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Clinical Impact of Analgesic-Sedative Agents and Peri-operative Clinical Status on White Matter Brain Injury in Preterm Infants Following Surgical NEC

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Abstract

Background: The potential influence of exposure to analgesic-sedative agents (ASA) before, during, and after surgical NEC and peri-operative clinical status on white matter injury (WMI) in preterm infants has not been fully defined, and a comprehensive evaluation may inform future research and clinical interventions.

Methods: A retrospective study comparing ASA exposure before/during /after surgical NEC and peri-operative clinical status in neonates with and without WMI.

Results: Infants with any WMI (grade 2–4, n=36/67, 53.7%) had a higher number of surgical procedures receiving ASA (5 [IQR: 3, 8] vs. 3 [2, 4]; p=0.002) and had a longer duration

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Author Contribution

PMG designed the study; PMG, MZ, JW, WH, MP, AR, CT, KR, TL, and TI collected and analyzed the data; PMG and WH wrote the manuscript. All the authors contributed to and approved the manuscript.

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of hypotension during their first (48.0 hours [26.0, 48.0] vs. 15.5 [6, 48]; p=0.009) and second surgery (20 hours [0, 48h] vs. 0 [0, 22]; p=0.017), received more hydrocortisone (35% vs.13.3%,p=0.04) than those without any WMI. There were no differences in fentanyl/morphine/midazolam exposure before/during/after the NEC onset in the two groups.

Infants with severe WMI (19/67, 28.3%, grade 3/4) had a higher incidence of AKI (P=0.004), surgical morbidity (p=0.047), more surgical procedures (6.5 [3, 10] vs. 4 [2, 5]; p=0.012), and received higher mean fentanyl doses(p=0.03) from birth until NEC onset than those without severe WMI. The univariate associations between these factors and severe WMI remained insignificant after multivariable logistic regression.

Conclusion: Infants with WMI had more surgical procedures receiving ASA and had a longer duration of hypotension during surgeries. A large multicenter prospective study is needed to understand the full impact of ASA.

Keywords

Analgesics-sedatives; Brain Injury; Neonate; Outcomes; Preterm Infant

Category of study:

Clinical science

Introduction:

Necrotizing enterocolitis (NEC) is a systemic inflammatory disease with multifactorial etiology affecting 3–10% of premature infants with a birth weight ≤ 1500 grams (1, 2). NEC remains a leading cause of morbidity and death among preterm infants and higher health care costs and resource utilization (3–9). Preterm infants with surgical NEC have elevated systemic levels of inflammatory markers, a higher likelihood of severe white matter abnormalities on brain imaging, and adverse neurodevelopmental outcomes at two years of age (10–14). The systemic inflammation secondary to NEC is hypothesized to cause neuronal injury via inflammatory pathway activation, microglial activation, and brain barrier disruption (15–18).

Preterm infants with surgical NEC are commonly exposed to several sedatives, pain, and paralytic medications to control pain and agitation during the initial surgical treatment and other follow-up surgical procedures (re-anastomosis of the bowel or for stricture/fistula repair). Recent studies have demonstrated that higher cumulative fentanyl doses in preterm infants correlated with a higher incidence of cerebellar injury and lower cerebellar diameter at term equivalent age (19, 20). Other studies have suggested adverse neurological effects in preterm infants exposed to opioids and benzodiazepines (21). These neuro-sedatives are hypothesized to contribute to adverse neurological outcomes via mechanisms including brain injury related to hypoperfusion, direct negative impact on brain growth and development, and antiproliferative and apoptotic effects on immature neuronal cell populations (20–22). Midazolam exposure has been associated with macro- and microstructural alterations in hippocampal development and adverse neurodevelopmental

outcomes consistent with hippocampal dysmaturation (21). Little is known about the risk of analgesic-sedative medications in preterm infants with systemic inflammation due to surgical NEC and drug exposure's potential additive detrimental effects.

Our previous retrospective observational cohort study reported the clinical and pathological factors associated with severe white matter injury (WMI) in the brains of preterm infants with surgical NEC (23). We have subsequently collected additional data on peri-operative clinical factors, including exposure to analgesic-sedative agents. Our objective was to assess the univariate and adjusted associations between analgesic-sedative agents' exposure and the development of WMI in preterm infants with surgical NEC. To our knowledge, no previous study has evaluated the association between exposure to analgesic-sedative agents and risk of WMI, adjusting for other potential confounding factors over the clinical peri-operative course in preterm surgical NEC infants. Intending to identify surgical NEC infants at higher risk of white matter injury, this study provides a comprehensive descriptive report and analysis of factors associated with WMI before, during, and after the disease onset in preterm infants with surgical NEC. Adding to previous evaluations, data on peri-operative risk factors and events are considered, including hypotension, inotropic support, hypothermia, number of surgical procedures receiving anesthesia, and cumulative exposure to sedative and analgesic agents. Our primary hypothesis was to determine whether exposure to analgesic-sedative agents, including specific agents, was independently associated with severe white matter abnormalities on terms equivalent to brain MRI in neonates suffering from surgical NEC.

We also determined the impact of peri-operative clinical factors on brain injury in preterm infants with surgical NEC.

Methods:

This retrospective study was undertaken at the University of Mississippi Medical Center (UMMC) in Jackson, Mississippi, after the Institutional Review Board (2017–0127) approval. UMMC houses a Level 4 neonatal intensive care unit (NICU), a regional referral center for neonates with surgical NEC for the entire state. A detailed review of electronic medical records identified 243 patients with medical and surgical NEC (NEC Bell stage II and above) (24) who underwent NEC management between January 2013 and December 2018. From this consecutive cohort, 67 infants with surgical NEC who had an MRI brain done at term equivalent age qualified for this study. The infants with medical NEC (n=108), data inconsistent with NEC diagnosis (n=14), and infants who died without any MRI brain data (n=30) or MRI brain not obtained due to any other clinical reason (n=22) were excluded.

Clinical information:

We recorded demographic characteristics including birth weight, gestational age, sex, race/ethnicity (African American, Caucasian, or Latino), mode of delivery (C-section/Vaginal), APGAR scores at 5 minutes, outborn status, and small for gestational age status. We collected information regarding maternal factors, including pregnancy-induced hypertension, chorioamnionitis, and antenatal steroids.

NEC information:

We recorded the NEC features such as the age of onset, pneumatosis, and clinical presentation (abdominal distension, feeding intolerance, and bloody stools). The NEC diagnosis was made by abdominal X-ray by board-certified pediatric radiologists based upon radiological NEC findings such as pneumatosis, pneumoperitoneum, and portal venous gas. Penrose drain placement, time to laparotomy following NEC diagnosis, length and region of bowel resected, and types of stoma creation during NEC surgery were recorded.

Peri-operative Clinical Data:

The indications, number, and duration of primary, secondary, and any other surgeries such as hernia repair or ROP surgery until term equivalent age were collected. The temperature during and after surgery (at NICU admission after the infant comes back from operation theater), hypotension, need and duration of dopamine or any other inotropes, steroids (hydrocortisone) received, type of fluid resuscitation (saline bolus, packed cell transfusion or albumin) received during surgery or after surgery (up to 72 hours) were recorded.

Analgesic-sedative data:

We collected information on the utilization of sedative, pain control, anesthetic, and paralytic agents in our consecutive cohort. The agents and their frequency of utilization in surgical NEC patients are detailed in Table 3,5. The commonly used neuro-sedatives in our NICU were fentanyl, morphine, and midazolam during three clinical time periods: before the NEC onset (birth until the day of NEC onset), during the NEC phase (from NEC onset until two weeks), and post-NEC (2 weeks after NEC onset until MRI). For each agent, the NICU pharmacist collected the cumulative medication dose for each of the three periods. In addition, the infant's average weight was calculated during each period, permitting calculation of the cumulative mg/kg of exposure to each neuro-sedative in each period.

Weight calculation during three-time frames:

For the time frame *"pre-NEC wt."* the birth weight and weight at NEC onset were averaged. For the period *"2 weeks post-NEC",* the weight at two weeks after NEC onset was utilized. For the period post-NEC weight., the two weeks post-NEC weight and weight at the time of the MRI were averaged.

Postoperative Morbidity:

To assess postoperative morbidity, we recorded the duration of postoperative ileus (defined as the number of days the infant kept NPO), total days of parenteral nutrition following NEC, development of short bowel syndrome, and time to achieve full feeds. Short bowel syndrome was defined as infants requiring TPN at discharge or more than 90 days after NEC onset. Days of parenteral nutrition were defined as the interval between postoperative Day 0 until full enteral feedings were achieved (defined as 120 ml/kg/day). Surgical morbidity was classified as surgical site infection (including dehiscence and abscesses), strictures, fistulas, adhesions, and perforations.

We recorded information on the length of stay and mortality. The length of stay was defined as the total hospitalization duration from the day of admission until discharge or death. Mortality was defined as death due to any cause before hospital discharge.

We collected data on bronchopulmonary dysplasia status at 36 weeks and the type of steroid (hydrocortisone/dexamethasone) used during the clinical course. (25).

Renal function data:

We captured all serum creatinine (SCr) measurements and daily urine output (UOP) before and five days after NEC onset. After NEC onset, the incidence of AKI was determined using the modified neonatal staging criteria as previously described in the *Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for AKI* (26–30).

Neonatal MRI data:

All MRI brain scans (without contrast) were scored independently by two pediatric neuroradiologists aware of the infants' clinical diagnosis of necrotizing enterocolitis. Our NICU standard of care is to obtain a brain MRI at 36 weeks, corrected age, or before discharge whenever clinically feasible in neonates with a birthweight less than 1500 grams. We used a standardized scoring system, as used by Woodward *et al.* and consisting of eight 3-point scales (11). The white-matter injury was graded according to five scales, which assessed the nature and extent of white-matter signal abnormality, the loss in the volume of periventricular white matter, and the extent of any cystic abnormalities, ventricular dilatation, or the thinning of the corpus callosum. The categories of white matter brain injury were none (a score of 5 to 6), mild (a score of 7 to 9), moderate (a score of 10 to 12), and severe (a score of 13 to 15). Gray matter was categorized as normal (a score of 3 to 5) or abnormal (6 to 9).

Statistical Methods:

Normally distributed continuous variables are summarized as means and standard deviations (± SD). Comparisons between normally distributed continuous measures for those with and without WMI were performed using Student's t-test for equal variance cases and Welch's unequal variances t-test for unequal variances. For continuous data exhibiting non-normal distributions by the Cramér-von Mises test, medians with interquartile range (IQR) [1^{st} quartile; 3^{rd} quartile] are presented, and differences were tested using Kruskal-Walli's test. Categorical data were summarized as counts with relative frequencies as percentages, and differences in the groups were analyzed using the Chi-squared test ($\chi 2$ test) or Fisher's exact test and the Fisher-Freeman-Halton extension for *IxJ* tables when expected cell counts failed to meet the Chi-squared test assumptions(31).

Univariable logistic regression analyses examined the unadjusted association between each of the risk factors and WMI. Logistic regression analyses compared clinical findings among infants with normal-mild WMI to those with moderate-severe WMI. We also compared groups with no WMI and infants with any grade of WMI. For continuous predictive factors, all odds ratios and their 95% confidence intervals are uniformly expressed per one standard deviation of the factor. Multivariable logistic regression models were used to evaluate the

adjusted associations between WMI and clinical factors, using the absence of WMI as the reference. Multivariable logistic regressions also were used to assess the associations between the moderate/severe WMI and clinical factors compared to mild/no WMI as the reference group. All tests were two-sided; a p-value < 0.05 was considered statistically significant. The statistical analyses were performed with SAS 9.4 statistical software.

Results:

Sixty-seven infants were included in the analysis. Analgesic and sedative medication utilization and demographic variables are shown in Tables 1–5, stratified by moderate/severe vs. mild/no WMI.

Moderate/severe WMI vs. mild/no WMI:

Out of 67 infants, 19/67 (28.3%) had moderate/severe WMI (grade 3–4), and 48/67 (71.6%) had mild/no WMI. Compared to infants with mild/no WMI, infants with moderate/severe WMI underwent a higher number of procedures with neuro-sedatives (6.5 [3, 10] vs. 4 [2, 5]; p=0.012) and received a higher mean fentanyl dose (p=0.029) from birth until NEC onset. Infants with moderate/severe WMI also had a greater likelihood of acute kidney injury (p=0.004), surgical morbidity (10/19 [52.6%] vs. 13/48 [27.1%]; p=0.047), and wound dehiscence (26.3% vs. 6.3%; p=0.036) compared those with mild/no injury. The data are summarized in Tables 1–5.

Any WMI vs. no WMI:

In our cohort, 36/67 (53.7%) had any WMI (mild, moderate or severe), and 31 /67 (46.3%) had no WMI. Similar to the comparison of infants with moderate/severe WMI vs. mild/no WMI, the infants with any WMI had a higher median number of surgical procedures needed (5 [3, 8] vs. 3 [2, 4]; p=0.002). There were no differences noted in exposure to fentanyl, morphine, or midazolam before, during, and after the NEC onset in infants with any WMI compared to the group without WMI. However, those with WMI had a longer duration of hypotension during the first pre-operative period (48.0 hours [26.0, 48.0] vs. 15.5 [6, 48]; p=0.009) and second surgery (20 hours [0, 48] vs. 0 [0, 22]; p=0.017) compared to those without any WMI.

In terms of other baseline characteristics, the infants with any WMI had lower gestational age (25 [23.6, 26.4] vs. 26.6 [25.2, 28.4] weeks; p=0.03]. In addition, those with WMI were more likely to experience more acute kidney injury by creatinine (p=0.001) or urine output (p=0.028) criteria, greater likelihood of the loss of the ileocecal valve following laparotomy (21/36 [65.6%] vs. 24/31 [92.3%]; p=0.015), need for dopamine support (29/36 [87.9%] vs. 15/31 [57.7%]; p=0.008) and a longer period of parenteral nutrition use (121 days [81, 159] vs. 87 [57, 118]; p=0.0350), achieved full feeds later (78 days [34, 109] vs. 57 days [27, 76]; p=0.034) and had longer hospital stay (175 days [136, 200] vs. 113 [85, 171]; p=0.005) compared to infants without any WMI **(See** Supplemental Tables 1,3,4,5 **and** 6).

Multi regression Modelling:

The results are summarized in Table 6. The significant univariate association seen on bivariate analysis with factors such as hypotension duration, AKI, inotrope support, number of anesthesia procedures, and TPN days did not persist on multi-logistic regression modeling.

Discussion:

WMI, associated with long-term cognitive function, is perhaps the most important outcome in preterm infants with surgical NEC other than survival. The care of preterm infants with surgical NEC requires the appropriate use of a wide variety of medications, including analgesic-sedative agents, anesthetics, steroids, and paralytics with potential direct and/or indirect effects on the central nervous system. Whether this medication exposure, including specific agents, poses an incremental risk of WMI is not well-defined, particularly adjusted for baseline comorbidities and clinical course. Our study quantifies the utilization of these agents and peri-operative clinical status in a consecutive series of 67 preterm infants with surgical NEC was associated with a higher likelihood of WMI in univariable, but not multivariable analyses.

In our cohort, infants with mild to severe WMI underwent more surgical procedures requiring neuro-sedatives/analgesic agents during anesthesia. However, WMI was not a predictor of the number of surgical procedures after multivariable adjustment for baseline comorbidities and clinical course. Preterm infants are at a greater risk of WMI and intraventricular hemorrhage due to repeated episodes of ischemia and reperfusion injury due to discordance between systemic blood flow and the innate regulation of cerebral blood flow in the germinal matrix and periventricular white matter (32, 33), increasing their susceptibility to hypotension. Consistent with this hypothesis in this cohort, infants with WMI were hypotensive for a longer duration and were more likely to receive dopamine during primary and secondary surgery compared to infants without any WMI on bivariate analysis. However, this association which did not persist after multivariate modeling suggests that it was not possible to isolate hypotension as the key pathway to WMI.

Prior studies in preterm infants have reported several adverse effects of opiates and benzodiazepines. More specifically, a higher cumulative fentanyl dose has been reported to have an association with greater risk for cerebellar injury (19). Detrimental impact from the exposure to opioids and benzodiazepines, such as midazolam, has also been hypothesized related to both hypotension and a direct negative neuronal impact on cellular proliferative and apoptotic pathways (20–22). Finally, midazolam exposure has been associated with macro- and microstructural alterations in hippocampal development, with adverse neurodevelopmental outcomes consistent with hippocampal dysmaturation (21). In our clinical study, we did not detect any association between the cumulative doses of fentanyl or midazolam and the presence or severity of WMI in preterm infants with surgical NEC.

In a recent prospective study, peri-operative cerebral oxygenation and electorencephalopgraphy (EEG) measurements in newborn infants undergoing surgical

repair of congenital diaphragmatic hernia (CDH) were compared based on intraoperatively administrated medication, using either a) the sevoflurane group (continuous sevoflurane, bolus fentanyl, bolus rocuronium); or b) the midazolam group (continuous midazolam, continuous fentanyl, and continuous vecuronium) (34). Sevoflurane-based anesthesia increased cerebral oxygenation and decreased cerebral EEG activity, suggesting adequate anesthesia. Midazolam-based anesthesia in infants with severe CDH led to alarmingly low $rScO_2$ values, below hypoxia threshold, and increased values of EEG power during the first 30 minutes of surgery. This may indicate a conscious experience of pain. Integrating population-pharmacokinetic models and multimodal neuromonitoring are needed for personalized pharmacotherapy in these vulnerable patients. Our study did not find any association of anesthetic agents and paralytics with WMI in preterm infants with surgical NEC.

In our previous report, we demonstrated that bowel hemorrhage was associated with higher odds of severe brain injury (OR 7.79 [95%CI: 2.19–27.72]; p = 0.002) (23). The intestine's significant blood loss may lead to hypovolemia with associated brain hypoperfusion leading to white or grey matter abnormalities.

In this cohort, the infants received normal saline, red blood-packed cell, dopamine, and hydrocortisone to manage hypotension. A recent multicenter study has shown that there is variability in blood pressure management due to a lack of consensus resulting in inter- and intra-center variability in clinical practice (35). Yasuoka *et al.* have shown that infants with late-onset refractory hypotension requiring steroids, also known as late-onset circulatory collapse, were at an increased risk for the development of cerebral palsy by three years of age (36). A recent double-blinded, placebo-controlled randomized trial did not detect any major differences in clinical outcomes between participants who were randomly assigned to saline bolus followed by either a dopamine infusion (standard management) or placebo (5% dextrose) infusion (restrictive management) (37).

In our study, infants with severe AKI by serum creatinine had higher rates of WMI. The association between AKI and WMI was seen in bivariate analysis but did not persist on multivariable modeling. Hypovolemia due to third spacing and hypotension seen in these infants can simultaneously place them at higher risk of AKI and ischemic brain injury, both from compromised perfusion. Mechanistically, we hypothesize that severe AKI in newborn infants with surgical NEC may exacerbate brain injury by acting as a catalyst or modifier of neuro-inflammation. Further studies are needed to understand the relationship between severe kidney injury and brain injury in infants with NEC.

This study's strengths include measuring the utilization of analgesic-sedative agents and cumulative doses as potential risk factors and an extensive set of other relevant risk factors for WMI in a consecutive series of preterm infants with surgical NEC. This permits assessment of whether these necessary medications, including specific agents, may confer incremental risk of WMI.

The limitations of our study include that it is a retrospective study without protocol-driven data collection. Nonetheless, missing data is relatively infrequent due to standardized care

pathways. This is a single-center experience where neuro-sedative/analgesics agent and anesthetic practice may not be generalizable to other centers. The small sample size limits the statistical power to detect associations between factors such as analgesic-sedative agents and WMI. Fortunately, surgical NEC is a relatively rare disease with inherently limited numbers, even at high-volume centers with a large and uniquely inclusive catchment area like ours. Secondly, the number of comparisons in our cohort generates a high probability of Type I errors. The study should be considered largely descriptive and exploratory, perhaps helpful in generating future hypotheses requiring independent or prospective evaluation and confirmation.

Conclusion:

Infants with surgical NEC appropriately require treatment with multiple neuro-sedatives and analgesic agents. Infants with moderate/severe WMI received higher mean fentanyl doses from birth until NEC onset. In multivariable analysis adjusting for baseline comorbidities and clinical course, such as the number of surgical procedures and duration of hypotension during surgery, an independent association between analgesic-sedative agents and WMI was not observed in our single, consecutive series of 67 preterm infants with surgical NEC. There is a need for a larger multisite prospective study to fully understand the potential impact of exposure to analgesic-sedative agents on the developing brain. In addition, accurate and clinically relevant assessment of cerebrovascular autoregulation remains limited (38). Future studies should focus on optimizing strategies for cerebrovascular autoregulation assessment in preterm infants in order to develop autoregulation-based cerebral perfusion treatment strategies alongside insights into the direct neurotoxicity or neuroprotection from sedatives and analgesics.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1:

Demographic and Clinical information in infants with moderate/severe WMI and mild/no WMI

Variable	N	Overall	Mild/no WMI	Moderate/Severe WMI	P-Value
		N=67	N=48	N=19	
Pregnancy-Induced hypertension, n (%)	59	15 (25.4%)	14 (34.1%)	1 (5.6%)	**0.024**
Chronic hypertension, n (%)	52	9 (17.3%)	5 (13.9%)	4 (25.0%)	0.43
Chorioamnionitis, n (%)	58	8 (13.8%)	6 (15.0%)	2 (11.1%)	0.99
Antenatal Steroids, n (%)	57	45 (78.9%)	32 (82.1%)	13 (72.2%)	0.49
Gestational Age (weeks), median, IQR	59	26 (24.3, 27.5)	26.4 (24.3, 28)	24.8 (24.3, 26.4)	0.28
Birth Weight (grams), median, IQR	59	740 (650, 990)	740.0 (650, 1000)	757.5 (670, 911)	0.90
Small for Gestational Age, n (%)	59	20 (33.9%)	17 (41.5%)	3 (16.7%)	0.06
Sex (Male), n (%)	59	20 (33.9%)	13 (31.7%)	7 (38.9%)	0.59
Ethnicity, n (%)					0.45
Caucasian		11 (18.6%)	6 (14.6%)	5 (27.8%)	
African American	59	44 (74.6%)	31 (75.6%)	13 (72.2%)	
Latino		2 (3.4%)	2 (4.9%)	0 (0.00%)	
Other		2 (3.4%)	2 (4.9%)	0 (0.00%)	
Mode of Delivery, C-section, n (%)		41 (69.5%)	29 (70.7%)	12 (66.7%)	0.76
Apgar Score <6 at 5 Minutes, n (%)	59	19 (32.2%)	12 (29.3%)	7 (38.9%)	0.47
Out born, n (%)	59	34 (57.6%)	25 (61.0%)	9 (50.0%)	0.43
Patent Ductus Arteriosus, n (%)	59	38 (64.4%)	26 (63.4%)	12 (66.7%)	0.81
Patent Ductus Arteriosus, Indomethacin Treated, n (%)	59	9 (15.3%)	5 (12.2%)	4 (22.2%)	0.43
Patent Ductus Arteriosus, Surgically Ligated, n (%)	59	5 (8.5%)	2 (4.9%)	3 (16.7%)	0.16
Central Line Present (days), median, IQR	58	49.5 (30, 93)	49.0 (29.0, 96.0)	50.0 (38.0, 65.0)	0.38
Positive Blood Culture Sepsis, n (%)	59	19 (32.2%)	14 (34.1%)	5 (27.8%)	0.63
CRP on Day of NEC Onset	51	3.2 (1.2, 8.2)	4.1 (1.4, 8.2)	1.9 (0.9, 7.4)	0.20
CRP 24h after NEC Onset	46	7.8 (3, 19)	7.7 (2.55, 19.4)	11.1 (3.4, 18.5)	0.57
CRP 48h after NEC Onset	37	9 (2.4, 21.9)	7.4 (2.3, 20.1)	15.6 (3.2, 22.1)	0.28
CRP at 96 Hours after NEC Onset	42	6.4 (4.2, 15.1)	5.4 (3.3, 15.1)	7.1 (4.2, 15.6)	0.45
CRP at 1 Week after NEC Onset	41	5.2 (2.5, 7.5)	5.2 (2.2, 7.6)	4.6 (2.5, 7.3)	0.97
CRP at 2 Week after NEC Onset	43	2.6 (1.4, 5.3)	2.6 (1.4, 5.3)	2.8 (1.7, 5.2)	0.73
Cholestasis at NEC Onset, n (%)	59	38 (64.4%)	24 (58.5%)	14 (77.8%)	0.16
AKI by Serum Creatinine					**0.004**
No AKI		27 (45.8%)	23 (56.1%)	4 (22.2%)	
Stage 1	59	12 (20.3%)	10 (24.4%)	2 (11.1%)	
Stage 2		9 (15.3%)	3 (7.3%)	6 (33.3%)	
Stage 3		11 (18.6%)	5 (12.2%)	6 (33.3%)	
AKI by Urine Output					0.45
No AKI		34 (57.6%)	22 (53.7%)	12 (66.7%)	
Stage 1	59	2 (3.4%)	1 (2.4%)	1 (5.6%)	

Variable	N	Overall	Mild/no WMI	Moderate/Severe WMI	P-Value
		N=67	N=48	N=19	
Stage 2		17 (28.8%)	14 (34.1%)	3 (16.7%)	
Stage 3		6 (10.2%)	4 (9.8%)	2 (11.1%)	
Severe AKI	67	42 (62.7%)	29 (60.4%)	13 (68.4%)	0.54
From Birth Until NEC onset					
Dexamethasone, mg/kg, mean (± SD)	63	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.99
Hydrocortisone, mg/kg, mean (± SD)	67	1.1 (5.1)	0.2 (1.1)	3.4 (9.2)	0.71
From NEC onset +2 weeks					
Dexamethasone, mg/kg, mean (± SD)	67	0.0 (0.1)	0.0 (0.1)	0.0 (0.0)	099
Hydrocortisone, mg/kg, mean (± SD)	67	7.9 (11.2)	7.7 (11.0)	8.6 (11.9)	0.83
From end of 2 weeks to MRI					
Dexamethasone, mg/kg, mean (± SD)	67	0.5 (1.7)	0.6 (2.0)	0.3 (0.8)	0.99
Hydrocortisone, mg/kg, mean (± SD)	67	7.8 (22.6)	6.4 (19.2)	11.4 (29.8)	0.88

Table 2:

NEC features in infants with severe WMI and non-severe WMI

Variable	N	Overall	Mild/noWMI	Moderate/Severe WMI	P-Value
		N=67	N=48	N=19	
Clinical presentation, n (%)	59				0.78
Abdominal Distension		54 (91.5%)	38 (92.7%)	16 (88.9%)	
Bloody Stools		3 (5.1%)	2 (4.9%)	1 (5.6%)	
Feeding Intolerance		2 (3.4%)	1 (2.4%)	1 (5.6%)	
Pneumatosis	59	22 (37.3%)	14 (34.1%)	8 (44.4%)	0.45
Pneumoperitoneum	59	35 (59.3%)	23 (56.1%)	12 (66.7%)	0.45
Portal Venous Gas	59	2 (3.4%)	1 (2.4%)	1 (5.6%)	0.52
Age of NEC Onset (days), median (IQR)	25	8 (6, 23)	7 (5, 16)	8 (7, 34)	0.32
Fulminant NEC, n (%)	59	4 (6.8%)	4 (9.8%)	0 (0.00%)	0.30
Presence of Penrose Drain, n (%)	57	25 (43.9%)	18 (45.0%)	7 (41.2%)	0.80
Surgery < 48 Hours, n (%)	59	40 (67.8%)	29 (70.7%)	11 (61.1%)	0.47
Length of Bowel Resected (cm), median (IQR)	59	12.7 (3.7, 28.8)	10.4 (3.7, 28)	15.7 (9.0, 28.8)	0.56
Region of Bowel Resected, n (%)	54				0.18
Small Bowel Resected		35 (64.8%)	27 (71.1%)	8 (50.0%)	
Large bowel resected		2 (3.7%)	2 (5.3%)	0 (0.00%)	
combined large and Small Bowel Resected		17 (31.5%)	9 (23.7%)	8 (50.0%)	
Presence of Ileocecal Valve, n (%)	58	45 (77.6%)	34 (82.9%)	11 (64.7%)	0.17
Surgical Morbidity (Infection, Adhesions, Strictures, Dehiscence), n (%)	67	23 (34.3%)	13 (27.1%)	10 (52.6%)	**0.047**
Single Surgical Morbidity (Infection, Adhesions, Strictures, Dehiscence), n (%)	67	15 (22.4%)	8 (16.7%)	7 (36.8%)	0.11
More than One Surgical Morbidity (Infection, Adhesions, Strictures, Dehiscence), n (%)	67	7 (10.4%)	4 (8.3%)	3 (15.8%)	0.40
Adhesions, n (%)	67	9 (13.4%)	7 (14.6%)	2 (10.5%)	0.99
Wound Dehiscence, n (%)	67	8 (11.9%)	3 (6.3%)	5 (26.3%)	**0.036**
Wound Infection, n (%)	67	3 (4.5%)	1 (2.1%)	2 (10.5%)	0.19
Stricture, n (%)	67	5 (7.5%)	4 (8.3%)	1 (5.3%)	0.99
Fistula, n (%)	67	3 (4.5%)	1 (2.1%)	2 (10.5%)	0.192
Compartment Syndrome, n (%)	67	1 (1.5%)	1 (2.1%)	0 (0.00%)	0.99
Short Bowel Syndrome, n (%)	50	29 (58.0%)	19 (54.3%)	10 (66.7%)	0.416

Table 3:

Primary Surgery Variables

	N	Overall	Mild/no WMI	Moderate/Severe WMI	P-Value
		N=67	N=48	N=19	
Primary Surgery Indication Penrose Drain	65	28 (43.1%)	20 (42.6%)	8 (44.4%)	0.89
Total Primary Surgical Duration (min)	60	97 (78, 123)	96.0 (75.0, 118.0)	106.0 (80.0, 135.0)	0.43
Number of Anesthetic Procedures	66	4 (2, 7)	4 (2, 5)	6.5 (3, 10)	**0.012**
Type of Anesthetic Agent Used	67				
Isoflurane/Sevoflurane/Desflurane		5 (7.5%)	4 (8.3%)	1 (5.3%)	0.99
Fentanyl, n (%)		54 (80.6%)	38 (79.2%)	16 (84.2%)	0.74
Propofol		11 (16.4%)	9 (18.8%)	2 (10.5%)	0.72
Hemodynamics	60				0.39
Normothermic		39 (65.0%)	30 (68.2%)	9 (56.3%)	
Hypotension		21 (35.0%)	14 (31.8%)	7 (43.8%)	
Fluids Used	67				
Normal Saline		14 (20.9%)	11 (22.9%)	3 (15.8%)	0.74
Albumin		41 (61.2%)	27 (56.3%)	14 (73.7%)	0.19
Blood		22 (32.8%)	14 (29.2%)	8 (42.1%)	0.31
Platelets		10 (14.9%)	8 (16.7%)	2 (10.5%)	0.71
Other		25 (37.3%)	18 (37.5%)	7 (36.8%)	0.96
Fluid Bolus	61	6 (9.8%)	4 (9.1%)	2 (11.8%)	0.99
Use of Inotropes	61	18 (29.5%)	12 (27.3%)	6 (35.3%)	0.54
Paralytic used During Surgery	60	51 (85.0%)	35 (81.4%)	16 (94.1%)	0.42
Type of Paralytic Used	51				0.99
Rocuronium		49 (96.1%)	33 (94.3%)	16 (100.0%)	
Other		2 (3.9%)	2 (5.7%)	0 (0.00%)	
Temperature Before Surgery	60				0.31
Hypothermic		5 (8.3%)	5 (11.9%)	0 (0.00%)	
Normothermic		55 (91.7%)	37 (88.1%)	18 (100.0%)	
Variables After Primary Surgery					
Temperature	61				0.22
Hypothermic		8 (13.1%)	4 (9.3%)	4 (22.2%)	
Normothermic		53 (86.9%)	39 (90.7%)	14 (77.8%)	
Duration of Hypotension (min)	59	36 (11, 48)	27.5 (7, 48)	44.0 (25.0, 48.0)	0.33
Number of Fluid Boluses Administered	61	2 (0, 3)	2 (0, 3)	2 (0, 3)	0.97
Hydrocortisone Use	62	26 (41.9%)	17 (38.6%)	9 (50.0%)	0.41
Duration of Hydrocortisone Use (days)	56	0 (0, 10)	0 (0, 9)	6 (0, 10)	0.75
Duration of Dopamine Use After Surgery (Hours)	56	46 (0, 48)	48.0 (0.0, 48.0)	40.5 (18.5, 48)	0.82

Table 4:

Postoperative and Clinical outcomes in infants with moderate/severe WMI and mild/no WMI

Variable	N	Overall	Mild/no WMI	Moderate/Severe WMI	P-Value
		N=67	N=48	N=19	
Postoperative Ileus Days (days), median (IQR)	56	13 (9.5, 17)	12.0 (9.0, 16.0)	16.0 (13.0, 26.0)	**0.006**
Postoperative Day at Starting Enteral Feedings (days), median (IQR)	55	14 (10, 18)	12.5 (10, 16)	17.0 (14.0, 26.0)	**0.006**
Day of Attainment of Full Enteral Feedings (120 mL/kg), median (IQR)	51	69 (30, 89)	63 (28, 83)	81 (41, 125)	0.09
Duration of Parenteral Nutrition (days), median (IQR)	59	108 (69, 147)	108 (58, 137)	116 (81, 159)	0.18
Breast Milk, n (%)	59	12 (20.3%)	8 (19.5%)	4 (22.2%)	0.99
Donor Milk, n (%)	59	13 (22.0%)	9 (22.0%)	4 (22.2%)	0.99
Formula Feeds, n (%)	59	36 (61.0%)	24 (58.5%)	12 (66.7%)	0.56
Breast Milk and Formula Feeds, n (%)	59	14 (23.7%)	9 (22.0%)	5 (27.8%)	0.74
Assisted Ventilation (intubated), n (%)	57				0.99
Intubated		50 (87.7%)	34 (87.2%)	16 (88.9%)	
High Flow Nasal Cannula		5 (8.8%)	3 (7.7%)	2 (11.1%)	
Room Air		2 (3.5%)	2 (5.1%)	0 (0.00%)	
24h Presser Support, n (%)	59	44 (74.6%)	28 (68.3%)	16 (88.9%)	0.12
Postnatal Use of Steroids, n (%)	59	36 (61.0%)	24 (58.5%)	12 (66.7%)	0.56
Length of Stay (days), median (IQR)	59	161 (108, 184)	133 (95, 178)	178 (136, 200)	0.06
Death, n (%)	59	53 (89.8%)	38 (92.7%)	15 (83.3%)	0.36

Table 5:

Exposure to different sedatives and analgesics before, during and after NEC Onset

Variable	N	Overall	Mild/no WMI	Moderate/Severe WMI	P-Value
		N=67	N=48	N=19	
From Birth Until NEC onset					
Morphine mg/kg, mean (± SD)	61	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.99
Fentanyl mg/kg, mean (± SD)	67	0.0 (0.1)	0.0 (0.1)	0.0 (0.0)	**0.029**
Midazolam, mg/kg, mean (± SD)	67	0.0 (0.1)	0.0 (0.1)	0.0 (0.0)	0.99
Methadone, mg/kg, mean (± SD)	67	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.99
From NEC onset +2 weeks					
Morphine mg/kg, mean (± SD)	67	0.0 (0.1)	0.0 (0.1)	0.0 (0.0)	0.99
Fentanyl mg/kg, mean (± SD)	67	0.3 (0.3)	0.3 (0.3)	0.4 (0.5)	0.22
Midazolam, mg/kg, mean (± SD)	67	0.2 (1.0)	0.2 (1.1)	0.1 (0.2)	0.99
Methadone, mg/kg, mean (± SD)	67	0.0 (0.0)	0.0 (0.1)	0.0 (0.0)	0.99
From end of 2 weeks to MRI					
Morphine mg/kg, mean (± SD)	67	2.0 (12.0)	2.7 (14.1)	0.2 (0.7)	0.99
Fentanyl mg/kg, mean (± SD)	67	382 (1051)	339 (955)	491 (1286)	0.46
Midazolam, mg/kg, mean (± SD)	67	2.1 (11.2)	2.6 (13.2)	0.8 (2.1)	0.99
Methadone, mg/kg, mean (± SD)	67	2.0 (10.3)	2.2 (11.5)	1.5 (6.6)	0.99

Table 6:

Multiple Logistic regression

Logistic regression for any WMI vs. No WMI				
Variable	**OR**	**95% CI**		**p-Value**
Gestational Age	0.877	0.574	1.339	0.54
TPN days	1.002	0.985	1.019	0.82
AKI by serum creatinine 2 vs 1	1.079	0.18	6.455	0.92
AKI by serum creatinine 3 vs 1	7.983	0.456	139.695	0.96
AKI by serum creatinine 4 vs 1	>999.999	<0.001	>999.999	0.93
Inotrope support 24 hour	1.351	0.153	11.936	0.79
Presence of ileocecal valve	0.71	0.062	8.188	0.78
Number of anesthesia procedures	1.206	0.902	1.611	0.21
Hypotension duration	1.026	0.982	1.073	0.25
Logistic Regression for Severe WMI vs. Non-severe WMI				
Variable	**OR**	**95% CI**		**p-Value**
Gestational Age	0.939	0.695	1.267	0.68
TPN days	1.004	0.988	1.019	0.64
AKI by serum creatinine 2 vs 1	0.477	0.039	5.862	0.07
AKI by serum creatinine 3 vs 1	8.058	0.765	84.855	0.12
AKI by serum creatinine 4 vs 1	7.356	1.011	53.545	0.08
Inotrope support 24 hour	0.922	0.082	10.364	0.95
Presence of ileocecal valve	0.821	0.11	6.125	0.85
Number of anesthesia Procedures	1.04	0.871	1.242	0.66
Hypotension duration	1.014	0.974	1.056	0.50