ORIGINAL ARTICLE

Enhanced recovery after surgery (ERAS) protocols in neonates should focus on the respiratory tract

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Abstract

Background/purpose Enhanced recovery after surgery (ERAS) protocols have shown significant benefits in terms of patient outcomes and institutional cost savings in colorectal and bariatric surgery. This has not, however, been tried in the neonatal setting. One of the major barriers to developing ERAS protocols in the neonatal intensive care unit (NICU) is the often-prolonged intubation of neonates after surgery. To this end, we evaluated our institutional data to determine if prolonged intubation post-operatively is associated with adverse events.

Methods This is a retrospective cohort study of neonates who were intubated for a surgical procedure from January 2012 to December 2016. Documented data included pre-operative intubation status, timing of post-operative extubation: immediate (< 24 h) or delayed (> 24 h), and adverse respiratory events. The Fisher exact test and Student's t test were used to study differences amongst categorical and continuous variables, respectively.

Results 58 surgical procedures were identified, where the patient was intubated specifically for the surgical intervention, of which 28 were extubated immediately and 30 were extubated in a delayed fashion. The overall incidence of adverse respiratory events was increased in the delayed extubation group ($P = 0.03$).

Conclusions Healthcare providers should encourage early extubation after neonatal surgery. Consideration should be given to implementing ERAS protocols in NICUs.

Level of evidence Prognosis study—level II.

Keywords Enhanced recovery after surgery · Neonates · Post-operative extubation · Intubation · NICU

Introduction

Enhanced recovery after surgery (ERAS) protocols have shown significant benefits in terms of patient outcomes (decreased complication rates) and facility cost savings in adult colorectal and bariatric surgery. ERAS is also being developed in the pediatric surgery setting in conditions such as appendicitis and elective colorectal operations. In pediatric cardiac surgery, early (< 24 h) extubation after surgery was associated with a lower mortality rate and a lower rate of re-intubation as compared with those who had delayed extubation (beyond 24 h) [1]. The authors in the study noted

that the benefits of early extubation could be extended to neonates and babies having complex cardiac surgery such as transposition and anomalous pulmonary venous return. The benefit of early extubation in the pediatric cardiac surgery setting has translated to improved resource allocation by reducing intensive care unit stay and overall hospital length of stay [2, 3]. Other than in the neonatal cardiac surgery setting, early extubation has not been attempted or reported after surgery in neonates [4, 5]. Any attempt at instituting ERAS in the neonatal surgery setting will have to address the often-prolonged mechanical intubation after surgery.

Intubation and mechanical ventilation is the most definitive method of accessing and maintaining the airway in patients undergoing complex surgery. Complications of intubation and mechanical ventilation have been identified in both the immediate and delayed settings. Incorrect intubation, unplanned accidental extubation, ventilator-associated atelectasis and pneumonia, hypoxemia, acidosis, bradycardia–apnea–desaturation, and extubation failure with

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subsequent need for re-intubation have all been identified as adverse events in the immediate phase [6]. Chronic consequences of prolonged intubation include neurological sequelae due to intra-ventricular hemorrhage (IVH) and bronchopulmonary dysplasia (BPD) [7, 8]. As a consequence of the increasing importance attributed to quality metrics, intubation days' being one of them, there has been an evolution in the management of respiratory support in the modern NICU with an emphasis on early extubation in premature infants and non-invasive measures of respiratory support [9, 10]. This evolution in care affords an opportunity to study the consequences of early extubation that would likely be the first step to instituting ERAS in the NICU. The objective of this study was to evaluate the incidence of adverse respiratory events after delayed extubation following non-cardiac neonatal surgery.

Materials and methods

This was a single-site retrospective cohort study in NICU patients in a level IV regional neonatal center from January 2012 to December 2016 who underwent a surgical procedure. Patients selected for the study were intubated for the operation. NICU patients who received surgery, but were not intubated and used other modalities of respiratory support such as an LMA or a spinal anesthesia and patients, whose intubation status was not clearly marked by the data set were excluded from the study. Patients were also excluded from this study if they were intubated and had ventilatory support in the immediate days leading up to their surgical procedures, due to the possible interference of their pre-existing respiratory conditions that was independent of the surgical intubation. A data sheet was used to record the gestational age, birthweight, type of procedure performed, pre-operative intubation status, the status of post-operative extubation, adverse respiratory events, and days spent in the hospital following the operation. For the purpose of this study, post-operative extubation status was defined as immediate extubation when patients were extubated within 24 h

of the procedure, or delayed extubation when the intubation persisted for greater than 24 h after the procedure. Adverse respiratory events that were tabulated include: extubation failure and need for re-intubation, unplanned or accidental extubation, atelectasis/pneumonia, bradycardia/apnea/desaturation, acidosis, and death (Table 1). The primary outcome for the study was determination of in-hospital adverse events due to decision to keep the patient intubated beyond 24 h post-operatively, and secondary outcomes focused on the length of hospital stay beyond the surgery.

We used descriptive statistics to determine inter-quartile ranges. As this was a small data set, even a single outlier could significantly influence the mean. The ROUT method was used to identify and discount outliers from non-linear regression (GraphPad Software, LaJolla, CA, USA). Briefly, in the ROUT method, one initially fits a model to the data, where outliers have little impact. Subsequently, a new outlier detection method, based on the false discovery rate (FDR), is used to decide which data points are far enough from the prediction of the model so as to be called an outlier. Chi-square and Student's t tests were used to evaluate categorical and continuous variables.

Results

There were 99 surgical procedures performed during this period in NICU patients. Of these, 33 of them were identified as patients who used airway measures alternative to intubation and mechanical ventilation. Another set of eight procedures were separated from the study, because these NICU patients were already intubated in the immediate days leading up to their surgical procedures. 58 remaining procedures were identified that fit the inclusion criteria for the study, of which 28 procedures were followed by immediate extubation and 30 procedures with delayed extubation (Tables 2, 3). From the clinical chart in the system, where the data were extracted from, the decision to keep neonatal patients intubated post-operatively was not always identified. In certain patients, the use of sedatives and narcotics such

Table 1 Complications from prolonged intubation

Extubation status	Immediate extubation (< 24 h)	Delayed extubation (> 24 h)	p value
	28	30	
Need for re-intubation	1 (3.6%)	3 (10%)	0.33
Unplanned extubation	0 (0%)	2 (6.7%)	0.16
Atelectasis/pneumonia	1 (3.6%)	4 (13.3%)	0.19
Bradycardia, apnea or desaturation	5 (17.9%)	7 (23.3%)	0.61
Acidemia	2 (7.1%)	1 (3.3%)	0.51
Death	0 (0%)	1 (3.3%)	0.33
Total number of events	9 (32.1%)	18 (60%)	0.03

Table 2 Clinical features of delayed extubation (> 24 h)

Case	GA birth	GA surgery	Co-morbidity	Pre-surgical diagnosis	Type of surgery	Respiratory complications
1	38.4	39	G-tube placement, RDS	TE fistula	Dilation of Upper Esophagus, repair trachea, repair esophagus, Open Approach, G-tube placement for ventilation, primary handsewn anastomosis	
2	39.1	39.3		Esophageal atresia with TE fistula	Repair of esophageal stricture, closure of other fistula of trachea	Extubation failure, atelectasis
3	34.6	35.1	VACTERL association	Esophageal atresia with TE fistula	Tracheoesophageal fistula ligation and primary repair of esophageal atresia	
4	36.1	36.2	Large PDA, PFO, RDS	Esophageal atresia with TE fistula	Tracheoesophageal fistula ligation and primary repair of esophageal atresia	Stridor
5	37	37.1	Dandy Walker variant, vasculopathy, RDS	Omphalocele	Repair of abdominal wall, open approach	
6	33	33	RDS	Gastroschisis	Repair Abdominal Wall, Open Approach, Repair Right Inguinal Region, Open Approach	atelectasis
7	35.1	35.1		Gastroschisis	Repair of gastroschisis, Abdominal Silo placement	
8	35.1	35.6		Gastroschisis with silo	Repair of gastroschisis, closure of gastroschisis	
9	34.1	34.1	Small bowel atresia with perforation	Gastroschisis	Repair of gastroschisis, ex-lap, closure of stoma of small intestine, partial resection of small intestine, small-to-small intestinal anastomosis, suture of laceration of small intestine, Lysis of adhesions, exteriorization of small intestine	
10	34	40.1	RDS	Spontaneous perforation	Ex-lap and closure of transverse colon perf	
11	34.6	36.1		Malrotation	Incision of peritoneum, intra-abdominal manipulation of small intestine, other appendectomy, ex-lap, LofA, manipulation of large intestine	
12	25.3	26.3		Small bowel perforation	Bypass Ileum to Cutaneous, excision of small intestine, repair abdominal wall, repair ileum, release small intestine, open approach	Acidosis, multiple episodes of brady/desat
13	28.6	30.3	RDS, NEC, DIC		Emergent exploratory laparotomy, ileostomy and mucous fitula placement	Metabolic acidosis, death

Table 2 (continued)

Case	GA birth	GA surgery	Co-morbidity	Pre-surgical diagnosis	Type of surgery	Respiratory complications
14	27	39.2		Gastric perforation	ex-lap, ileostomy, gastrostomy, reanastomosis and closure of ileostomy	Extubation failure, multiple brady/desats
15	26.1	37.2	RDS, anemia, short gut syndrome	NEC	ex-lap, jejunocolostomy, colocolostomy, fistula repair	Atelectasis, multiple apnea/brady
16	34.4	34.6	Dehescience, VRE bacteremia	NEC	Open and other right hemicolectomy, other permanent ileostomy, Lysis of Adhesions, small-to-large intestinal anastomosis, closure of stoma of small intestine	
17	25.2	25.6	CLD, abdominal wall cellulitis	Perforated bowel	Other partial resection of small intestine, ileostomy not otherwise specified, open biopsy of small intestine, other appy, closure of stoma of small intestine	
18	31.3	31.4		Intestinal atresia	Other partial resection of small intestine, Small-to-small intestinal anastomosis (side to side duodenal reanastomosis)	
19	37.3	37.4	Meckel's diverticulum	Small perforated omphalocele	Repair abd wall, Local excision of lesion or tissue of small intestine, except duodenum, Other partial resection of small intestine	
20	34.2	34.4	VACTERL association, CAKUT	Duodenal atresia, imperforate anus	Resection of Rectum, Open Approach, Repair Duodenum, Open Approach, duodenoduodenostomy, G-tube placement, anoplasty	
21	28.3	41.2	Prior surgery (resection)	NEC	Reanastomosis of small intestine, appendectomy	Episode of desat
22	25.2	40.2	Prior surgery (resection), CLD, abdominal wall cellulitis	Perforated bowel	Reanastomosis of small intestine	Stridor
23	35	44	Prior surgery (resection)	NEC with perforation	Reanastomosis of ileum	Atelectasis
24	24.4	38.1	CLD, hypothyroidism, hydrocephalus	B/L IVH	Ventricular shunt to abdominal cavity and organs	
25	29	36.2	Porencephaly, ventriculomegaly, periventricular leukomalacia	IVH	Ventricular shunt to abdominal cavity and organs	Frequent desats/brady episodes

Table 3 Clinical features of immediate extubation (<24 h)

Case	GA birth	GA surgery	Co-morbidity	Pre-surgical diagnosis	Type of surgery	Respiratory complications
1	28.5	42.1	IVH, BPD	B/L inguinal hernia	Bilateral Inguinal Hernia Repair	
2	24.1	42.4	IVH, BPD			
3	33	38.2	Gastroschisis			
4	25.6	36.1	CLD			Desats
5	28.4	34.4	CLD			
6	25	39.1	CLD			
7	28	48.4	CLD, PIE, PDA requiring ligation, septic arthritis of shoulder, E. Coli bacteremia			
8	25.3	38.6	CLD, MRSA bacteremia			
9	26.5	40.3	CLD	Uni inguinal hernia	Unilateral Inguinal Hernia Repair	Brady and Desats
10	37	37.3		Omphalocele	Repair of abdominal wall, repair of omphalocele	
11	37.1	39.1	IUGR	Malrotation	Ladd procedure, exploratory laparotomy, ligation of adhesions	
12	35.2	35.6	RDS	Midgut volvulus	Intra-abdominal manipulation of small intestine, LAD procedure, correction of malrotation	
13	36.5	36.5			Exploratory laparotomy with resection of distal jejunum/proximal ileum, primary reanastomosis	
14	40.1	40.1		Hirschsprung Disease	Excision of Large Intestine, Percutaneous Endoscopic Approach, Excision of Descending Colon	
15	39	39.1		Mesenteric duplication cyst, mesenteric defect w/ internal hernia, midgut volvulus	Partial resection of small intestine, hernia repair, resection of mesenteric cyst, exploratory laparotomy	
16	29.2	37.4	NEC, RDS, abdominal abscess	Temporary ileostomy	Bowel reanastomosis	
17	34.1	37.1	Gastroschisis, small bowel atresia with perforation	Temporary ileostomy	Reversal of ileostomy	
18	25.3	34.6	Small bowel perforation	Temporary ileostomy	Ileostomy closure and enterolysis	
19	23.6	38.4	RDS, BPD, NEC		Excision of Left and right Vocal Cord, bronchoscopic procedure	Intermittent stridor
20	38.4	39.2	E. Coli bacteremia, encephalomalacia, anemia, renal failure, seizure	Grade 2 teratoma	Excision of peritoneal tissue	Respiratory depression, acidosis
21	28.2	28.4		Expanding IVH	Intracranial ventricular shunt placement	Desats
22	35.1	42.4	Subdural hemorrhage, hypotonia, shoulder dystonia, inspiratory stridor	Granulomatous laryngeal mass	Excision of granulomatous mass in the larynx	Stridor
23	23.2	49.6	CLD, BPD, Persistent neutropenia, renal dysfunction		Gastrostomy, G-tube placement	Stridor, atelectasis, desat

Table 3 (continued)

| Case	GA birth	GA surgery	Co-morbidity	Pre-surgical diagnosis	Type of surgery	Respiratory complications
24	39.4	40.2		B/L hydronephrosis, posterior urethral valves, grade 5 vesicoureteral reflux	Posterior urethral valve removal	
25	39.2	39.4		In-utero ovarian torsion	Unilateral salpingo-oophorectomy	
26	36.6	38.2		Choanal stenosis	Repair Nasopharynx, Via Natural or Artificial Opening Endoscopic, Dilation of Pharynx with Intraluminal Device, Via Natural or Artificial Opening Endoscopic, b/l nasal stent placement	
27	40.5	41.2	Seizure, tethered spinal cord, CNS infarct	Myelomeningocele	Repair of spinal myelomeningocele	
28	31.4	32	Sacral vertebral anomaly	Imperforate anus	Anorectoplasty	
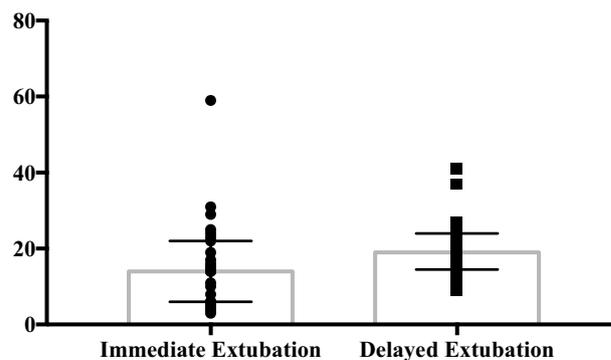
Fig. 1 Post-operative hospital stay (days)

as fentanyl and morphine intraoperatively leads to the decision to maintain intubation and prolong ventilator dependence until the patient clinically appeared aware enough to maintain their airway. In other cases, it was unclear if post-operative pain control, time of surgery completion, or neonatologist/anesthesia preference determined that the baby be left intubated.

The incidence of adverse respiratory events overall was found to be higher in patients who had a delayed extubation post-operatively as opposed to patients who were extubated within 24 h of the operation (0.6 vs 0.32, respectively), and this was found to be statistically significant using the Chi-squared analysis for categorical variables (P value 0.03) (Table 1). In each category of adverse respiratory events, the incidence of extubation failure, unplanned extubation, atelectasis, bradycardia/apnea/desaturation, and death was all higher in the delayed extubation group of patients, while respiratory acidosis was found to have a higher incidence in the immediate extubation group. However, when each of these results were studied as their own categorical variable, they were not found to be statistically significant following stratification likely because of inadequate numbers.

The length of post-operative hospital stay was calculated based on the last procedure that the NICU patient underwent prior to their discharge, excluding procedures that the patient may have experienced earlier within the hospitalization. The median length of hospital stay post-operatively in the immediate extubation group was 14 days (inter-quartile range 6–19.75), while those who were in the delayed extubation category had a median length of hospital stay post-operatively of 19 days (inter-quartile range 14.5–24) after accounting for an outlier identified through the ROUT method, with statistically significant difference established through use of unpaired t test (0.02) (Fig. 1).

The median gestational age of neonates intubated beyond 24 h was 33 weeks, in comparison with those who were extubated within 24 h, whose median gestational age was 28 weeks and 5 days. Greater importance in analysis was

accorded to corrected gestational age at surgery as that was considered to be a more important parameter. Corrected gestational age was 36 weeks in those who were extubated beyond 24 h and 38.5 weeks in those extubated before 24 h ($P = 0.01662$).

Discussion

This retrospective study focused on consequences of delaying extubation following a surgical procedure in neonatal patients. The main finding of this study is the significant incidence of overall adverse respiratory events in neonatal surgical patients who were not extubated within 24 h after surgery. It appears that early post-operative extubation benefits surgical neonates by reducing their respiratory complications. Furthermore, early extubation translates to decrease in length of stay and resultant cost savings for the hospital system. These findings corroborate what has been pointed out by our pediatric cardiac surgery colleagues [1].

Pediatric cardiac surgery leads the way in early extubation protocols [1–3]. The greater coordination between surgeons, pediatric intensive care specialists, and pediatric cardiac anesthesia appears to be the primary driver of quality metrics driven care in that setting. The care for pediatric cardiac surgery patients happens in pediatric cardiac care units (in larger cardiac surgery programs) or in the pediatric intensive care unit (PICU) (in smaller cardiac surgery programs) that are distinct from the NICU and care follows strict protocols. We found that internationally, it is not uncommon for NICUs to not have a written guideline or protocol regarding extubation and weaning steps for their non-cardiac neonatal patients [11].

Aside from a lack of a clear protocol to post-operative extubation, another factor that may lead to the delay in extubation in these patients is the concern for pain management and the effect of pain medications on the respiratory drive. Neonatal patients have a history of having their pain under treated in the past [12–14]. The excessive physiologic stress due to pain after surgical procedures in neonatal patients leads to alteration in stress hormone production and has an adverse homeostatic effect. However, the paradigm of pain management in neonatal patients appears to have shifted too far, where patients are now getting exposed to narcotics and sedatives at an increased rate [15]. An unintended consequence of sedative and narcotic use in intubated neonatal patients is the extension of time that these patients become dependent on mechanical ventilator use [16]. In our study, while we were not able to access pain medication use data due to multiple documentation changes in the hospital system, we did anecdotally notice excessive opioid use in some of these patients that had prolonged intubation times. In the establishment

of a post-operative extubation protocol of NICU patients, pain management is a technique that must be addressed to aid transitioning these patients to a smooth and expedited extubation. Developing closer coordination between the surgeon, anesthesiologist, and neonatal intensivist and developing protocols to mimic practice in the pediatric cardiac surgery units will likely improve extubation rates and thereby outcomes.

Enhanced recovery after surgery (ERAS) protocols in adults has lowered complications and facilitated discharge lowering medical costs. While it is not possible to compare the fully developed physiology in adults to that of a preterm infant, we feel that the benefits of enhanced recovery pathways should not be overlooked even in this age group. In our study, the corrected gestational age in the delayed extubation group (36 weeks) was lower than in the immediate extubation group (38 weeks). While prematurity may theoretically be an explanation for the delayed extubation, the groups were not statistically different when the hernia population was excluded, suggesting that the two groups were more similar than different. Furthermore, research suggests that even premature patients can be successfully managed by non-invasive respiratory support and re-intubation after failed extubation should not necessarily be deemed as failure [9, 10]. A duplication of this study in a multicenter prospective setting or a large database retrospective analysis should help shed more light on this important matter.

As seen with this study, in 30 of the 58 identified NICU surgical procedures, patients returned to the NICU while still intubated, and their extubation was dependent on the clinical judgement of the NICU intensivists and the health care team. The clarification of the responsibility and leadership in determining the extubation steps of NICU patients and implementation of a standardized protocol are a possible aspect of medical management that could lead to improvement of care [17]. We believe that developing ERAS protocols for neonates will translate the benefits noted in the adult population to the neonatal population. These findings represent the first report in the non-cardiac neonatal surgery setting of the adverse effects of delayed extubation after surgery and its impact on hospital length of stay. Through an improvement in extubation metrics, we can hope to shorten the course of ICU stay for neonatal surgical patients, possibly decreasing risks of hospital acquired complications, as well as an increased cost efficiency in the NICU department.

The drawbacks of this study are not classifying the operations based on severity of the presenting condition, variable lengths of procedure/anesthesia, having multiple practitioners involved in the care, and the small numbers of cases. However, all of the chosen cohorts were breathing independently prior to the procedure. We feel that perioperative care is an aspect of neonatal care that is neglected and needs greater attention.

Conclusions

This study suggests that delaying extubation post-operatively in NICU patients adversely affect the patients' respiratory status that can lead to an increase in length of stay in turn leading to an increased risk of further complications and an increased cost of care. Addressing this critical issue will facilitate advancing the baby along ERAS protocols for other body systems and hopefully lower post-surgical morbidity and cost of care.

Compliance with ethical standards

Conflict of interest Neither author has a conflict of interest.

Ethical approval The study is retrospective. Study was performed after institutional review board approval and in accordance with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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