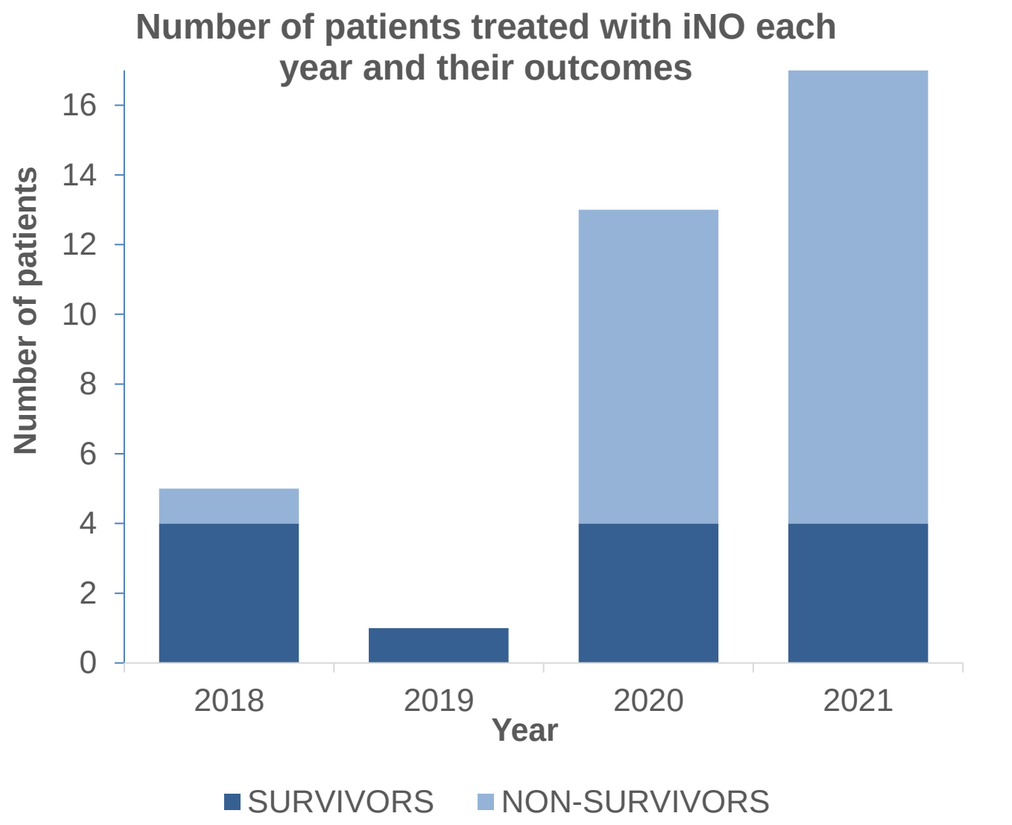

Figure 1. iNO set-up.[3]

Local protocol outlines that iNO should be delivered via the ventilatory circuit to intubated patients at a continuous dose of 20ppm for up to 14 days.

Patients response to therapy is assessed at 1 hour.

Once the primary disease process has been addressed and adjunct therapy optimised, patient must be assessed daily for suitability to wean. The weaning process is important to avoid rebound pulmonary hypertension.

Discussion

There has been a marked increase in the use of the iNO since the start of the COVID-19 pandemic.

We observed that in some patients, iNO was associated with an increase in PF ratio at 6 hours, though we did not observe a significant difference at any other time point. iNO may therefore offer a temporary reprieve in the face of severe hypoxia, offering clinicians some time to consider whether any further therapeutic options remain.

Despite the lack of identifiable benefit beyond 6 hours, patients were on average treated for approximately 5 days with iNO. Interestingly we did not observe a difference in the treatment duration of patients who had shown a response to iNO in the first 6 hours versus those who showed no response. This may suggest clinician reluctance to discontinue therapy once started, possibly through fear of precipitating deterioration, belief that iNO has halted decline or reluctance to recognize futility when there are few other therapeutic options.

Clinicians should regularly review the effect of iNO and consider carefully whether an appreciable improvement has been achieved. In patients who have not responded by 6 hours, a subsequent positive response is unlikely and should prompt consideration of cessation of this therapy.

We observed that patients had typically been in ICU for several days prior to iNO trial, in keeping with its current place as a rescue therapy. Whether earlier use of iNO may have greater effect is an interesting avenue for further research.

Conclusions

iNO therapy may offer short-term improvement in oxygenation in a minority of patients by 6 hours.

Duration of iNO therapy appeared similar regardless of response.

The rising use of iNO since the start of the COVID-19 pandemic should prompt units to evaluate their own practice with this therapy.

We advocate for ‘non-responders’ to be identified earlier and for consideration of discontinuation of iNO to be made where there is no objective clinical response.

References

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