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QUALITY IMPROVEMENT ARTICLE

A quality improvement project improving the value of iNO utilization in preterm and term infants

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Abstract

Objective Inhaled NO (iNO) is used in the NICU for management of hypoxemic respiratory failure. The cost of iNO is significant and does not consistently improve outcomes in infants <34 weeks.

Project design Our team used The Model for Improvement to design a quality improvement project to utilize iNO for appropriate indications, ensure response to therapy and initiate timely weaning. The project was carried out at a Level IV NICU and successful interventions spread to a smaller Level III NICU.

Results This project demonstrated significant improvement in all measures; total iNO hours per month, average iNO hours per patient, and the percentage of prolonged iNO courses. With an estimated cost of $115/h, the cost per patient for iNO use declined by half from $21,620 to $10,580.

Conclusions Our team improved the value of iNO utilization at our institution and spread successful interventions to another NICU in our network.

Introduction

Background

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator indicated for management of hypoxemic respiratory failure secondary to persistent pulmonary hypertension (PPHN) in the neonatal intensive care unit (NICU). iNO use has improved survival for term and early term infants with PPHN by decreasing mortality and the need for extracorporeal membrane oxygenation (ECMO) support [1]. A Cochrane Review of multiple randomized controlled trials showed that use of iNO for treatment of hypoxic respiratory failure or for prevention of bronchopulmonary dysplasia (BPD) did not consistently improve respiratory or neurodevelopmental outcomes in infants <34 weeks [2]. The use of iNO is not approved by the Federal Drug Administration in infants <34 weeks [3], and routine use in this population is not supported by the National Institute of Health [4], nor American Academy of Pediatrics [5].

There continues to be considerable variation in iNO utilization in preterm infants across the United States [6]; its use has persisted despite recommendations for limitations in this population [7]. The cost of using iNO is significant [8] and variable based on institutional contracts. In term or early term infants, iNO use increased total costs per patient but was found to be cost-effective overall [9]. A study evaluating the cost of iNO in preterm infants showed that it did not have a favorable cost-effectiveness profile at 1 year corrected age [8]. Therefore, it is important to utilize iNO for appropriate indications, ensuring response to therapy, and initiating timely weaning to maximize value.

Previous studies have demonstrated that guidelines for iNO use and an iNO stewardship program can significantly decrease the number of hours and cost associated with iNO utilization [10–12]. The population of preterm infants was not specifically addressed, but would likely benefit from similar methods for improving iNO utilization.

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Setting

Norton Children's Hospital neonatal ICU comprises a 105 bed Level IV regional perinatal referral center with over 1300 admissions annually. Our downtown campus serves as the academic teaching center for the University of Louisville with academic neonatologists, neonatal fellows, neonatal nurse practitioners, and over 300 staff nurses. In 2006, our center participated in the NO CLD research study in which infants <1250 g were randomized to 24 days of prophylactic iNO or placebo with a primary outcome of survival without BPD [13]. This study found a small but statistically significant decrease in the rate of survival without BPD in the group treated with iNO with no short-term adverse effects. Since that study, results of multiple randomized controlled trials, meta-analyses and an individualized patient data meta-analysis have not consistently confirmed these results in a broader population and do not support the routine use of iNO in improving survival or preventing BPD in preterm infants [2, 14, 15]. Despite these findings, the culture of our unit has been that iNO is safe and potentially beneficial in the preterm population. This led to indiscriminate use of iNO and persistent utilization of the original research protocol consisting of 24 days of gradual weaning, contributing to prolonged iNO courses.

Problem description

At Norton Children's Hospital NICU, the length of iNO course per patient from January 2017 to April 2018 ranged from 3 to >1000 h. Preterm infants <34 weeks comprised a substantial proportion of those infants utilizing iNO (38% in 2017) and disproportionately contributed to prolonged courses of iNO, comprising 48% of courses >120 h and 78% of courses >336 h. Our center had no standard recommendations for iNO initiation and management in term or preterm infants resulting in wide variability in provider utilization. Our institution was experiencing denials of service for iNO by insurance providers, particularly in infants <34 weeks. Our team was developed with the support of key stakeholders to improve value when utilizing iNO in our NICU.

Project aims

The global aim of this project was to improve iNO utilization in the NICU so that iNO is used when indicated and weaned in a timely and appropriate manner to reduce unnecessary cost and waste. The Institute of Medicine Aims addressed during this project included improving effectiveness and decreasing waste. Our specific aims were as follows:

(1) To decrease total iNO hours per month from a baseline mean of 1585 h to <1200 h per month (25% decrease) by December 2018.
(2) To decrease the average number of hours of iNO therapy per patient per month from a mean of 100 h to <75 h (25% decrease) by December 2018.
(3) To decrease the percentage of patients with length of iNO treatment >120 h from a mean of 52% to <25% by December 2018.

Methods

The Model for Improvement was used as a guiding framework for this project and principles of high reliability were used to design interventions [16]. Our theory was that a standardized framework for initiating, managing and weaning iNO would support timely and effective clinical decision making. This would decrease variability and provide a lifesaving intervention to those patients that demonstrated a clinical response and limit use where it was ineffective. Our Quality Improvement team consisted of neonatal faculty, respiratory therapy (RT), and nursing leadership. Other key stakeholders included the hospital medical director and ICU nursing administrator, who supported the project and were vested in the results.

Our team developed the above aim statements and a key driver diagram for the project (see Supplementary material). The key drivers focused on providing evidence-based recommendations for iNO initiation, management, and weaning, as well as elements to support use, change the culture surrounding iNO utilization, and provide feedback to our teams.

Process mapping of our baseline process for iNO utilization demonstrated that iNO was currently initiated at provider discretion, the threshold to initiate weaning was variable, and weaning parameters were based on provider preference. The bedside nurse and RT were under-utilized in this model. The team used principles of high reliability [17] to redesign this process to facilitate standardization and incorporate nursing and RT expertise (see Supplementary material).

iNO guidelines were developed based on best evidence when available, provider experience and review of other institutional guidelines (Fig. 1). A checklist was included prior to iNO initiation to help guide practitioners in maximizing oxygen carrying capacity and ventilation prior to escalation to iNO. Objective indications for iNO initiation were included. Nonresponder and partial responder pathways were developed to facilitate early discontinuation of iNO within the first 1–2 h in those infants who did not

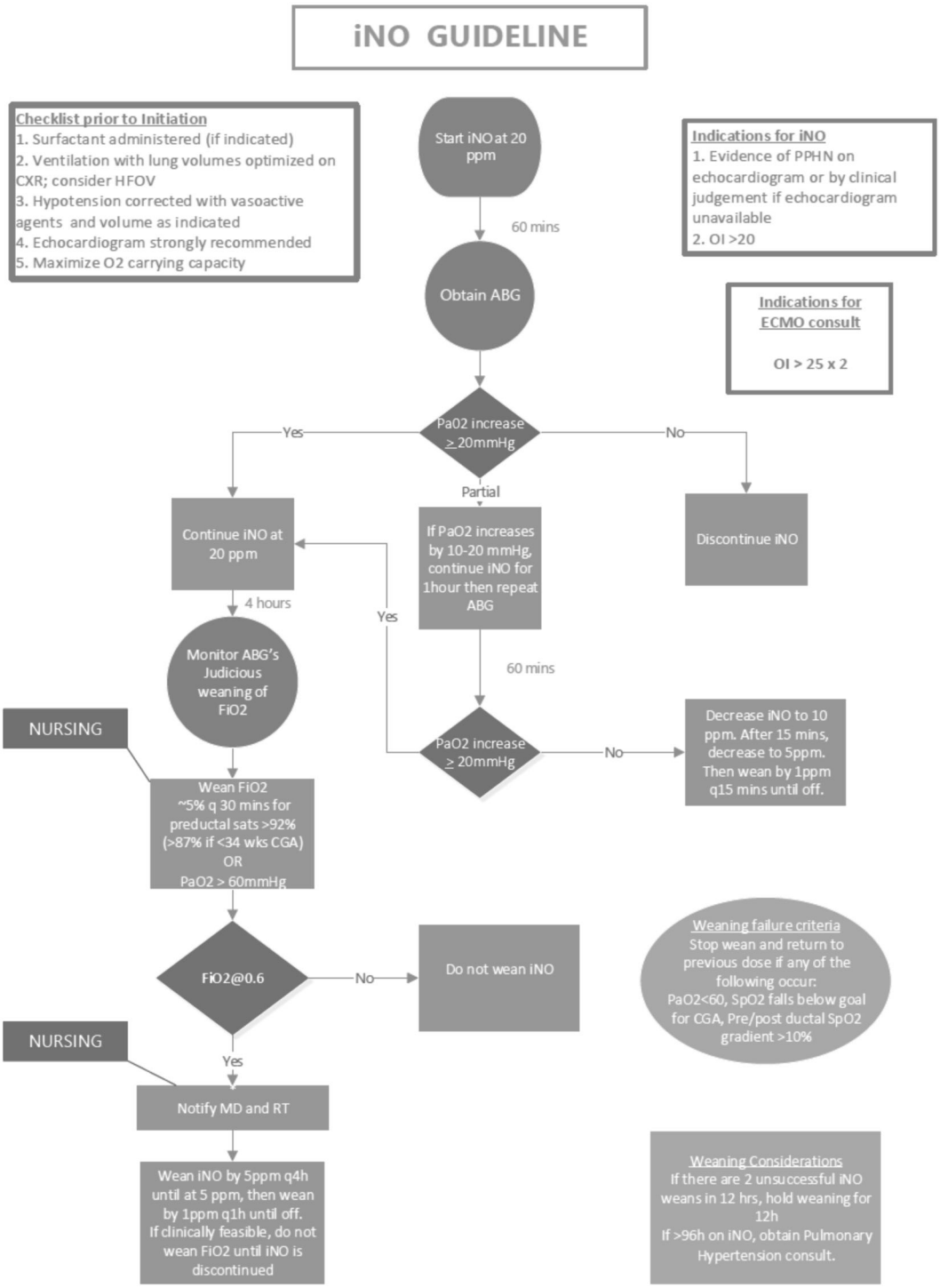

Fig. 1 iNO management guideline. Guidelines incorporated iNO initiation criteria, a nonresponder and partial responder pathway, a physiologic trigger to wean iNO and an automated weaning process driven by RTs and nurses from the bedside.

demonstrate a clinical response. A weaning pathway was developed to promote timeliness and automation. In the new process, a trigger for physiologic readiness to wean was determined; once a patient hit this threshold (FiO_2 of 0.6) there would be notification of the provider and RT by the bedside nurse in order to implement automatic weaning guidelines.

A key clinical component of the guidelines was judicious weaning of FiO_2 while weaning iNO. Both oxygen and iNO are potent pulmonary vasodilators, and failed iNO weans

were thought to be related to concurrent adjustments of both these inhalants. Our guidelines encouraged a change in practice where FiO_2 would remain at 0.6 until iNO was weaned off, unless saturation ranges were outside of the goal for gestational age. By weaning one vasodilator at a time, we could be more effective and timelier in decreasing both.

The last practice change to our guidelines was the recommendation for a pulmonary hypertension team consult if the patient was unable to be weaned off iNO within 4–5 days. This recommendation allowed for earlier recognition of infants with a complicated course who might benefit from alternative management options.

PDSA cycles were performed to test the content of the guidelines and changes made based on feedback. Further PDSA cycles were performed testing methods to support use of the new process. A checklist and the algorithm were placed on the iNO tanks by the RT at the time of iNO initiation. Patients on iNO were added to our twice daily shift huddle to facilitate awareness and discussion around plans for iNO and weaning. A NICU iNO order was developed, encompassing the key pieces of the algorithm. Monthly data were presented in the form of control charts at NICU division meetings, clinical practice team meetings and displayed at the huddle board. Surveys were done to gain feedback about these new processes. "Just in time" education was provided at the bedside by the physicians and RTs when iNO was initiated. Interventions were quickly adopted and spread to all practitioners in the unit.

Measures and analysis

Baseline data were collected from January 2017 to April 2018 from an existing database maintained by unit RTs, including month/year, hours of iNO per patient, gestational age at time of iNO initiation, and indication for iNO. Infants with a diagnosis of congenital diaphragmatic hernia were excluded from our data set, as iNO use in this population is directed by our NICU pulmonary hypertension team. Infants > 34 weeks gestational age at birth were considered term. Infants born ≤ 34 weeks were considered preterm until a corrected age of 40 weeks, at which time they were considered term. During data analysis, patients were assigned to the month based on the date iNO was initiated. Total iNO hours per month, average iNO hours per patient per month and the percentage of infants with iNO course >120 h were calculated and stratified by gestational age. We chose >120 h as a prolonged course based on opinion that reversible causes of pulmonary hypertension should improve within this time period.

Statistical process control charts were used to evaluate each measure during the course of this project and data were updated monthly using the software package QI Charts (Version 2.0.23) and Microsoft Excel (Version 16.16.4). Since the data for the measures were highly skewed and covered three orders of magnitude, a log10 transformation was used for the control chart analysis and the limits transformed back to hours when displaying the charts [18]. The baseline control limits and mean for each chart were calculated using data from January 2017 to April 2018. Rules for special cause variation were utilized for evaluation, including eight data points above or below the centerline to indicate a shift, six down trending or up trending points to indicate a trend, and two consecutive points near a control limit or one point outside a control limit as evidence of special cause variation [18]. New control limits and centerline were calculated if these signals were observed and the data pattern indicated new performance.

Results

During our 16-month baseline period, there was common cause variation present in our outcome measures (Figs. 2–4) indicating a stable system. Special cause variation was identified in March 2017 for total hours per month for infants <34 weeks (Fig. 2b); no preceding event was identified, and this value was removed from baseline calculations. Our census remained stable during the course of the project (Table 1). After initiation of the interventions, our team was able to demonstrate improvement in all measures. Total iNO hours per month for all infants decreased by 72% from a mean of 1585 to 440 h (Fig. 2a). Total iNO hours per month stratified for gestational age showed a 92% reduction in infants <34 weeks from a mean of 398 to 31 h (Fig. 2b). The average number of hours of iNO therapy per patient decreased by 50% from a mean of 100 to 50 h (Fig. 3a). The average number of iNO therapy per patient <34 weeks quarterly was approaching the lower control limit at 29 h for the last quarter from a mean of 131 h (Fig. 3b). The percentage of prolonged iNO courses (>120 h) for all infants decreased from a mean of 52% to 17%, a 67% reduction (Fig. 4a). There was one special cause event for this measure in November 2018, which was attributed to a decrease in compliance with the weaning guideline. Education was provided, and subsequent data points have remained below the mean. These reductions in our primary measures were well beyond the aims for our project.

As our project progressed, fewer infants were started on iNO each month compared to the baseline period (Tabel 1); we believe this to be a result of our iNO guideline and culture change regarding iNO utilization. During our project, mortality did not increase in the population of infants requiring iNO and the number of infants requiring escalation to ECMO decreased (Table 1). We did not see an

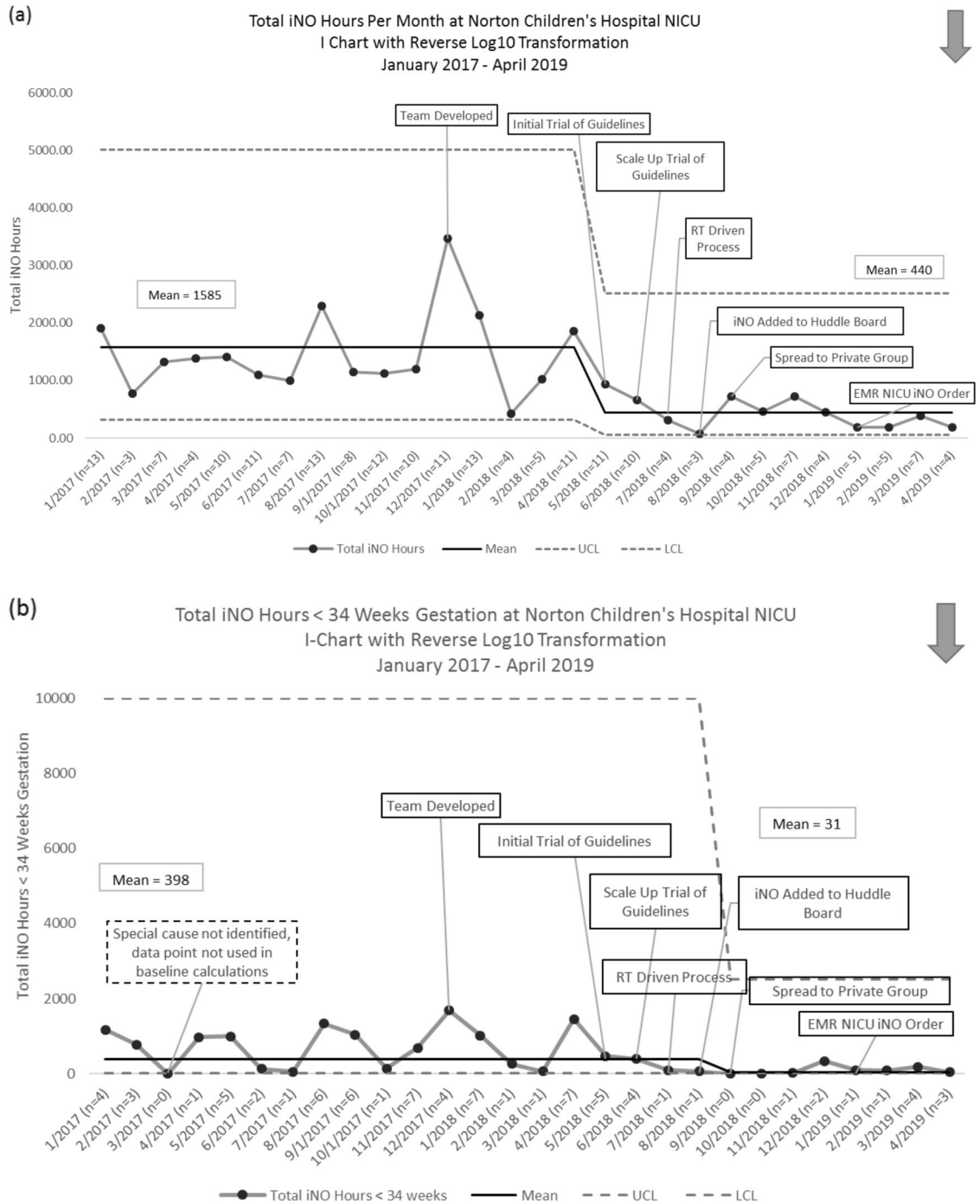

Fig. 2 Total iNO hours per month for term (a) and preterm (b) infants. An I-chart with a reverse logarithmic transformation was used to demonstrate the change in total hours per month over time; **a** measure decreased from a mean of 1585 to 440 h with a shift of eight consecutive points below the mean starting at 5/2018. **b** Decreased from a mean of 398 to 31 h with a shift of eight consecutive points below the mean starting at 6/2018.

increase in the number of infants requiring reinstitution of iNO within 24 h of using the weaning guideline or an increase in the number of pulmonary hypertension team consults (Table 1). Feedback from our RT, nursing, physician, and nurse practitioner staff was constructive with high satisfaction with the new process.

Estimating the direct cost of iNO to be $115 per hour, cost per patient declined from $21,620 to $10,580, proportional to that of Karsies et al. [19] and Tzanatos et al. [11]. Cost for premature infants < 34 weeks decreased from $84,640 per month to $19,780. Claims data on iNO denials were evaluated, however, this data may be biased based on

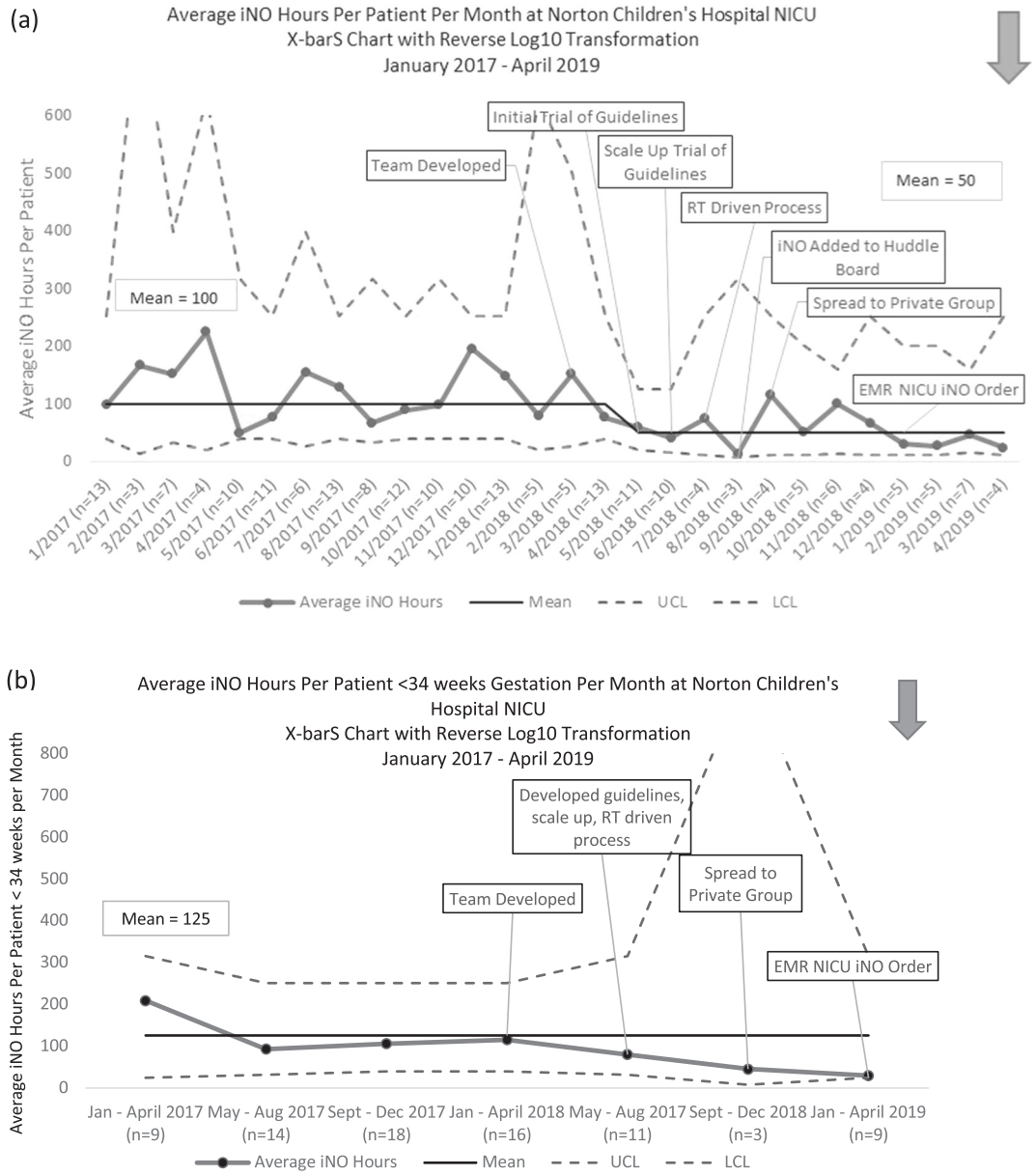

Fig. 3 Average iNO hours per patient per month for term (a) and preterm (b) infants. An X-bar-S-chart with a reverse logarithmic transformation was used to demonstrate the change in average hours per month per patient over time; **a** measure decreased from a mean of 100 to 50 h with a shift of eight consecutive points below the mean starting at 5/2018. **b** There are insufficient data points to meet rules for special cause variation, the last quarter is near the outer control limit.

private and public insurer's practices. For the baseline period of January 2017 to April 2018, there were 15 denied claims for iNO usage exceeding $3.4 million in charges. This decreased to three denied claims in the year following initiation of the QI project, totaling <$110,000 in charges.

Discussion

Value in healthcare can be defined as the optimal outcome for the minimal cost and waste [20]; this project sought to address both of these parameters. We standardized our practices, reduced variation and achieved our aims of improving iNO utilization in the NICU while maintaining clinical outcomes, consistent with other studies [10–12, 19]. The greatest improvements were seen in our preterm infants, leading to substantial cost-savings in this population, particularly as this population comprised a great majority of our insurance denials. Our project is one of the first to address iNO utilization in preterm infants, demonstrating that we can match care to science in this population without adversely affecting outcomes, even when there is conflicting evidence.

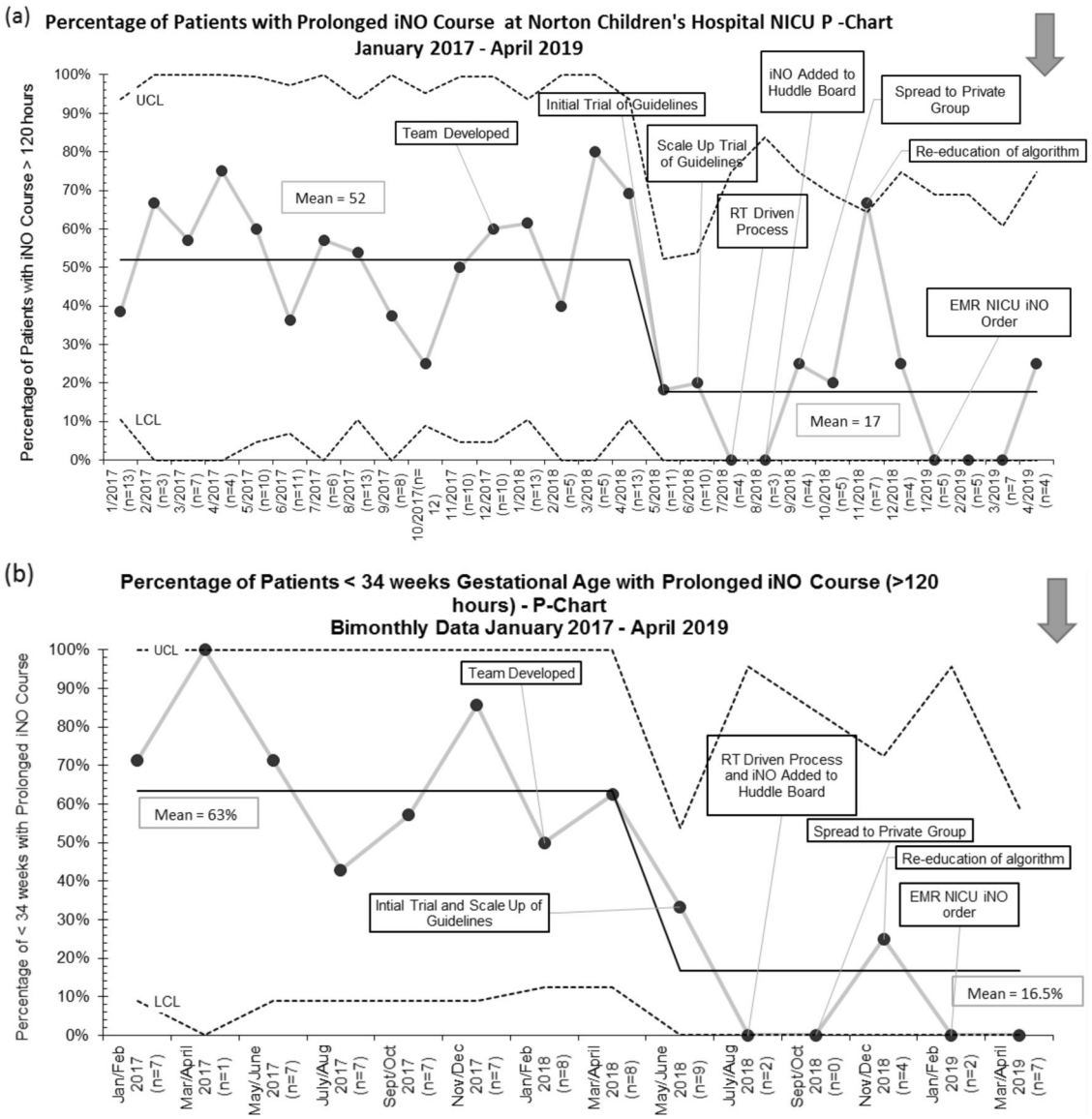

Fig. 4 Percentage of prolonged iNO courses > 120 h per month for term (a) and preterm (b) infants. A P-chart was used to demonstrate the change in percentage of patients with prolonged iNO courses (>120 h) per month over time; **a** measure decreased from a mean of 52% to 17% with greater than two points at a control limit on 7/2018 and 8/2018. **b** Decreased from a mean of 63% to 16.5% with greater than two points at a control limit on July/Aug2018, Sept/Oct2018, Jan/Feb 2019, and March/April 2019.

A recent study found that individual provider experience is a key factor in the decision to start iNO in preterm infants with hypoxic respiratory failure despite knowledge regarding limited clinical effectiveness and cost considerations [6]. The culture of our unit emphasized provider experience and autonomy, contributing to considerable variation in practice and was identified as a potential barrier to our success. This QI project was designed to bridge the gap between provider experience and evidence-based practice. We were able to design guidelines that helped providers approach instituting iNO systematically making decisions based on physiologic response. The "non-responder" and "partial responder" pathways, in particular, provided autonomy to trial iNO when a patient met criteria, but the support to discontinue if physiologic criteria were not subsequently met. This provision decreased the tension between the desire to provide life-saving care options to a critically ill patient while considering the broader picture of evidence and cost.

We believe our project was successful because it was supported by key people on our team and we addressed potential barriers to our project at multiple phases. At the frontline, giving the RTs a clear role facilitated buy-in and made them reliable drivers of this new process. Engaging neonatal faculty with a variety of experience and practices helped overcome the barriers of provider buy-in and autonomy. Incorporating these

Table 1 Balancing measures and census data.

	Baseline November 2017 to April 2018		Testing May to October 2018		Post-implementation November 2018 to April 2019	
Census	642		589		629	
N receiving iNO (% of census)	54 (8.4%)		36 (6.1%)		31 (4.9%)	
Mortality in patients started on iNO	11 (20%)		4 (11%)		7 (22%)	
	>34 weeks gestation	<34 weeks gestation	>34 weeks gestation	<34 weeks gestation	>34 weeks gestation	<34 weeks gestation
N	25	29	24	12	17	14
ECMO	5 (20%)	NA	3 (12.5%)	NA	1 (5.8%)	NA
Mortality	2 (8%)	9 (31%)	4 (14%)	0	3 (17%)	4 (23%)
Reinstitution of iNO within 24 h of weaning	0	1 (3.5%)	1 (3%) *iNO guideline not used	0	0	0
Pulmonary HTN consult	4 (16%)	0	2 (7%)	1 (5%)	2 (7%)	0

team members allowed them to provide input and mitigate potential concerns, which facilitated ownership of the new process. Support by key stakeholders in administration helped the project gain momentum and importance. The team successfully shared and communicated their vision throughout the project, further engaging our frontline providers. We addressed reliability from the beginning and incorporated principles such as deference to expertise, situational awareness, making the desired action the default and standardizing where it made sense into the design of our interventions. This increased the reliability with which the desired interventions occurred and drove us to achieving our aims. Sharing data in real time helped provide feedback and accountability and kept our care providers engaged. Barriers to performing the process were formally evaluated using a survey during the testing phase and results used to drive further PDSA cycles to improve performance; this provided a venue for staff to engage in the project.

The interventions for iNO stewardship were spread to our 28 bed Level III University Hospital NICU where the majority of iNO utilization has been directed to the very preterm patient population. Prior to spread of the interventions, the average length of treatment per patient was 250 h and 64% had iNO courses >120 h. In the 6-month period since spread of these interventions, there has been only one infant started on iNO with a total course of 37 h. The successful spread of these interventions increases our degree of belief that they are generalizable to NICU's with different levels of acuity, patient mix and contextual factors.

One limitation of this quality improvement project is that we were not able to provide individualized data to practitioners regarding their iNO utilization practices as multiple providers cared for each patient during their iNO course. This information would provide another layer of accountability and feedback that might improve compliance with the guidelines. However, when special cause was identified in our control charts, our team investigated and provided support to practitioners in using the new process. Since implementation, we have maintained a level of iNO utilization consistent with or better than our testing periods, leading us to believe that our compliance is at an acceptable level.

Conclusion

Using principles of reliability to redesign our process and The Model for Improvement to test interventions, our team was able to significantly improve iNO utilization in our Level IV NICU, particularly in preterm infants where effectiveness is limited. We were able to match care to science and provide iNO therapy to those patients who met specified criteria and demonstrated a physiologic response. We were able to decrease waste and cost by decreasing variation in care, discontinuing iNO in nonresponders and weaning iNO in a physiologic and automatic manner without causing harm. We were able to change the culture of our unit regarding our iNO experience. The results of this work decreased the financial burden of an expensive intervention to families, insurance companies and the hospital. This success was able to be spread to a Level III NICU with even greater financial implications. The interventions in this project our evidence based, low cost and maximize the people and processes already in place. Our project improved the value of iNO use in our NICUs by maintaining outcomes and decreasing cost.

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Author contributions HF and TS conceptualized the study design, collected and analyzed data, implemented interventions, drafted, reviewed, and revised the paper. LD, SD, OO, TR, SS, and ST participated in designing and testing interventions, analyzing data, drafting, and reviewing the paper. All authors approved the final paper as submitted and agree to be accountable for all aspects of the work.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This project was determined to be nonhuman subjects research by the University of Louisville Institutional Review Board and Norton Children's Hospital Research Board. Balancing measures monitored for prevention of patient harm included mortality, escalation of care to ECMO, the number of infants requiring reinstitution of iNO within 24 h of weaning, and utilization of the pulmonary hypertension consult.

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