Adverse Events after Voluntary Medical Male Circumcision in Swaziland

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Background: The Luke Commission (TLC) provides comprehensive mobile healthcare in rural Swaziland, a country with a 26% prevalence of HIV. Voluntary medical male circumcision (VMMC) has been shown to reduce the rate of HIV transmission by 60%. Initial national guidelines have recommended circumcision for infants and HIV-negative men ages 15-24 but have not included recommendations for boys ages 60 days-ten years old. This study evaluated the safety of circumcision in younger boys and those with HIV.

Methods: Forceps-guided circumcision was performed under local block in 1,500 male patients. Incidence of adverse events (AEs)--infection, bleeding and dehiscence - was examined as a function of age, weight, HIV status and season.

Results: The AE rate was 2.1% (31/1500); boys age ≤ 12 had 2.0% (20/1022) compared to 2.3% (11/478) in patients age ≥ 13 (p=0.66). Patients ≤ 29kg had 2.4% (16/662) AE compared to 1.8% (15/838) in patients >30kg (p=0.40). HIV-positive patients had 0% (0/76) AE. 2.9% (10/343) of patients who underwent circumcision during the summer incurred wound dehiscences, compared to 1.6% (10/640) in the fall and 0% (0/517) in the winter [p=0.001].

Conclusions: The novel use of double povidone-iodine prep with close follow-up produced adverse event rates comparable to those reported in the literature, even in rural settings. Circumcising younger patients or HIV-positive males did not result in higher adverse event rates.

Introduction

For over a decade, research has shown the efficacy of circumcision as a method to help prevent the spread of HIV[1,2,3]. Studies report up to a 60% reduction of the risk of HIV infection[1,2,3,4]. Mathematical models have suggested that widespread implementation of a circumcision program in sub-Saharan Africa would eliminate two million new cases of HIV over the first ten years[5].

Voluntary Medical Male Circumcision (VMMC) has been shown to reduce the risk of HIV transmission through several mechanisms[6]. First, the mucosa and submucosa of the foreskin contain a dense population of T cells, macrophages and Langerhans' cells that are positive for the CD4 cell marker, the target of the HIV virus[7]. Second, circumcised individuals have fewer microabrasions secondary to trauma during sexual intercourse, reducing the transmission of blood-borne infections such as HIV[8]. Third, circumcision has been shown to decrease the occurrence of syphilis and gonorrhea, both of which are associated with higher rates of HIV infection[9,10]

Swaziland currently has the highest prevalence of HIV in the world, with over a quarter of its adult population (27% of 800,000 people ages 15-49) being HIV positive[11,12]. To combat this epidemic, the Swaziland Ministry of Health (MOH) began its VMMC program with guidelines recommending the procedure for all Swazi males ages 15-24 who had tested negative for HIV[13].

Data from the United States President's Emergency Plan for AIDS Relief (PEPFAR) indicate that 81,381 Swazi men have undergone VMMC between 2007-2015[14]. While TLC circumcises male patients of all ages who come to an outreach clinic for VMMC regardless of HIV status, staff found that boys under four years old were unable to cooperate for the procedure performed under local anesthetic penile block.

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Swaziland's MOH published new guidelines in 2016 encouraging a two-phase scale up program for VMMC: the catch-up phase addressing male Swazis ages ten and 49, prioritizing those between ten and 24, and the sustainability phase establishing an early infant male circumcision (EIMC) program requiring circumcision within 60 days of birth (NERCHA, 2016).

The Luke Commission (TLC) is a healthcare organization that for 11 years has provided comprehensive healthcare services to Swaziland's rural population, which encompasses >70% of the country's population of 1,297,378. TLC is faith-based and has partnered with the United States government through PEPFAR and is supported by both the United States Agency for International Development and Swaziland's Ministry of Health (The Luke Commission, 2013). TLC introduced its voluntary medical male circumcision (VMMC) program when the importance of circumcision in the battle against HIV became apparent.

TLC reasoned that circumcising younger boys would provide increased protection throughout their active sexual lifetimes, thereby decreasing HIV transmission potential. They also believed that with support from elders, who were also invited to undergo the procedure, the social acceptance of VMMC would be greater. Lastly, TLC reasoned that circumcising both HIV positive and negative male Swazis would reduce the stigma associated with being turned away from the healthcare facility after a positive test, leading to subsequent unwillingness by others to pursue the procedure[15].

This study investigates the safety of TLC's policy of circumcising all male patients, regardless of age, weight, and HIV status, by

examining the adverse event rate between groups. TLC uses extensive methods to minimize the rate of adverse events (AE), including the povidone-iodine double prep technique, as well as meticulous post-procedural follow-up on all patients.

The Swazi Male Circumcision for HIV Prevention Clinical Protocol, which details a single sterile patient preparation with povidone-iodine solution[13]. Since many of TLC's patients have limited or no access to running water or soap, preoperative hygiene and postoperative wound care are significant obstacles. TLC has dealt with this issue by using a double prep procedure that goes beyond the government's required single prep[15].At TLC, a Swazi staff member first washes the patient with povidone-iodine from the nipple line to mid-thigh. The patient is then prepped with povidone-iodine solution using sterile technique and is draped by a nurse to ensure readiness for the surgical procedure. Another important part of TLC's standard procedure is to provide all patients with transportation back to the sites of their surgeries on postoperative day two. On postoperative day two and day seven, a TLC nurse also removes the bandage to examine the wound and check for signs of adverse events. TLC has a telephone hotline available at all times to address the needs of their patients[15]. This close follow-up ensures that complications can be addressed early.

After the surgical procedure was completed, patients were sent to the recovery room, usually for several hours, until they could urinate without difficulty. Adverse events were identified at any point in the process, including immediately postoperatively, on one of two follow-up days or later by phone. A TLC nurse performed follow-up visits on postoperative days two and seven when she returned to the community, removed bandages, and examined the incision and surrounding tissue to check the healing progress. Most (29/34 or 85%) adverse events were identified during one of the two follow-up visits[15].

Material and Methods

The Wright State University Institutional Review Board approved this study. TLC staff reviewed and tested the validity and reliability of all data files.

The study sample included all male patients who underwent circumcision at a TLC mobile outreach between January and June of 2014. Consent from the patient and, in the case of minors (under 18 years old,) from a parent, was obtained. Staff members collected information on age, weight, HIV/TB status and sexual history. After performing a focused history and physical examination, a nurse recorded this information on an internal TLC procedural checklist to be transcribed into the permanent medical record and entered into the electronic database used for this study.

We examined wound infection, disruption/dehiscence and excessive bleeding since these three AEs could be assessed objectively and were the most critical (i.e. requiring immediate medical attention). Other AEs proposed for consideration by the World Health Organization include pain, swelling, anesthesia reactions, penile damage, erectile dysfunction, scarring, torsion, excessive/insufficient skin removal and voiding problems.

Several of these AEs require long-term data collection that would not be possible until the child reaches adulthood.

A secondary analysis was also conducted to examine the seasonal variation of adverse events (bleeding, infection and dehiscence). We hypothesized that the rate of adverse events for VMMC would be low and that HIV positive patients or individuals under the age of 15 would have similar AE rates as compared to older or HIV negative patients. The study's findings will contribute to Swaziland's future policy decisions and recommendations for the performance of male circumcision.

The chi-squared test or Fisher's Exact Test (FET) was used for comparisons between two groups (age, weight, HIV status) or three groups (season) and adverse events (any AE, dehiscence, infection and/or bleeding). FET was used when 20% or mor e of the cross-tabulation cells had expected counts less than 5.00 or one or more cell(s) had an expected count less than 1.00. Inferences were made at the 0.05 level of significance with no corrections for multiple comparisons. Analyses were conducted using IBM SPSS Statistics 22.0.

Table 1: Risk factors for adverse events among 1500 circumcised males in Swaziland

Risk Factor	Total Adverse Events	Wound Dehiscence	Infection
Age			
12 or younger	20/1022 (2.0%)	12/1,022 (1.2%)	10/1,022 (1.0%)
13 or older	11/478 (2.3%)	8/478 (1.7%)	3/478 (0.6%)
	p=0.66	p=0.43	p=0.77
Weight			
29kg or lower	16/662 (2.4%)	11/662 (1.7%)	8/662 (1.2%)
30kg or higher	15/838 (1.8%)	9/838 (1.1%)	5/838 (0.6%)
	p=0.40	p=0.32	p=0.20
HIV Status			
Positive	0/76 (0%)	0/76 (0%)	0/76 (0%)
Negative	31/1424 (2.2%)	20/1424 (1.4%)	13/1424 (0.9%)
	p=0.40	p=0.62	p=1.00
Season			
Summer	10/343 (2.9%)	10/343 (2.9%)	1/343 (0.3%)
Fall	15/640 (2.3%)	10/640 (1.6%)	6/640 (0.9%)
Winter	6/517 (1.2%)	0/517 (0%)	6/517 (1.2%)
	p=0.17	p=0.001*	p=0.39
Totals	31/1500 (2.1%)*	20/1500 (1.33%)	13/1500 (0.87%)

*Twenty-eight patients had 1 AE and three patients had 2 AEs.
**Single episode of bleeding was identified during the fall in a 12 year old, 30kg patie
**For pairwise comparisons: Summer > Winter (p<0.001) and Summer>Fall (p=0.003

Results

For the 1500 patients in the study, follow-up was 99.7% at two days and 98.4% at seven days. Overall, 34 adverse events were reported in 31 patients: 20 wound dehiscences, 13 infections and one patient with excessive bleeding. The adverse event rate for all patients was 2.1%.

Age

Table 1 shows that in total there were 20 AE incidences among patients 12 years of age or younger (2.0%), and patients 13 years of age or older had 11 AEs in 478 circumcisions (2.3%) [p = 0.66].

For patients ≤ 12 years old, 12/1022 (1.2%) had wound dehiscence, and in the group ≥ 13 years old, 8/478 (1.7%) patients experienced wound dehiscence (p=0.43). Of those in the ≤ 12 years old group, 10/1022 (1.0%) experienced wound infection, while 3/478 (0.6%) had wound infection in the ≥ 13 years old group (p=0.77). The one case of bleeding was in the ≤ 12 years old group.

Weight

Table 1 shows that patients ≤ 29kg had 16 AEs in 662 patients (2.4%) while patients ≥ 30kg had 15 AEs in 838 circumcisions (1.8%) [p=0.40].

For patients ≤29kg, 11/662 (1.7%) had wound dehiscence, and in the ≥30 kg group, 9/838 (1.1%) experienced wound dehiscence (p=0.32). Of those in the ≤29kg group, 8/662 (1.2%) had wound infection, while 5/838 (0.6%) had wound infection in the ≥30kg group (p=0.20). The one case of bleeding was in the ≥30kg group.

HIV Status

Table 1 shows that there were no AEs reported in 76 HIV-positive patients and 31 AEs in 1424 (2.2%) HIV-negative patients [p=0.40].

For the HIV positive group, no patient (0/76, 0%) had wound dehiscence while 20/1424 (1.4%) experienced wound dehiscence in the HIV negative group (p=0.62). The incidence of infection was 0% (0 of 76) for the HIV positive group and 0.9% (13 of 1424) for the HIV negative group (p=1.00). The patient with bleeding was in the HIV negative group.

Season of Procedure

While the incidence of AEs in winter (6 of 517 or 1.2%) was less than half that of summer (10 of 343 or 2.9%) and fall (15 of 640 or 2.3%), the difference was not significant (p=0.17) [Table 1]. Wound dehiscence occurred more frequently in summer (10 of 343 or 2.9%) and fall (10 of 640 or 1.6%) than in winter (0 of 517 or 0%) [p < 0.001 and 0.003, respectively].

Discussion

Previous Swaziland national guidelines have been directed towards older HIV negative patients[13]. These guidelines specified circumcising only HIV negative men over the age of 15; TLC's patient population is notably younger than the national average. A 2009 study found that the average onset of puberty was 10.5 years old in surrounding areas of Africa[17]. For our analysis age groups were separated at 12 years old to ensure that the older group was composed primarily of post-pubertal patients in case puberty contributed to increased adverse events. Research regarding the average age of puberty and sexual engagement is lacking in our study's geographical area, and a large portion of the patient population (ages 10-14) could be considered a high-risk group whose medical needs are often overlooked[18]. We found that age and HIV status were not related to adverse events – i.e. younger and HIV positive patients were not more likely to have adverse events.

Initially, Swaziland targeted ages 15-24 since they were at greatest risk of HIV infection[19]. On behalf of Swaziland's Ministry of Health (MOH), a 2016 study showed which age-at-circumcision groups benefited most in prevention of HIV and cost-effectiveness[20]. Kripke et al. sought to address whether circumcision was more effective and cost-efficient in certain age groups using mathematical models. They found that the greatest magnitude of impact is seen in young men ages 15-29 but boys ages 10-14 have the longest-term benefits both for themselves as well as all future sexual partners[21]. Based on these findings, the MOH implemented a "scaled up" circumcision program for males, with coverage of 50% for newborns, 80% for 10-29 year olds, and 55% for ages 30–34.

TLC does not perform circumcision for infants, an important part of Swaziland's VMMC scale up. Infant circumcision must be performed within 60 days of birth.

The rural population served by TLC does not have regular access to health care nor the financial resources to travel to a clinic, and since circumcision was previously not part of Swazi culture, homebirth attendants historically do not perform the procedure.

The research investigating whether circumcision prevents the spread of HIV from infected men to uninfected partners is currently inconclusive. Theoretically, the transmission rate should decrease for the same reasons established in previous reports, such as lack of a hospitable environment for the virus and decreased trauma during intercourse[7,10]. Although research has not yet established the effectiveness of circumcising HIV positive patients to reduce the spread of HIV, TLC changed its policy to include these patients in its VMMC program in the hope of limiting stigmatization associated with publicly verbalizing a person's HIV status by turning him away from the outreach[20]. Under the Swaziland Ministry of Health directive of circumcising only HIV negative males, both those confirmed as positive and those who do not seek HIV testing due to apprehension would not be circumcised. Our findings support TLC's protocol since it shows that there is no greater incidence of

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adverse events in HIV positive patients who undergo VMMC.

Our finding of no difference in adverse events (wound dehiscence, infection and bleeding) between age groups supports TLC's decision to widen its age range for circumcision. Currently, the guidelines for prophylactic HIV circumcision in Swaziland do not include circumcision in patients 60 days to ten years old. Circumcision in boys before the initiation of sexual activity will provide increased protection throughout their active sexual lifetimes, decreasing HIV transmission potential. With the support from the traditional leadership of community elders, the willingness of parents to allow their sons to undergo VMMC rose from 28% to 48%[22].

The only AE difference in subgroups was the increase in wound dehiscence during the summer rainy season. While this result indicates that the best times of year for circumcision would be during cooler, dry months, the benefit of decreased transmission of HIV outweighs the harm of a minor surgical complication.

Several topics are worth further explanation and exploration. First, the analysis of adverse events by season was limited to six months within one year due to seasonal variations of temperature and precipitation. For example, traveling to rural mountainous areas on dirt roads is impossible during the rainy season. Impediments to travel are a common ISSUE IIn healthcare delivery throughout Africa. A study in Ghana showed that in a similar environment straight-line distance to the nearest healthcare facility is much shorter than the actual travel time due to difficulties such as dirt roads, mountainous terrain or vehicle accessibility issues, which are aggravated during the rainy summer months[23].

Secondly, while the 2.9% incidence of dehiscence during the summer months was the highest among the seasons, this rate is still lower than rates in most other sub-Saharan studies. A systematic review reported rates between 0%-24%, including 0% (Nigeria), 1.7% (Kenya), 2.8% (Tanzania), 3.5% (Kenya), 3.7% (Uganda), 3.8% (South Africa), 11.2% (Nigeria/ Kenya), 20.2% (Nigeria) and 24.1% (Nigeria)[24]. Comparisons of AE rates among organizations are difficult since the definitions of adverse events are variable. TLC uses the World Health Organization (WHO) definitions. TLC's youngest patients are four years old, with the majority between 10-14 years. The studies within the meta-analysis that contained similar age groups (15-49 years old) were conducted in South Africa and two in Kenya[22,24,25,26]. They reported AE rates of 3.8%, 3.7%, 1.7%%, and 3.5%, respectively. Most studies were conducted in major hospitals in large cities. TLC's program differs in that mobile hospital outreaches travel into rural mountainous regions without electricity or running water and set up the clinic using generators and buckets of water driven to the site.

Third, of the eleven adverse events listed by the WHO, we chose the three that could be assessed objectively and were the most critical since they require immediate medical attention. For example, if an infection is identified, the wound must be drained and antibiotics initiated. A more complete understanding of adverse events especially in younger and smaller patients would require assessing the other eight adverse events (pain, swelling, anesthesia reactions, penile damage, erectile dysfunction, scarring, torsion, excessive/ insufficient skin removal and voiding problems) over a longer period of time and with more patients as the incidence is very low.

Fourth, we only have follow-up data for patients on days two and seven postoperatively. With Swaziland's challenging, mountainous terrain, as well as with other logistical matters such as limited personnel and resources, adverse events requiring long-term follow-up can be addressed using TLC's hotline, but routine data are not collected.

Conclusions

In summary, we found that the combined adverse event rate for wound dehiscence, infection and bleeding among 1500 male Swaziland circumcision patients did not differ by age, weight or HIV status. While seasonal variation was found to be statistically significant, the slight increase in AE rate by season was not important clinically. We have provided support for The Luke Commission's circumcision policy, including circumcising younger, older, and HIV positive patients. TLC's adverse event rate of 2.1% is less thanthat of many other African circumcision programs and comparable to worldwide rates. Countries where HIV is epidemic, such as Swaziland, benefit when evidence-based voluntary medical male circumcision programs are instituted.

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