ORIGINAL CLINICAL RESEARCH REPORT

A Randomized Controlled Trial of Enhanced Recovery After Surgery Versus Standard of Care Recovery for Emergency Cesarean Deliveries at Mbarara Hospital, Uganda

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BACKGROUND: Enhanced recovery after surgery (ERAS) expedites return to patient baseline and functional status by reducing surgical trauma, stress, and organ dysfunction. Despite the potential benefits of enhanced recovery protocols, limited research has been done in low-resource settings, where 95% of cesarean deliveries are emergent and could possibly benefit from the application of ERAS protocols.

METHODS: In a prospective, randomized, single-blind, controlled trial, mothers delivering by emergency cesarean delivery were randomly assigned to either an ERAS or a standard of care (SOC) recovery arm. Patients in the ERAS arm were treated with a modified ERAS protocol that included modified counseling and education, prophylactic antibiotics, antiemetics, normothermia, restrictive fluid administration, and multimodal analgesia. They also received early initiation of mobilization, feeding, and urethral catheter removal. The primary end point was length of hospital stay. The secondary end points were complications and readmission rates. Mean length of stay in the intervention and control arms were compared using *t* tests. Statistical analyses were performed using STATA version 13 (College Station, TX).

RESULTS: A total of 160 patients were enrolled in the study, with 80 randomized to each arm. There was a statistically significant shorter length of stay for the ERAS arm compared to SOC, with a difference of −18.5 hours ($P < .001$, 95% confidence interval [CI], −23.67, −13.34). The incidence of complications of severe pain and headache was lower in the ERAS arm compared to SOC ($P = .001$ for both complications). However, pruritus was more common in the ERAS arm compared to SOC ($P = .023$).

CONCLUSIONS: Use of an ERAS protocol for women undergoing emergency cesarean delivery in a low-income setting is feasible and reduces length of hospital stay without generally increasing the complication rate. (Anesth Analg 2020;130:769–76)

KEY POINTS

- **Question:** Is the hospital length of stay among mothers undergoing enhanced recovery after surgery shorter compared to that of women undergoing standard of care for emergency cesarean deliveries?
- **Findings:** Enhanced recovery is associated with shorter hospital length of stay without generally increasing the complication rate.
- **Meaning:** Enhanced recovery after surgery is feasible in a resource-limited setting, and reduces length of stay for women undergoing emergency cesarean delivery.

GLOSSARY

ASA = American Society of Anesthesiologists; **CD** = cesarean delivery; **CI** = confidence interval; **CONSORT** = Consolidated Standards of Reporting Trials; **ERAS** = enhanced recovery after surgery; **HIC** = high-income country; **ITM** = intrathecal morphine; **ITT** = intention to treat; **IV** = intravenous; **LIC** = low-income country; **LOS** = length of stay; **MRRH** = Mbarara Regional Referral Hospital; **NSAID** = nonsteroidal anti-inflammatory drug; **OD** = once daily; **PONV** = postoperative nausea and vomiting; **SD** = standard deviation; **SOC** = standard of care; **VAS** = visual analog scale

Cesarean delivery (CD) rates are increasing worldwide, in both high-income countries (HICs) and low-income countries (LICs).[1] CDs constitute approximately 3% of the total surgical volume in HICs and a much higher proportion, up to 30%, in LICs.[2] The high rate in low-income settings comes

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Accepted for publication September 18, 2019.

Funding: This research was funded by the Kayanja Fellowship Scholarship, a university grant scheme. The funders did not participate at any stage of the study.

DOI: 10.1213/ANE.0000000000004495

The authors declare no conflicts of interest.

Trial registration at ClinicalTrials.gov: NCT03518463.

Reprints will not be available from the authors.

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with challenges including postoperative complications, shortage of beds, and consequently delays in undertaking operations. These challenges are accompanied by increased costs for patients and health facilities.[3]

Enhanced recovery after surgery (ERAS) reduces hospital length of stay (LOS).[4,5] Following the implementation of ERAS, Wrench et al[3] found that the proportion of women discharged on the first postoperative day increased from 1.6% to 25.0% with no increase in 30-day readmission and complication rates. A recent systematic review of studies involving elective CD showed a reduction in LOS of 12–36 hours following implementation of ERAS protocols.[6]

Despite the potential benefits of ERAS protocols, ERAS has not been tested in emergency situations in low-income settings, and there is uncertainty as to whether the same benefits observed in the HICs will be replicated in resource-limited settings, especially in emergency CDs, which constitute 95% of cesarean deliveries. We hypothesized that emergency CD patients undergoing ERAS will have a shorter duration of hospital stay compared to those undergoing standard of care (SOC) recovery. Therefore, we conducted a randomized controlled trial to compare length of hospital stay between ERAS and SOC. A secondary aim was to determine whether there was an increase in complications in patients assigned to the ERAS arm.

METHODS

Study Design and Setting

This prospective, randomized, single-blind study was approved by the Research Ethics Committee of Mbarara University of Science and Technology (REC # 34/05-17). All participants gave written, informed consent. The trial was registered before patient enrollment with ClinicalTrials.gov (NCT03518463, principal investigator: Dr Moris Baluku, date of registration: May 7, 2018). The study setting was Mbarara Regional Referral Hospital (MRRH), located in Mbarara district of South Western Uganda. It is a tertiary facility for the region, serving >2.5 million people. The facility performs >3000 CDs per year, with a CD rate of 40% in 2016.[7]

Participants

Participants admitted with an indication for delivery by emergency CD using spinal anesthetic technique were enrolled from June to August 2018. The CD was to be performed through a lower transverse incision. Participants were American Society of Anesthesiologists (ASA) IIE according to the ASA classification. We excluded mothers with pregnancy complicated by preeclampsia, antepartum hemorrhage, malaria, gestational diabetes mellitus, and physical disability that might restrict postoperative mobilization. These complications, depending on severity, could make compliance with protocols by patients or caregivers difficult. We also excluded mothers with mental illness because of challenges with comprehension of protocols and obtaining informed consent.

Randomization and Blinding

Mothers listed for delivery by emergency CD were randomly assigned to either an ERAS arm or an SOC arm in a ratio of 1:1. We conducted simple randomization to assign the women to either the ERAS or SOC arm without blocks. We used a computer algorithm to generate a list of random numbers that were tagged to either the control or intervention group. The random numbers with group assignments were placed in identical sealed opaque envelopes. A statistician not involved in the research generated the random number list and sealed the envelopes. The envelopes were opened sequentially by the anesthetist when an eligible patient was identified and consented to participate. Mothers were recruited into the study by 2 nurse research assistants. Patients allocated to either arm were counseled and educated about the arm to which they had been assigned. We blinded the principal investigator and outcome assessors comprising trained obstetricians and midwives who ensured patients met the discharge criteria before being allowed home. Participants were not blinded because they received counseling and education about the intervention.

Perioperative Management

We adopted ERAS protocols for gynecologic/oncology surgery and consensus guidelines from the consensus workshop and survey in the United Kingdom, with modifications to our setting and urgency of the surgery.[8,9] The main differences between ERAS and SOC are summarized in Table 1. The modifications are described below.

Preoperative. We did not have preoperative optimization or fasting given that the CDs were emergencies. Thromboprophylaxis was not given, nor was ondansetron for postoperative nausea and vomiting (PONV) because the medications are expensive in our low-income setting.

Intraoperative. Phenylephrine is not available at our hospital. Ephedrine is in short supply, so we sought to use it sparingly by combining it with adrenaline. Regarding skin closure, we allowed both interrupted and subcuticular closure techniques depending on the availability of skin sutures. Local infiltration analgesia with bupivacaine formed part of our multimodal strategy for analgesia in the ERAS

Table 1. Comparison of Perioperative Strategies Between ERAS and SOC

ERAS	SOC
Preoperative	
Counseling and ERAS education	Counseling and education on SOC
No fasting to both solids and liquids	No fasting to both solids and liquids
Prophylactic antibiotics	Prophylactic antibiotics
Prophylaxis against PONV (8 mg of IV dexamethasone)	
Prophylaxis against pulmonary aspiration (100 mg of IV ranitidine and 10 mg of IV metoclopramide)	
Intraoperative	
Single-shot spinal with 10–12.5 mg of plain hyperbaric bupivacaine and 100 μg of preservative-free ITM	Single-shot spinal with hyperbaric bupivacaine. Quincke needle 25G was used similar to ERAS
Restrictive fluid administration to ensure normovolemia	Liberal fluid administration including preloading every mother
Treatment of hypotension with a continuous adrenaline infusion of 100 μg in 500 mL of lactated Ringer's solution and 6-mg boluses of ephedrine	Adrenaline and ephedrine used based on anesthetist's clinical impression
Prevention of hypothermia with warm IV fluids and warm clothing cover	At the discretion of anesthetist
Local wound infiltration analgesia with 2 mg/kg of bupivacaine	
Rectal diclofenac (100 mg)	
Rectal misoprostol (400 μg)	Rectal misoprostol (400 μg)
Postoperative	
Carbohydrate drink within 1 h	Feeding after 6 h
Cessation of IV fluids within 1 h	Continued for 12 h
Early breastfeeding, within 30 min	Breastfeeding within 1 h
Analgesia with oral single fixed-dose combination of 400 mg of ibuprofen and 500 mg of acetaminophen every 8 h. Breakthrough pain was treated with 25 mg of IV pethidine.	IV pethidine (100 mg every 8 h)
Early mobilization at 8 h	Mobilization at 12–24 h
Early urethral catheter removal at 6 h	Urethral catheter removal at 24 h
Oral antibiotics (850 mg of amoxicillin-clavulanate q12h and 500 mg of metronidazole every 8 h)	IV antibiotics (2 g of ceftriaxone OD and 500 mg of metronidazole every 8 h)

Abbreviations: ERAS, enhanced recovery after surgery; ITM, intrathecal morphine; IV, intravenous; OD, once daily; PONV, postoperative nausea and vomiting; SOC, standard of care.

group only. Counseling was continued throughout the intraoperative period because the time was not adequate in the preoperative period. However, we refrained from adding new information given the stressful time for the mother.

Postoperative. We used rectal misoprostol instead of an oxytocin infusion for the prevention of postpartum hemorrhage. We gave postoperative antibiotics because the surgeries were emergencies, and many mothers were at high risk of puerperal and surgical site infection. Such mothers included those with prolonged labor, obstructed labor/contracted pelvis, many of whom had multiple vaginal examinations from their referral centers. We did not provide a standard carbohydrate drink for early oral feeding; rather, we allowed mothers to drink anything that contained carbohydrates or sugar. Postdischarge follow-up was done via telephone because we do not have community midwives in our health system.

Discharge Criteria and Follow-up

We evaluated the following 7 outcomes every morning and evening before a patient was considered eligible for discharge: adequate oral intake; good pain control with oral analgesia at visual analog scale (VAS) <5; adequate mobilization; afebrile; clean wound; normal urinary bladder; and bowel function. If a patient met all of these criteria, she was discharged and given an emergency contact telephone number to report any health concerns while at home. After discharge, patients were contacted by blinded outcome assessors via telephone for follow-up on days 7, 14, and 30. Patients who developed symptoms that could not be managed at home were asked to return to MRRH for evaluation.

Study Outcomes

The primary outcome for our study was length of hospital stay, measured as the duration in hours from the time of surgery to discharge. Secondary outcomes were postoperative pain measured using the VAS at 6 hours postoperatively and subsequently assessed every 6 hours until discharge. A pain score ≥7 on VAS was considered severe pain. The VAS was used because it has visual guides that can be easily understood by anyone regardless of education level. PONV, pruritus, urinary retention, headache, wound infection, puerperal sepsis, fever, and readmission were also assessed as additional study end points. Pruritus, urine retention, and PONV were assessed within the first 24 hours. We evaluated mothers for headache daily for at least 7 days. We assessed for puerperal sepsis, wound infection, pyrexia, and readmission up to 30 days postoperatively.

Statistical Analysis

We summarized the baseline characteristics by using mean and standard deviation (SD) for continuous variables and proportions for categorical data.

We compared the mean LOS in the intervention and control arm using *t* tests. To compare the incidence of postoperative complications among patients in the ERAS and the SOC arms, χ^2 tests were used. We used Fisher exact tests when the expected number of observations in a cell was <5. We conducted both an intention to treat (ITT) and a per-protocol analysis. We did not adjust for multiplicity in the analysis because we had only one primary outcome, as the complications were considered secondary outcomes. Adjustment for multiplicity is required if there is >1 primary end point.[10] The level of statistical significance was $\alpha = .05$; therefore, probability values <.05 were considered statistically significant.

To calculate the sample size, we estimated the SD for LOS to be 15 hours,[6] and assuming a difference of 7 hours between intervention and control arm, we needed at least 75 women per arm to detect this difference in LOS with 80% power. A 95% confidence interval was calculated for outcome measures. All statistical analyses were performed using STATA version 13 (College Station, TX).

RESULTS

Baseline Demographics

We assessed 213 participants for eligibility. Of these, 53 were excluded. Of the 53 patients, 45 did not meet the inclusion criteria, and 8 declined participation, leaving 160 for randomization. We allocated 80 mothers to each group. Seven mothers were lost to follow-up after discharge. Four mothers in the ERAS arm and 3 in the control arm could not be reached, likely due to a poor telephone network where they lived. Protocol violation occurred among 6 mothers in the SOC arm. These 6 mothers mistakenly received intraoperative ERAS protocols but had been randomized to the control arm. We analyzed 160 participants as shown in the Consolidated Standards of Reporting Trials (CONSORT) flow diagram (Figure). Of these, 92.0% (147/160) were <35 years of age, with an overall mean age of 26 years. The mean

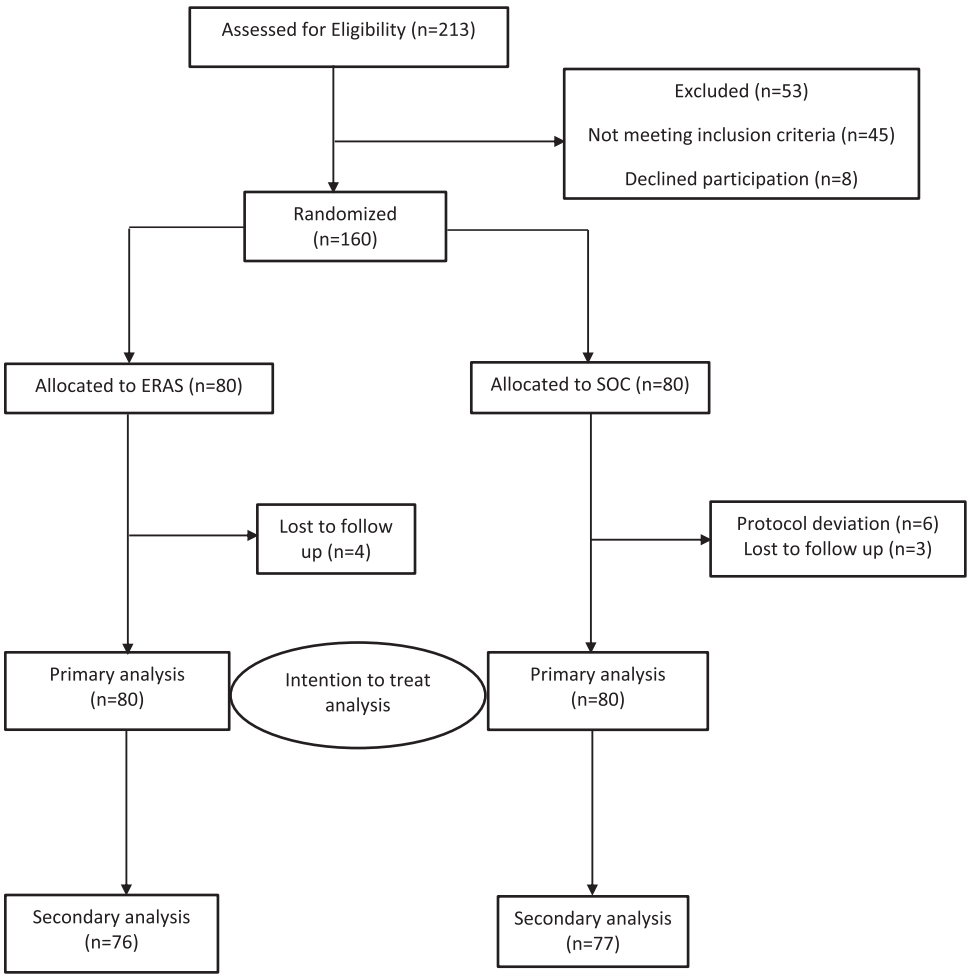

Figure. CONSORT diagram for enrollment, allocation, follow-up, and analysis. CONSORT indicates Consolidated Standards of Reporting Trials; ERAS, enhanced recovery after surgery; SOC, standard of care.

Table 2. Demographic Characteristics of Mothers Enrolled in the ERAS Trial

Characteristic	ERAS (n = 80)	SOC (n = 80)
Age in years (mean ± SD)	26.2 ± 5.4	25.1 ± 5.5
Age categories, n/N (%)		
<25	33/80 (44.6)	41/80 (51.3)
25–34	40/80 (50.0)	33/80 (41.3)
35–40	7/80 (8.6)	6/80 (7.5)

Data are mean ± SD or number (proportion). Age was broken down into categories based on the risk of obstetric complications for which some vary with age.

Abbreviations: ERAS, enhanced recovery after surgery; n, number in each arm; N, total number; SD, standard deviation; SOC, standard of care.

age was comparable in the 2 arms at 26.2 years (SD ±5.4) in the ERAS arm and 25.1 years (SD ±5.5) in the SOC arm. The results are shown in Table 2.

The obstetric characteristics are summarized in Table 3, and they were all comparable in the 2 arms. The majority of mothers ([93.6%; 74/158] and [90.8%; 59/152]) in the ERAS and SOC arms respectively were gravida <5. Contracted pelvis was the most common indication for CD in both ERAS (29.1%; 23/79) and SOC (21.5%; 17/79) arms.

LOS in Hours

There was a significantly lower mean hospital LOS in the ERAS arm compared to the SOC arm for both ITT and per-protocol analysis. In the ITT analysis, mean hospital LOS was 43.6 hours in the ERAS arm compared with 62.1 hours in the SOC arm, a difference of −18.5 (P < .001, confidence interval for the difference was −23.67, −13.34). In the per-protocol analysis, mean hospital LOS was 44.6 hours in the ERAS arm compared to 61.4 hours in the SOC arm, a difference of −16.8 (P < .001, confidence interval for the difference was −21.8, −11.9).

Complication Rates by Study Arms

Generally, there were more complications in the control than the ERAS group. The results are shown in Table 4. Notably, about 13% of patients in the SOC arm experienced severe pain compared to 0% in the ERAS group, and this difference was statistically significant (P = .001). The incidence of headache was higher in the SOC than in the ERAS group (30.4% vs 6.6%, P = .001). However, the incidence of pruritus was significantly higher in the ERAS arm at 8.9% compared to 1.5% in the control group (P = .023).

Wound infection, puerperal sepsis, PONV, and readmissions were not different between the groups. Fetal Apgar scores were also similar in both groups.

DISCUSSION

In this study assessing the impact of ERAS on emergency CD in Uganda, we found that ERAS is feasible and significantly reduced hospital LOS by an estimated 18.5 hours. The patient complaints of headache

Table 3. Baseline Obstetric Characteristics of Mothers Enrolled in the ERAS Trial

Characteristic	ERAS n = 79	SOC n = 79
Gravidity		
1	22/79 (27.8)	32/76 (46.2)
2–4	52/79 (65.8)	27/76 (44.6)
5–9	5/79 (6.3)	7/76 (9.2)
Indication for CD		
Obstructed labor	5/79 (6.3)	8/78 (10.3)
Prolonged labor	11/76 (13.3)	17/69 (25)
Fresh scar	6/78 (7.7)	9/79 (11.4)
≥2 previous scars	19/79 (24.1)	14/79 (17.7)
Cord prolapse	1/79 (1.3)	1/79 (1.3)
Severe oligohydramnios	4/78 (5.1)	3/79(3.8)
Fetal distress	6/79(7.8)	4/79 (5.1)
Multiple pregnancy	2/79 (2.5)	1/79 (1.3)
Contracted pelvis	23/79 (29.1)	17/79 (21.5)
Macrosomia	5/79 (6.3)	4/79 (5.1)
Failed induction	1/79 (1.3)	0/79 (0.0)
Malpresentation	6/79 (7.6)	6/69 (7.6)
Malposition	1/79 (1.3)	0/79 (0.0)

Data are number (proportion). Denominators differ from the 80 per group because of missing data in some variables.

Abbreviations: CD, cesarean delivery; ERAS, enhanced recovery after surgery; n, number in each arm; N, total number; SOC, standard of care.

Table 4. Comparison of Complication and Readmission Rates Between ERAS and SOC

Complications	ERAS n = 76	SOC n = 77	P
Severe pain (≥7)	0 (0.0)	9 (13.0)	.001[a]
PONV	5 (6.6)	6 (8.7)	.631
General headache	5 (6.6)	21 (30.4)	.001
Pruritus	16 (8.9)	1 (1.5)	.023[a]
Urine retention	1 (1.3)	0 (0.0)	>.99[a]
Wound infection	2 (2.6)	5 (7.3)	.183[a]
Foul-smelling lochia	0 (0.0)	2 (2.9)	.225[a]
Fever	3 (4.0)	4 (5.8)	.446[a]
Readmission	0 (0.0)	2 (2.6)	.225[a]

Data are number (proportion).

Abbreviations: ERAS, enhanced recovery after surgery; PONV, postoperative nausea and vomiting; SOC, standard of care.

[a]P value generated from Fisher exact test, else P values generated from a χ^2 testing for difference in the proportions of complications between SOC and ERAS arms.

and severe pain were also less. Our study shows ERAS is effective in emergency CDs. To the best of our knowledge, this is the first study to apply ERAS in emergency CDs in sub-Saharan Africa.

Previous studies on ERAS in obstetrics have been conducted among mothers having elective CD.[3,11] Emergency CDs differ from elective procedures because the surgical team has less time to prepare the patient for surgery, which puts them at an increased risk of complications. This is particularly important in LICs where patients incur significant costs to meet their surgery needs.[12]

ERAS has potential to increase early discharge rates and hence reduce overcrowding on the postnatal ward in large hospitals in sub-Saharan Africa. More African studies should be conducted to evaluate this potential. The available experience is from HICs. A study at

Sheffield Hospital, United Kingdom, showed that the proportion of mothers discharged on day 1 after CD increased from 1.6% to 25% following ERAS implementation.[3] A clinical trial in France showed a reduction in length of hospital stay of 10 hours between intervention and control arms.[13] Overall, a review of ERAS protocols in elective CD showed a reduction in LOS of 12–36 hours and this reduction was attributed to early urethral catheter removal which facilitated early mobilization, minimally invasive Joel-Cohen incision, and prophylactic antibiotics,[6] procedures provided as part of ERAS. The reduction in hospital LOS in our study comes close to that in studies in HICs despite the differences in study populations and resources.

Complications after CD may result in longer hospital stays.[14] ERAS involves minimum interruption in oral intake, excellent analgesia, prevention of PONV, and early mobilization which affect recovery and postoperative complications.[15] Notably, we found decreased postoperative complications of pain and headache in the ERAS arm compared to the control. However, the opposite was true for pruritus. The other complications including PONV, fever, puerperal sepsis, and wound infection were not significantly different in the 2 groups. None of the study patients developed constipation or required recatheterization in either group.

Pain management is a very critical component of postoperative care and ERAS. Pavlin et al[16] demonstrated that poorly controlled pain could lead to delayed discharge and complicate recovery in hernia surgery. The incidence of severe pain was significantly higher in the SOC than ERAS in our study. This difference is likely due to a multimodal analgesia approach adopted in ERAS and especially the use of intrathecal morphine (ITM).[17,18] It is known that adequate postoperative analgesia accelerates normalization, quality of life, and functionality.[19–21] Nonsteroidal anti-inflammatory drugs (NSAIDs) have benefits including analgesic, anti-inflammatory, and opioid-sparing effects.[22] Oral acetaminophen and ibuprofen provided effective analgesia. The combination of NSAIDs and acetaminophen given in ERAS arm is more effective than either medication given alone.[23] Regular pain assessment, counseling, and education likely further minimized breakthrough pain and improved coping.

Headache was notably significant at proportions of 6.6% in the ERAS compared to 30.4% in the SOC arm. This difference was probably due to the superior analgesia in the ERAS arm relative to the SOC arm. Whereas much information may have been missed by not classifying the headache but we did not design the study to do a detailed investigation of the variables.

We recorded a higher incidence of pruritus in the ERAS compared to standard recovery of 8.9% vs 1.5%. This is due to the use of ITM, with itching as one of its common side effects. Itching resolved within 24 hours on oral cetirizine and so did not preclude discharge, which, in most cases, was after 24 hours. Marroquin et al[24] in a comparative study of postcesarean analgesia found incidence of pruritus of 35.8% in the ITM group. However, that study used a higher dose of morphine: 200 µg compared to 100 µg in our study. The higher the ITM dose, the more complications, pruritus inclusive.[25] While comparing the analgesic effects of ITM and transversus abdominis plane block after CD at our hospital, Kwikiriza et al[26] found incidence of pruritus in the ITM group of 9% at a similar dose of 100 µg.

There was no evidence for a difference in PONV between ERAS and SOC groups (P = .631), occurring in proportions of 6.6% and 8.7%, respectively. This is in contrast to what would be expected because PONV is expected to be more frequent in the SOC arm. According to a previous study, PONV had an incidence of 35.1% associated with the use of ITM at doses of 200 µg.[24] This low dose is probably responsible for the nonsignificant differences in the occurrence of PONV in ERAS and SOC in this study.[25] Use of spinal morphine could have also exacerbated PONV and negated the role of dexamethasone and metoclopramide in PONV prophylaxis in the ERAS arm. Kwikiriza et al[26] noted a rate of PONV in the ITM and transversus abdominis plane block group as 6% and 5%, respectively (P = .907) at 8 hours postoperatively, a nonsignificant differences similar to our study. PONV prophylaxis was not given in either group. A multimodal approach to antiemesis is highly recommended in ERAS to increase potency.[27] Serotonin receptor antagonists such as Ondansetron (which was not used) are the most recommended medication for prophylaxis against PONV.[27,28]

Our study has important strengths. First, it is a randomized controlled trial and the randomization was successful as evidenced by the balance in baseline characteristics in 2 study arms. Second, the trial is conducted in settings that represent a typical large hospital in sub-Saharan Africa where patient volumes are large yet functioning with limited local resources. However, our study also has several limitations. We were unable to blind the intervention group because the mothers had to cooperate and comprehend the ERAS protocols. This could have potentially affected the efficacy of the protocols. We also did not design this study to analyze the cost-effectiveness of ERAS compared to SOC practice, which should be considered in future research. To eliminate bias, we performed an ITT and per-protocol analysis. There was no significant difference in the results of the ITT and the per-protocol analysis as we have demonstrated.

In conclusion, in a referral hospital in southwestern Uganda, we found that ERAS reduces LOS, with no accompanying increase in complications except for pruritus. Our study shows ERAS is feasible and effective in emergency CD in an LIC. We recommend that the use of ITM be part of SOC. Our results should motivate multicenter trials to assess feasibility and implementation issues on a large scale. Our trial provides experience at a tertiary level. Future trials should consider implementation at district level health facilities with patient satisfaction surveys. Moreover, a cost-effectiveness analysis should be conducted to assess the cost implications if this program is to be scaled up and to guide policy decisions.

ACKNOWLEDGMENTS

We acknowledge the Kayanja Fellowship Scholarship program and Massachusetts General Hospital for the scholarship awarded to Dr Moris Baluku during his residency. We also recognize Mbarara Regional Referral Hospital for providing administrative clearance to conduct the study. We further acknowledge Mbarara University Research Training Institute (MURTI) for the training program in manuscript writing.

DISCLOSURES

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