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Randomised trial of early infant circumcision performed by clinical officers and registered nurse midwives using the Mogen clamp in Rakai, Uganda

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Objectives

To assess the safety and acceptability of early infant circumcision (EIC) provided by trained clinical officers (COs) and registered nurse midwives (RNMWs) in rural Uganda.

Subjects and Methods

We conducted a randomised trial of EIC using the Mogen clamp provided by newly trained COs and RNMWs in four health centres in rural Rakai, Uganda. The trial was registered with clinicaltrials.gov # NCT02596282. In all, 501 healthy neonates aged 1–28 days with normal birth weight and gestational age were randomised to COs (n = 256) and RNMWs (n = 245) for EIC, and were followed-up at 1, 7 and 28 days.

Results

In all, 701 mothers were directly invited to participate in the trial, 525 consented to circumcision (74.9%) and 23 were found ineligible on screening (4.4%). The procedure took an average of 10.5 min. Adherence to follow-up was >90% at all scheduled visits. The rates of moderate/severe adverse events were 2.4% for COs and 1.6% for RNMWs (P = 0.9). All wounds were healed by 28 days after circumcision. Maternal satisfaction with the procedure was 99.6% for infants circumcised by COs and 100% among infants circumcised by RNMWs.

Conclusions

EIC was acceptable in this rural Ugandan population and can be safely performed by RNMWs who have direct contact with the mothers during pregnancy and delivery. EIC services should be made available to parents who are interested in the service.

Keywords

non-physicians, Mogen clamp, Rakai, Uganda, early infant circumcision

Introduction

Medical circumcision (MC) reduced HIV incidence in men by 50–60% in three randomised trials [1–3], and observational studies of men circumcised in infancy or childhood [4] show long-term protection from HIV acquisition in adulthood. MC has been recommended by the Joint United Nations Programme on HIV/AIDS (UNAIDS), as a major component of HIV prevention strategies in 14 priority countries in East and Southern Africa with high rates of HIV and low prevalence of MC [5]. The goal is to provide 20.3 million MCs in order to achieve 80% coverage, and WHO estimates that a cumulative total of >9 million procedures had been performed in adolescents and adults by 2014 [6]. Although HIV prevention has been achieved through scale up of MC in adolescents and adults, long-term sustainability will likely be achieved through early infant circumcision (EIC). EIC is technically simpler, safer, and less expensive compared to MC performed in older children or adults, and wound healing is faster after EIC [7]. Also, EIC avoids the risk of premature resumption of sexual activity before complete wound healing observed in men after circumcision. Additionally, EIC provides protection from infant male UTIs and foreskin pathologies such as phimosis and balanitis [8].

With the exception of Muslims and some ethnic/tribal groups, EIC is not routinely performed in most of the 14 priority countries. Randomised trials of different procedures for EIC provided by physicians have been conducted in

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Botswana and Zambia [9,10]. However, there are insufficient physicians to provide a scale up of EIC, especially in rural areas, so future programmes will depend on task shifting to less skilled but more numerous personnel such as clinical officers (COs; equivalent to physicians assistants), nurses or nurse midwives who are better distributed geographically. A Kenyan programme assessed the safety of EIC using the Mogen clamp provided by nurses and COs, and found that the rate of adverse events (AEs, 2.7%) did not differ by type of provider [11].

The personnel with most access to new-borns are registered nurse midwives (RNMWs), who have the advantage of working in peripheral clinics, with direct contact with mothers during pregnancy, delivery and postpartum. RNMWs are trained in general nursing, obstetrics and gynaecology, and are licensed to perform episiotomies and repair first- or second-degree tears, but are not currently trained and licensed to perform circumcision. The Ugandan Ministry of Health and the Ugandan Nursing Council (UNC) were willing to allow RNMWs to perform EICs, if safety could be demonstrated. Therefore, we conducted a trial of EIC using the Mogen clamp provided by either COs or RNMWs in Uganda. The primary outcomes were safety, wound healing, and acceptability of EIC.

Subjects and Methods

The trial was conducted in four health centres in the rural Rakai district of southwestern Uganda. Radio messages were broadcast to inform parents of the availability of services. Mothers of new-born male infants aged ≥18 years were provided with information on the risks and benefits of EIC using the WHO/Johns Hopkins Programme for International Education in Gynecology and Obstetrics (JHPIEGO) guidelines [7] and were invited to participate in a randomised trial of EIC performed by COs or RNMWS. Women who were willing to participate and provided written informed consent were enrolled. The criteria for infant eligibility were age 1–28 days, birth weight ≥2.5 kg and a gestational age ≥37 weeks, no illness requiring medical treatment, no penile abnormality requiring surgical repair (e.g., hypospadias), and no family history of bleeding disorders. The goal was to enrol 500 eligible infants. The study statistician prepared random study assignments using a random number generator and assignments were sealed in unmarked envelopes placed in boxes of 10 envelopes. Mothers, were asked to select an envelope at random, and were assigned 1:1 to a CO or RNMW with replacement. Concurrent enrolment at four sites had a potential of creating a maximum of 20 more participants in one arm compared to the other given a block size of 10. Mothers were interviewed at the time of enrolment to assess their sociodemographic characteristics, behaviours and health, and to assess their views on EIC. Pain associated with surgery was assessed by the Neonatal Infant Pain Scale (NIPS) [12], based on facial expression, crying, breathing patterns, movement of arms and legs, and state of arousal. NIPS scores of zero were classified as no pain, scores 1–2 as mild, scores 3–4 as moderate, and >4 as severe pain.

Analgesia was provided by topical 2.5% lidocaine and 2.5% prilocaine (eutectic mixture of local anaesthetics [EMLA] or Fougera cream) <1 g applied to the prepuce 60 min before surgery. A 40 mg acetaminophen suppository was provided 30 min before the procedure, and infants were given a 24% sucrose solution as a pacifier if needed. Infants aged <14 days were given a preoperative injection of 1 mg Vitamin K (s.c.) to avoid bleeding [13]. The infants were swaddled with knees restrained on a strap board, the perineum cleaned, and the penis swabbed three times with povidone iodine. The foreskin was marked by a sterile pen or gentian violet at the corona and preputial glandular adhesions were freed with a probe/haemostat. Haemostats were applied to the foreskin at the 3 and 9 o'clock positions and the glans pushed down for protection. The foreskin was lightly pinched to retract the glans. Traction was applied before placing the Mogen clamp with a 2.5-mm gap distance (concave side facing the glans penis), using the surgical mark as a guide. The glans was palpated to ensure it was not trapped, and the clamp was closed for 5 min to achieve haemostasis. The foreskin was removed with a scalpel using the outer flat surface of the clamp as a guide. Under gentle pressure the glans was allowed to emerge from under the crushed foreskin. All instruments were sterilised using standard hospital procedures.

Pure petroleum jelly (e.g., Vaseline) was applied to the glans and the wound covered with sterile gauze. Infants were observed for 1 h before discharge. Mothers were instructed to remove and replace the gauze with each diaper change for the first 24 h postoperatively. They were also shown how to apply petroleum jelly every 3 h on postoperative days 2 and 4 to prevent adhesions. They were provided with sterile gauze and petroleum jelly.

Follow-up after circumcision included a telephone call at 1 day after the circumcision, a visit at 4–7 days and at 28 days, and unscheduled visits could be made as needed. Infants were examined to assess wound healing and any complications by clinicians who were blinded to the personnel (CO or RNMW) who had performed the procedure.

AEs were pre-specified using WHO/JHPIEGO definitions of the nature and severity of AEs, and classified as related or unrelated to EIC [7]. Moderate and severe AEs were photographed for subsequent review. Severe AEs were reported to the principle investigator, NIH Medical Officer and the cognisant Institutional Review Boards (IRBs) within 48 h of notification.

A Data Safety Monitoring Committee (DSMC) was established and comprised of a statistician, neonatologist and urologist who monitored the study. Recruitment was paused after 100 procedures and safety was reviewed by the DSMC prior to continued enrolment.

The trial was reviewed and approved by three IRBs, the Scientific and Ethics Committee, now named the Research Ethics Committee, of the Uganda Virus Research Institute, the Uganda National Council of Science and Technology, and the Johns Hopkins University, Bloomberg School of Public Health IRB.

Statistical Analysis

The characteristics of the mothers and infants at enrolment were assessed by study arm to determine comparability. Acceptability was defined as the number of mothers who consented to EIC as a proportion of the numbers directly invited to enrol in the trial.

The primary endpoint was AEs related to the study, obtained from infant caretakers' reports and direct observation. Definitions of AEs were based on the WHO/JHPIEGO Manual for early infant circumcision. AEs were classified as mild requiring no intervention, moderate requiring treatment, and severe requiring surgery or hospitalisation. Analyses were by intention-to-treat with AE rates (percentage) estimated as the number of AEs per 100 EICs. AE rates were stratified by trial arm, and compared using chi-square tests in bivariate analyses. Multivariable analysis used a logistic mixed effects model (xtmelogit in Stata) to generate random effects at provider and health facility level in order to account for clustering effects. The measures of association were the adjusted odds ratios (adj.ORs) of AEs and corresponding 95% CIs. In the supplementary figures, we also report a generalised linear model with AE as the main outcome to predict the probability of an AE by study arm associated with time to complete the procedure, number of proceeding surgeries performed by the provider, preoperative temperature, preoperative weight, and infant's age (Figs S2–S6). The NIPS scores were classified as zero no pain, 1–2 as mild, 3–4 as moderate, and >4 as severe pain. A binary outcome variable was constructed with no pain/mild pain as the referent vs moderate/severe, and the adjusted prevalence risk ratios (adj.PRRs) estimated using modified Poisson regression, adjusting for clustering at the provider and facility level and covariates of infant characteristics. The average time taken by each cadre was estimated using a *t*-test and multivariable analysis used a mixed effects model in Stata to estimate time to completion adjusting for provider experience and generating random effects at provider and health facility level in order to account for clustering effects.

Results

Figure 1 shows the Consolidated Standards of Reporting Trials (CONSORT) diagram for the trial. A total of 701 women with new-born male infants were contacted and registered of whom 18 (2.6%) declined to participate and 158 (23.1%) were not consented. A total of 525 mothers provided consent for enrolment, of whom 424 (81%) consented after consultation with the child's father. Thus, estimated acceptability was 74.9% (525/701). At screening 23 (4.4%) infants were found to be ineligible due to low birth weight or preterm (four), illness (six), penile abnormalities (eight) or a history suggestive of bleeding disorder (five). In all, 502 infants were randomised but one child was found to have a penile abnormality at the time of surgery and was excluded, leaving 501 circumcised infants, 256 performed by COs and 245 by RNMWs.

There were no differences in maternal characteristics by study arm (Table 1), and infants were comparable in most respects except that the mean birth weight of infants circumcised by RNMWs was 0.1 kg higher than those circumcised by COs ($P = 0.04$) (Table 2).

The mean time (95% CI) to completion of an EIC by the COs was 11.78 (10.73–12.92) min vs 10.47 (9.54–11.41) min for the RNMWs. The time for RNMWs to complete an EIC decreased with more experience ($r = -0.13$, 95% CI −0.072, −0.182), but the time required by COs did not decline with experience ($r = 0.025$, 95% CI −0.037, 0.086) (Table S1, Fig. S1).

The distribution of NIPS scores during surgery were: 10.4% no pain, 65.9% mild discomfort, 22.2% moderate pain, and 1.6% severe pain. If crying were excluded from the NIPS assessment, 42.5% of infants were classified as having no pain. Overall, 24.6% of infants experienced pain with the COs compared to 22.9% with the RNMWs (adj.PRR 0.92, 95% CI 0.42–2.02). The NIPS scores increased with infants' age. Compared to infants aged 0–6 days, the risk of pain was higher among infants aged 7–13 days (adj.PRR 1.81, 95% CI 1.00–3.30; $P = 0.052$), and ≥14 days (adj.PRR 2.40, 95% CI 1.27–4.52; $P = 0.007$). The number of circumcisions performed, use of a pacifier, and infant's bodyweight were associated with a lower prevalence of pain but these differences were statistically not significant in the adjusted analyses (Table 3).

There were a total of 13 AEs and the AE rate was similar among infants circumcised by COs, 2.3% (six of 256) and RNMWs, 2.9% (seven of 245; adj.OR 1.21, 95% CI 0.38–3.85; $P = 0.784$). Moderate/severe AE rates were 2.3% (six of 256) for the CO surgeries and 1.6% (four of 245) for the RNMW surgeries ($P = 0.9$; (Table 4). Infants with an elevated preoperative temperature (>37.1 vs 36.0–36.5 °C) had a

Fig. 1 CONSORT diagram for the trial.

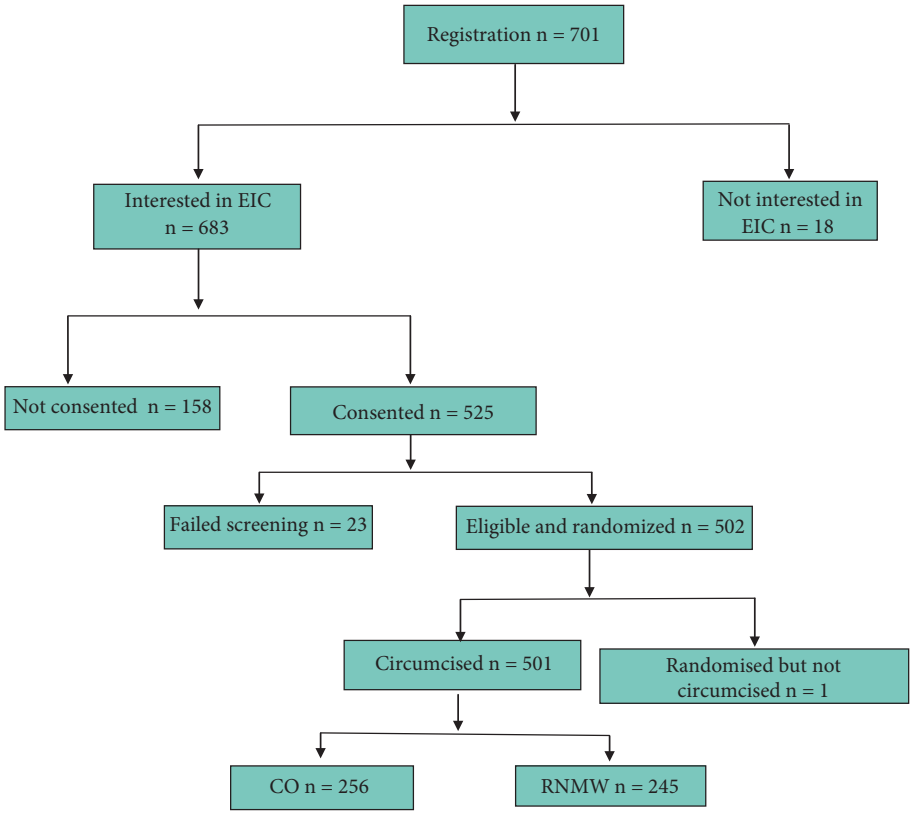

Table 1 Maternal characteristics by study arm.

Variable	CO, *n* (%)	RNMW, *n* (%)	*P*
Total	256 (100)	245 (100)	
Age, years			
18–19	34 (13.3)	34 (13.9)	0.543
20–24	78 (30.5)	79 (32.2)	
25–29	61 (23.8)	67 (27.3)	
30–34	46 (18.0)	41 (16.7)	
≥35	37 (14.5)	24 (9.8)	
Education			
Primary	128 (50.0)	111 (45.3)	0.683
Secondary	79 (30.9)	80 (32.7)	
Technical/university	18 (7.0)	21 (8.6)	
Vocational training	25 (9.8)	23 (9.4)	
No education	6 (2.3)	10 (4.1)	
Currently married			
Yes	226 (88.3)	221 (90.2)	0.565
No	30 (11.7)	24 (9.8)	
HIV status			
Negative	225 (87.9)	215 (87.8)	0.963
Positive	31 (12.1)	30 (12.2)	
Total number of pregnancies			
1	62 (24.2)	71 (29.0)	0.455
2–3	84 (32.8)	77 (31.4)	
4–5	60 (23.4)	60 (24.5)	
≥6	50 (19.5)	37 (15.1)	

higher odds of AEs (adj.OR 6.30, 95% CI 0.94–42.33), which was of borderline statistical significance (P =0.058). The more circumcisions performed, and older and heavier infants tended to have lower odds of AEs, but these were not statistically significant. Infants with HIV-positive mothers, or mothers with post-secondary education tended to have nonsignificant higher odds of AEs (Table 5).

Details of the AEs are given in Table 6. There were five cases of bleeding, two of which were classified as severe because suturing was required for haemostasis. There were four cases of adhesions and four cases of insufficient skin removal classified as mild or moderate as none required surgical interventions.

Retention rates were >90% at all scheduled follow-ups and did not differ between study arms (Table 7). Among infants seen at the 28-day visit, wound healing was complete in 100% of CO and RNMW surgeries. Maternal satisfaction was 99.6% for infants circumcised by COs and 100% among infants circumcised by RNMWs.

Discussion

Previous studies in Rakai showed that COs can perform adult MCs as safely as physicians [14]. In Uganda, COs are licensed to perform minor surgery and provide circumcision services in peripheral health facilities. Thus, they are an appropriate category of personnel for comparison with RNMWs, who care for new-borns but are not licensed to perform EIC, despite evidence from similar settings such as

Table 2 Infant characteristics by study arm.

Infant characteristics	CO		RNMW		*P*
	Median (IQR)	Mean (SD)	Median (IQR)	Mean (SD)	
Gestational age, weeks	38 (2)	38.8 (1.1)	38 (2)	38.7 (1.0)	0.56
Age, days	7 (15)	9.6 (8.5)	7 (14)	9.3 (8.5)	0.91
Birth weight, kg	3.2 (0.6)	3.2 (0.4)	3.3 (0.5)	3.3 (0.5)	0.04
Preoperative weight, kg	3.4 (0.9)	3.5 (0.6)	3.5 (0.8)	3.6 (0.6)	0.08
Preoperative temperature, °C	36.7 (0.5)	36.7 (0.3)	36.7 (0.6)	36.7 (0.4)	0.37
Preoperative pulse rate	142 (18)	140.5 (12.9)	142 (19)	140.5 (13.2)	0.85
Preoperative respiratory rate	50 (8)	50.1 (5.3)	50 (7)	50.6 (6.4)	0.48

Kenya suggesting that EIC may be performed by a lower cadre of healthcare workers than adult MC [11]. We opted to compare newly trained COs and RNMWs because the objective was to establish whether RNMWs who have not previously provided EIC could be trained to provide safe EIC compared to newly trained COs, rather than highly experienced COs.

Table 3 PRRs of pain by study arm and infant characteristics.

	Adj.PRR of pain	95% CI		*P*
Trial arm				
CO	1.00			
RNMW	0.92	0.42	2.02	0.826
Infant age, days				
0–6	1.00			
07–14	**1.81**	**1.00**	**3.30**	**0.052**
≥14	**2.40**	**1.27**	**4.52**	**0.007**
Circumcision time (min)	0.95	0.86	1.05	0.288
Preoperative temperature, °C				
36.0–36.4	1.00			
36.5–37.0	1.10	0.79	1.53	0.572
37.1–37.9	0.95	0.51	1.76	0.87
Preoperative pulse rate				
101–130	1.00			
131–160	**1.71**	**0.99**	**2.96**	**0.053**
161–176	**3.53**	**1.43**	**8.75**	**0.006**
Preoperative respiratory rate	1.00	0.98	1.03	0.671
Preoperative weight, kg				
≤3.1	1.00			
3.101–3.49	0.95	0.54	1.69	0.871
≥3.5	0.79	0.43	1.44	0.444
Prior circumcisions performed	0.98	0.94	1.03	0.482

Bold values indicate younger infants and those with preoperative pulse rates closer to 100 were more likely to have lower pain scores.

The present randomised trial showed that the safety of EICs performed by the RNMWs did not differ from those performed by COs. In addition, the levels of AEs observed in the present randomised trial (2.6%) are similar to or lower than those reported elsewhere in sub-Saharan Africa. There have been two African trials of infant circumcision performed by physicians using the Mogen clamp; in Zambia the AE rate was 4.7% [10] and in Botswana the rate was substantially higher, primarily because of insufficient skin removal (22.3%) [9]. A programme in Kenya of EIC performed by COs or nurses using the Mogen clamp reported an AE rate of 2.3%, excluding insufficient skin removal and 4.0% with the latter included, among infants with active follow-up [11]. A systematic review of 16 prospective studies estimated a median AE rate of 1.5%. [15]. In the present study, we found no cases of infection and healing was complete by 28 days in all infants. Thus, the rate of AEs observed in the present study is comparable to that reported in the majority of other studies, including those in Zambia and Botswana involving physicians [9,10], suggesting that EIC is safe when performed by trained RNMWs in Uganda.

Of 701 mother–infant pairs registered as potential participants, 525 consented to surgery (74.9%). Thus, the acceptability of EIC appears to be high in this population, although there is a possibility of self-selection of parents who responded to the radio messages about EIC availability. In Botswana, 60% of mothers who said they wanted their son circumcised brought their child to the hospital for the procedure. This is in contrast to the findings from hospital-based studies in Lusaka, Zambia where only 11% of mothers

Table 4 AEs related to EIC by arm.

Severity	CO		RNMW		Total	
	N	AE proportion, % (*N* = 256)	*N*	AE proportion, % (*N* = 245)	*N*	AE proportion, % (*N* = 501)
Mild	0	0	3	1.2	3	0.6
Moderate	5	2.0	2	0.8	7	1.4
Severe	1	0.4	2	0.8	3	0.6
		0.0		0.0		0.0
Total	6	2.3	7	2.9	13	2.6

Table 5 Adjusted ORs of AEs by trial arm and infant characteristics.

	Adj.OR	95% CI		P
Trial Arm				
CO	1.00			
RNMW	1.21	0.38	3.85	0.330
Infant age, days				
1–6	1.0			
7–13	0.31	0.03	2.85	0.298
≥14	0.58	0.12	2.86	0.504
Circumcision time (min)	0.91	0.75	1.11	0.356
Preoperative baby weight, kg				
≤3.1	1.0			
3.101–3.49	0.55	0.10	3.07	0.499
≥3.5	0.86	0.20	3.58	0.832
Preoperative temperature, °C				
36–36.5				
36.6–37.1	2.50	0.512	12.15	0.257
>37.1	6.30	0.94	42.33	0.058
Prior number of circumcisions	0.93	0.86	1.01	0.103
Education				
Primary				
Secondary	0.45	0.09	2.24	0.333
University, Technical	1.51	0.591	6.76	0.665
HIV negative	1.0			
HIV positive	1.62	0.32	8.33	0.562

Table 6 Adverse events.

Provider	Description	Severity	Time of AE, days
CO	Bleeding	Moderate	1
RNMW	Adhesions	Mild	28
RNMW	Adhesions	Mild	28
CO	Adhesions	Moderate	28
RNMW	Adhesions	Mild	28
RNMW	Insufficient skin removal	Moderate	28
RNMW	Bleeding	Severe	1
CO	Insufficient skin removal	Moderate	After study
RNMW	Bleeding	Moderate	1
CO	Insufficient skin removal	Moderate	28
CO	Insufficient skin removal	Moderate	After study
RNMW	Bleeding	Severe	1
CO	Bleeding	Severe	1

Table 7 Retention rate by study arm.

	CO, *n* (%)	RNMW, *n* (%)
Number circumcised	256 (100.0)	245 (100.0)
Follow-up		
1-day telephone call	243 (94.9)	239 (97.6)
7-day visit	252 (98.4)	241 (98.4)
28-day visit	240 (93.8)	230 (93.9)

who said they planned to circumcise their sons actually brought their child to the hospital for surgery [9,10].

The studies in Zambia, Botswana, and Kenya all used a dorsal penile nerve block for anaesthesia, but we were reluctant to use injectable local anaesthesia in this rural setting due to the risk of convulsions with accidental i.v. injections. We chose to use combined analgesia with paracetamol suppositories, 2.5% lidocaine/2.5% prilocaine cream and oral sucrose, and with this regimen, NIPS scores suggested 22.2% of infants experienced moderate pain and 1.6% experienced severe pain. However, crying was a major component of these scores, and if it was excluded, the rate of moderate/severe pain with surgery was reduced to 3.4%. A USA study of EMLA cream analgesia and Plastibell circumcision found substantially higher rates of moderate/severe NIPS scores [16]. Thus, we conclude that the multiple analgesia regimen used in the present study ameliorated but did not abolish infant pain.

In conclusion, we think that RNMWs can be trained to safely provide infant circumcisions using the Mogen clamp in health centres with minimal surgical facilities, and as the RNMWs have direct contact with mothers during pregnancy and delivery, they are ideally situated to offer these services for new-born boys. In the long-term, provision of EIC could be important for sustaining high rates of circumcision in order to prevent HIV and sexually transmitted infections when adolescents become sexually active and would provide immediate benefits to young boys by prevention of UTIs and foreskin pathologies.

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Conflicts of Interest

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Abbreviations: AE, adverse event; CO, clinical officer; CONSORT, Consolidated Standards Of Reporting Trials; DSMC, Data Safety Monitoring Committee; EIC, early infant circumcision; EMLA, eutectic mixture of local anaesthetics; IRB, Institutional Review Board; JHPIEGO, Johns Hopkins Programme for International Education in Gynecology and Obstetrics; MC, medical circumcision; NIPS, Neonatal Infant Pain Scale; (adj.)OR, (adjusted) odds ratio; (adj.)PRR, (adjusted) prevalence risk ratio; RNMW, registered nurse midwife.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1 Time to complete EIC surgery by number of previous EICs performed by COs and RNMWs.
Fig. S2 Probability of AE by time to complete EIC by provider (CO or RNMW).
Fig. S3 Probability of AE by number of preceding EICs by provider (CO or RNMW).
Fig. S4 Probability of AE by preoperative temperature by provider (CO or RNMW).
Fig. S5 Probability of AE by preoperative weight by provider (CO or RNMW).
Fig. S6. Probability of AE by baby's age by provider (CO or RNMW).
Table S1 Time taken to complete a procedure stratified by provider.