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SHORT COMMUNICATION

Feasibility and acceptability of a diagnostic randomized clinical trial of bowel ultrasound in infants with suspected necrotizing enterocolitis

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Abstract

We conducted a pilot diagnostic randomized clinical trial (RCT) to examine the feasibility, acceptability, and preliminary outcomes of adding bowel ultrasound (BUS) to the diagnostic evaluation for necrotizing enterocolitis (NEC). Infants ≤ 32 weeks' gestational age with NEC concern were randomized to undergo abdominal X-ray (AXR) or AXR + BUS. The primary outcome was study feasibility. Secondary outcomes included rates of NEC diagnosis and duration of treatment with bowel rest and antibiotics. A total of 56 infants were enrolled; 16 developed NEC concern and were randomized. Rates of recruitment (56/82 = 68%), retention (16/16 = 100%), and protocol compliance (126/127 = 99%) met pre-specified thresholds for feasibility. No significant differences in rates of NEC diagnosis were found between the two groups. Durations of bowel rest and antibiotic treatment were also similar.

Conclusion: Our study supports the feasibility of conducting a definitive diagnostic RCT to establish safety and efficacy of BUS for NEC.

Clinical trial registration: The study was registered at https://clinicaltrials.gov (NCT03963011).

What is Known:
- *Bowel ultrasound (BUS) is increasingly being utilized as an adjunct to abdominal radiographs in evaluating for necrotizing enterocolitis (NEC).*
- *The impact of BUS on patient outcomes is unknown.*

What is New:
- *A diagnostic randomized controlled trial study design to determine safety and effectiveness of adding BUS to NEC evaluation is feasible and acceptable.*

Keywords Sonography · Ultrasound · Necrotizing enterocolitis · Prematurity · Clinical trial

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Abbreviations

AXR	Abdominal radiographs
BUS	Bowel ultrasound
NEC	Necrotizing enterocolitis
RCT	Randomized controlled trial

Introduction

Necrotizing enterocolitis (NEC) is a devastating intestinal disease of preterm infants that can be difficult to diagnose [1]. While abdominal radiographs (AXR) remain the imaging standard for evaluating NEC, pathognomonic findings such as portal venous gas and pneumatosis can be difficult to identify on AXR, and the absence of such findings cannot entirely exclude the diagnosis [2]. Bowel ultrasound

(BUS) is a non-invasive imaging modality that is increasingly used to aid in diagnosing NEC [3–5]. Evidence for the use of BUS is based on small, retrospective diagnostic cohort studies from single centers that have adopted BUS in their NEC evaluation [6–8]. Such studies are insufficient to evaluate whether the addition of BUS leads to actual benefit or potential harm with over-diagnosis and over-treatment [9]. Instead, diagnostic randomized clinical trials (RCTs) are needed to determine whether a new diagnostic modality is clinically beneficial [10]. As diagnostic RCTs can be challenging to perform, we conducted this pilot study to first establish the feasibility of a diagnostic RCT of BUS in preterm infants with suspected NEC.

Materials and methods

We conducted a pilot diagnostic RCT (December 2018–September 2020) in the level IV NICU of a free-standing children's hospital with 24/7 coverage by pediatric sonographers, radiologists, and surgeons. The study was registered at ClinicalTrials.gov (NCT03963011), approved by the local institutional review board, and written following Consolidated Standards of Reporting Trials guidelines [11].

Eligible infants included preterm infants ≤ 32 weeks' gestation at birth and < 36 weeks' postmenstrual age at time of informed consent who did not have major gastrointestinal anomalies (i.e., gastroschisis or omphalocele). Study infants who developed an episode of NEC concern were randomized to either standard imaging (*AXR group*) or experimental imaging (*AXR + BUS group*). We defined NEC concern as the presence of clinical signs and symptoms of NEC for which an evaluation with imaging *and* blood work was warranted by the treating neonatologist. Sealed envelopes opened at time of NEC concern were used to identify the infant's randomization.

Infants randomized to the AXR group were evaluated with a portable AXR as per standard of care and consisted of anteroposterior view, with additional cross table or left lateral decubitus view per neonatologist discretion. In the AXR arm, BUS was not available unless the neonatologist deemed it was clinically warranted. Infants randomized to the AXR + BUS group had a BUS performed within 6 h of the standard of care AXR. The BUS protocol consisted of standard grayscale, color Doppler, and spectral Doppler images of the abdomen supplemented with cine acquisitions in both transverse and sagittal planes as previously described (Supplemental Fig. 1) [4, 12]. The BUS evaluation for NEC was composed of 10 sonographic features and was reported using a standardized template (Supplemental Fig. 2).

Repeat imaging was left to the neonatologist's discretion and consisted of the imaging modality in which infants were randomized to. Enrolled patients who had multiple "suspected NEC" encounters remained in the same arm throughout the study. All AXR and BUS exams were performed and interpreted as per usual clinical practice by on-call sonographers and radiologists, all of whom had subspecialty training and board certification in pediatric imaging. All imaging results were also available for radiologists and neonatologists to review. The diagnosis of NEC was made by the treating neonatologist based on interpretation of infant's clinical features, laboratory data, and imaging results, as per usual clinical practice (Supplemental Table 1). The treatment of NEC, including duration of antibiotics and bowel rest, was also left to the discretion of the treating neonatologist. In general, infants diagnosed with medical NEC were treated with antibiotics and bowel rest for 7–10 days, while infants diagnosed with surgical NEC were treated for 14 days, in addition to either laparotomy or peritoneal drainage.

Our primary outcome was study feasibility as assessed by recruitment rate, randomization rate, retention rate, and protocol compliance. Our secondary outcomes consisted of clinical outcomes related to each episode of NEC concern including rates of NEC, duration of bowel rest and antibiotic treatment, and number of imaging tests.

Data were presented as means ± standard deviations, median and interquartile range, or numbers and percentages. A priori, we defined study feasibility by the following benchmarks: (1) recruitment rate of ≥ 50%; (2) randomization rate of ≥ 30%; (3) retention rate of ≥ 80%; and (4) protocol compliance rate of ≥ 95%. Baseline characteristics and clinical outcomes were compared using chi-square test for categorical variables, and either Kruskal–Wallis test or *t*-test for continuous variables. Statistical analysis was performed using SPSS v23 (IBM Corp, Armonk, NY), with statistical significance at $P < 0.05$.

Results

We screened 1613 infants, of whom 117 were eligible for enrollment. In the second year of the study, we had a 7-month institution-wide pause in enrollment because of the COVID-19 pandemic. Consequently, we were able to approach only 82 eligible families for consent, and 56 agreed to be included in the study. Of the 56 consented infants, 17 underwent randomization into the study. One infant who did not have clinical concern for NEC but inadvertently randomized to AXR + BUS arm was excluded from all analyses. In total, 8 infants each were randomized to the AXR and AXR + BUS arm (Supplemental Fig. 3). The pilot study ended when the 2-year funding for the study was exhausted.

There were no significant differences in baseline characteristics between the 2 groups (Table 1). The 16 infants randomized into the study had 23 distinct episodes of NEC

concern evaluated with 128 imaging tests—104 AXR and 24 BUS.

For our primary outcome of study feasibility, we had a recruitment rate of 68% (56/82), a randomization rate of 29% (16/56), and a retention rate of 100% (16/16). Of the 127 imaging tests conducted, we had one instance of protocol deviation for a protocol compliance rate of 99% (126/127). The protocol deviation involved one infant in the AXR + BUS arm who did not receive BUS because the stat AXR showed free air, and the infant subsequently underwent surgical intervention.

For our secondary outcomes, we found similar rates of NEC diagnosis and similar duration of treatment with bowel rest and antibiotics between the two groups (Table 1). Despite the additional imaging with BUS, infants randomized to experimental imaging had a similar number of AXR per NEC episode as infants randomized to standard imaging with AXR only (Table 1).

We also looked at the agreement between paired AXR and BUS for pneumatosis, portal venous gas, and free air. In total, the 8 infants randomized to experimental imaging underwent 24 paired AXR and BUS examinations. The median time from AXR to BUS acquisition was 2 h (interquartile range [IQR] 1 to 4.5 h). The rate of agreement for pneumatosis was 75% (18/24). Of the 6 cases of disagreement, we had 4 instances where the AXR identified mottled

Table 1 Baseline characteristics and clinical outcomes of the study participants

Baseline characteristics of infants	AXR ***N = 8 infants***	AXR plus BUS ***N = 8 infants***	*P* value
Gestational age, weeks	26.9 ± 2.5	27.4 ± 2.1	0.68
Birth weight, g	1056 ± 399	1022 ± 381	0.87
Male sex, no. (%)	5 (63)	2 (25)	0.32
White race, no. (%)	4 (50)	6 (75)	0.61
Small for gestational age, no. (%)	0 (0)	1 (13)	1.0
Maternal age, years[a]	25 ± 7	31 ± 7	0.08
Caesarian delivery, no. (%)	3 (38)	5 (63)	0.62
Apgar score < 5 at 1 min, no. (%)[b]	4 (50)	7 (88)	0.15
Apgar score < 5 at 5 min, no. (%)[b]	3 (38)	2 (25)	0.86
Antenatal corticosteroids, no. (%)	8 (100)	7 (88)	1.0
Surfactant, no. (%)	8 (100)	6 (75)	0.47
Age at time of initial NEC concern			
Postmenstrual age, weeks	32.5 ± 3.0	33.2 ± 4.0	0.69
Postnatal age, days	38.9 ± 18.8	40.6 ± 27.3	0.89
Clinical outcomes per NEC episode	**AXR** ***N = 10 NEC episodes***	**AXR plus BUS** ***N = 13 NEC episodes***	*P* value
No NEC or other pathologies	4 (40%)	3 (23%)	0.76
NEC	3 (30%)	6 (46%)	0.62
Medical NEC	2	5	
Surgical NEC	1	1	
Other pathologies	3 (30%)	4 (31%)	0.96
Sepsis	1	3	
Cow milk protein allergy	1	0	
Ileal atresia or stricture	1	1	
Spontaneous ileal perforation	0	0	
Duration of NPO, days*			
No NEC	1.5 (0.25–2.75)	1.0 (0–8)	1.0
NEC	7 (5–89)	8.5 (7–36)	0.74
Duration of antibiotics, days*			
No NEC	0 (0, 0)	0 (0, 0)	1.0
NEC	7 (7–21)	7 (7–11)	0.82
No. of NEC concern episodes	1 (1–3)	1 (1–3)	0.36
No. of radiographs per NEC concern	3 (1.25–7)	5 (3.5–6.25)	0.29

Data presented as number (percentage), mean ± standard deviation, or median (interquartile range)

[a]1 mother with unknown age

[b]2 infants with unknown Apgar scores

*Infants diagnosed with other pathologies not related to NEC were excluded

lucencies concerning for pneumatosis, but the BUS did not. In the remaining 2 instances, BUS identified areas concerning for pneumatosis, but the AXR did not (Supplemental Table 2). We had no cases of portal venous gas or free air in both AXR and BUS (Supplemental Table 2).

Discussion

In this pilot diagnostic RCT of adding BUS to NEC evaluation, we found that recruitment and retention of infants for the study were both feasible and acceptable. Our recruitment rate of 68% indicated that families were receptive to participating in a study that randomly allocates infants with suspected NEC to receive or not receive additional non-invasive imaging evaluation with BUS. The high rate of protocol compliance and timely acquisition of BUS likewise support feasibility of the diagnostic RCT study design. Taken together, our findings support the feasibility of conducting a larger diagnostic RCT to properly evaluate the safety and effectiveness of BUS for NEC evaluation.

Our pilot study met all pre-specified parameters for study feasibility except for randomization rate, which we missed by 1 percentage point (goal = 30%; actual = 29%). The unforeseen restrictions by the COVID-19 pandemic, which included a 7-month-long stoppage in recruitment, played a major role in missing this target. Another contributing factor was our trigger for randomization, which we set as NEC concern evaluated by both imaging *and* blood work. While intended so that only infants with high suspicion for NEC were included into the study, this higher threshold likely contributed to our study's lower randomization rate. Overall, we remain confident that had it not been for the COVID-19 pandemic, we would have met our randomization goal. A less stringent threshold of NEC concern could also be considered to promote higher randomization rates. When a less stringent threshold of NEC concern without the need for blood work was retrospectively applied to our cohort, our randomization rate would have increased from 29% (16/56) to 38% (21/56).

In our study, infants allocated to experimental imaging had a similar number of AXRs to infants allocated to receive AXR only despite undergoing additional evaluation with BUS. While the exact reasons for these preliminary findings are not clear, we hypothesize that disagreements between AXR and BUS led to more AXRs being ordered. In our study, the rate of disagreement between paired AXR and BUS was 25%, with all cases of disagreement arising from pneumatosis intestinalis. In a recent study by Tracy et al. [13], the rate of disagreement for pneumatosis was even higher at 37%. Inherent differences in imaging technology, as well as the time elapsed from when BUS was obtained after AXR, are likely factors that drive disagreements between the two imaging modalities [14]. A recent report by Elsayed and Seshia [15] described integrating neonatologist-performed point-of-care intestinal ultrasound with the standard evaluation for NEC. This novel approach allows for real-time correlation between AXR and BUS, which may decrease disagreements between the two modalities and decrease radiation exposure from multiple AXRs.

We acknowledge several limitations. First, this pilot diagnostic RCT was not powered to detect meaningful differences in clinical outcomes. Although we reported on diagnostic and therapeutic outcomes related to the addition of BUS, these results should be treated as preliminary findings. Second, the high threshold for NEC concern biased our cohort towards a sicker population and limited our ability to study the potential advantage of BUS for early detection of mild cases of NEC. Third, we had a lower than expected sample size due to the COVID-19 pandemic and high threshold of randomization. Despite these challenges, our pilot study met its goals of determining feasibility and testing study design. Lastly, our study was conducted in a free-standing children's hospital where the radiology staff is experienced with BUS for NEC evaluation. Whether a diagnostic RCT would be feasible in level III NICUs where staff may be less experienced with BUS remains unknown.

Currently, the best evidence for using BUS for NEC evaluation is limited to diagnostic accuracy studies. While appropriate for early investigation, diagnostic accuracy studies are insufficient for evaluating the impact of a diagnostic test on patient outcomes, as even more advanced and accurate diagnostic tests may not translate to improved patient outcomes [9]. The results of this pilot study demonstrate that a protocol of randomizing BUS in addition to standard imaging with AXR to infants with suspected NEC is feasible and acceptable to both families and clinicians. Our study thus supports the conduct of a larger clinical trial designed to determine whether add-on BUS increases diagnostic accuracy for NEC compared to AXR alone, and whether add-on BUS can improve patient outcomes.

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Author's contributions AC contributed to the design of the study, conducted the initial data analysis and interpretation, drafted the initial manuscript, and approved the final manuscript as submitted. AR, MS, and KR were responsible for the collection, management, and retrieval of data, critically revised the manuscript, and approved the final manuscript as submitted. SC, JJ, and EO contributed to the design of the study, supervised the radiological aspects of the study, critically reviewed and revised the manuscript, and approved the final manuscript as submitted.

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Availability of data and material Not applicable.

Code availability Not applicable.

Declarations

Ethics approval Approval was granted by the Institutional Review Board Committee of Children's Mercy Kansas City.

Consent to participate Written informed consent was obtained from the parents.

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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