WHO Technical Advisory Group on Innovations in Male Circumcision

Report of teleconferences October 2018 and June 2019

Key Populations and Innovative Prevention, Department of HIV and Hepatitis, World Health Organization, Geneva Switzerland, October 2019

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Abbreviations

AE	adverse event
CI	confidence interval
FRP	foreskin removal procedure
IM	intramuscular
MC	male circumcision
RCT	randomized controlled trial
TAG	Technical Advisory Group on Innovations in Male Circumcision
TT	tetanus toxoid
TTCV	tetanus toxoid-containing vaccination
WHO	World Health Organization

Introduction

In October 2018 the World Health Organization (WHO) Technical Advisory Group (TAG) on Innovations in Male Circumcision held a teleconference to consider updates on the clinical evaluations of 1) the elastic collar compression device[1] Day_0 foreskin removal procedure, designed to mitigate tetanus risk associated with the standard Day_7 elastic collar compression device method, and 2) the vice clamp surgical assist device (see Annex 1. Agenda and Annex 2. List of participants). A follow up virtual TAG consultation was undertaken in June 2019 with the purpose to review additional expert opinions provided by the manufacturer of one device.

The WHO Secretariat opened the teleconference and introduced the members present as well as the external consultant on tetanus.

All TAG members and consultants were reminded that some information shared with TAG is confidential and not publicly available. TAG members were asked to maintain this confidentiality in accordance with their signed confidentiality agreements. Each member was asked in turn to declare verbally any potential interests related to the subject of the teleconference. All members responded that they had no interests to declare.

The key discussion points and recommendations from the consultation were to be shared with the WHO Guideline Development Group meeting in November 2018 and would be used to inform the WHO male circumcision device prequalification process.

TAG co-chair Tim Hargreave was asked to lead the meeting.

Elastic collar compression device[1] Day_0 foreskin removal procedure

Clinical data and reports

Reports were reviewed on the clinical safety of the Day_0 foreskin removal procedure (Day_0 FRP) from the first study in Zambia (no new information was added to the report reviewed in September 2017) and three new studies – two conducted in Kenya and one in Rwanda. These reports were supplemented with a specially commissioned expert review, presented in the report *Voluntary medical male circumcision and tetanus risk* (Annex 3).

The clinical reports included a total of 1507 placements from the four studies, all of which followed a common protocol for foreskin removal approximately 30 minutes after device placement (thus, Day_0), with the device then removed seven days after placement. Day_0 FRP was developed during the Zambia study as an alternative to the standard Day_7 foreskin removal procedure (Day_7 FRP), in which the foreskin and device together are removed seven days after device placement. Day_0 placements numbered 381 in the second phase of the Zambia study, 101 in a randomized trial (Kenya) comparing Day _0 with the Day 7 FRP and two field studies - in Kenya (515 clients) and in Rwanda (510 clients (Table 1). The RCT compared the 101 Day_0 FRP clients with 42 Day_7 FRP clients.

The procedure to prepare for device removal after seven days varied somewhat across the studies. In Zambia the instructions were for the client to wet his penis by dampening a piece of paper towel with clean water and holding it wrapped around the device for at least 20 minutes. These same instructions

[1] PrePex™

were annexed to the reports from the other sites, but the Kenya RCT report stated that, in addition to the dampened paper towel, wet gauze soaked in povidone iodine was applied for about five minutes before device removal, and the Kenya field study stated that gauze soaked in normal saline was applied for 10 minutes.

Across the four studies a total of 13 adverse events (AEs) were reported among the 1507 Day_0 FRP clients following revision of the Zambia foreskin removal protocol, for a risk rate of 0.9%. This rate is substantially less than the rate of 5.9% in Zambia Phase 1 (seven AEs reported in the first 119 placements). Of these 13 AEs, 10 occurred within the first week – severe bleeding immediately or soon after foreskin removal (6), self-removals on Day 2 (2), bleeding on Day 2 (1) and bleeding controlled with pressure (day relative to device placement or removal not reported) (1). The three remaining AEs occurred after removal of the device on Day 7; they included two wound infections treated with oral antibiotics and one tetanus case.

The tetanus case was documented in the Kenya field study report, which included clinical reports, notes, expert opinions and correspondence about this case. This client had received a tetanus toxoid-containing vaccination (TTCV) dose at the time of device placement. The patient was admitted to hospital on Day 22 after device placement (Day 15 after device removal). Symptoms had first appeared five days before hospitalization. He was treated with intramuscular (IM) diazepam, IM ceftriaxone and human tetanus immune globulin. He was discharged four days later.

Table 1. Clinical data on elastic collar compression Day_0 foreskin removal procedure

Study	Design	Period	Number	Adverse events	Remarks	TTCV provision*
Zambia Phase 1	Cohort	Mar 2017	119	7	Pilot phase, first assessment of Day_0 FRP	None
Zambia Phase 2	Cohort	Mar 2017	381	3	Revised Day_0 FRP protocol	None
Kenya randomized controlled trial	Day_0 FRP versus Day_7 elastic collar compression removal procedure	Apr–Aug 2017	101	2	Day_0 FRP protocol as in Zambia Phase 2 cohort	1 dose at time of placement
			42 with Day_7 foreskin and device removal	1		2 doses before placement**
Kenya field study	Cohort	Sep–Nov 2017	515	4	Day_0 FRP protocol as in Zambia Phase 2 cohort	1 dose at time of placement
Rwanda field study	Cohort	Oct–Nov 2017	510	4	Day_0 FRP protocol as in Zambia Phase 2 cohort	2 doses before placement**

FRP = foreskin removal procedure; TTCV = tetanus toxoid-containing vaccination

* Information added after TAG discussion

** Two doses at least four weeks apart, with the second at least two weeks before device placement (WHO-recommended protocol)

The TAG considered key points from the expert consultant's review on tetanus risk with different circumcision methods (Annex 3), which incorporated reviews by a clinician with expertise in several thousand tetanus cases and a microbiologist. The expert consultant discussed the new tetanus case. Although there was some uncertainty about the diagnosis, she concluded that the case should be classified as being consistent with a causal association (signs and symptoms of tetanus within a plausible incubation period, with reportedly normal wound healing and no alternative tetanus entry points evident elsewhere on the body).[1] She also noted that the circumcision clients in the Rwanda cohort had all received two TTCV injections before device placement in accordance with WHO recommendations and were likely protected from tetanus. They could not be considered in the "at risk" denominator when assessing tetanus incidence.

Summary points and recommendations

Key points and recommendations from the TAG emanated from the June 2018 meeting. An additional opportunity in June 2019 was provided to review additional expert opinions provided by the manufacturer. The June 2019 feedback showed consensus that the summary points should not be altered. These points are:

- The main safety concern of the Day_0 foreskin removal procedure was bleeding during the first week after placement and before device removal on Day 7. The proportion of clients experiencing an adverse event (10 in 1507 placements, or 7 per 1000 placements, 95% confidence interval (CI) 3 to 12 per 1000) appeared similar to the proportion observed with the Day_7 device and foreskin removal procedure, although the timing and clinical nature of the AEs differed.
- The clinical presentation and course of the tetanus case was considered consistent with mild tetanus. The clinical notes and examinations did not identify any wounds or other potential sites of infection other than the recent circumcision procedure.
- It was considered that the patient would likely have received tetanus toxoid injections as an infant through the routine vaccination programme, and the dose given at the time of device placement may have provided a booster response that contributed to the successful treatment outcome.
- The two study reports from Kenya also referred to TTCV prior to device placement. The TAG members requested a more thorough analysis of the number of Day_0 FRP clients according to their TTCV history and a comparison with previous information on tetanus risk, specifically incidence based on TTCV provision for study participants.
    - The one mild tetanus case had occurred in a total of 616 clients with one TTCV dose at placement and 500 clients with none. The incidence was approximately 90 per 100 000 procedures (95% CI 2.3 to 500) in clients about half of whom may have had partial protection from tetanus and half of whom may have had no or insufficient protection. This compared with approximately five cases per 100 000 Day_7 procedures and 0.2 cases

[1] WHO Informal Consultation on Tetanus and Voluntary Medical Male Circumcision: Report of meeting convened in Geneva, Switzerland, 9–10 March 2015. Geneva, World Health Organization, 2015. https://www.who.int/hiv/pub/malecircumcision/tetanus-male-circumcision/en/.

per 100 000 conventional surgical circumcisions, all in clients with no TTCV injections at the time of or prior to circumcision.[1]

- It was considered that there was no evidence of lower tetanus risk with the new Day_0 FRP protocol than with the Day_7 procedure.
- It was **recommended** that no modification should be made to the previous advice[1] that clients be fully protected against tetanus by vaccination before placement of the elastic collar compression device.
- The clinical data on Day_0 FRP was considered promising, and it was **recommended** that further use and clinical monitoring of safety, acceptability and reproducibility be undertaken in settings where proper tetanus protection, per WHO guidance, could be assured.
- Minor variations were noted in the removal procedures among the different studies and that some removals had been quite difficult, possibly due to desiccated foreskin remnants preventing easy inner ring extraction. Further exploration was recommended of good device removal procedures after foreskin excision on Day_0.
- The findings were to be shared with the meeting of the WHO Guideline Development Group (on Updated recommendations on safe male circumcision for HIV prevention and related service delivery for adolescent boys and men in generalized HIV epidemics) in November 2018 for their perspective on tetanus risk, tetanus risk mitigation and circumcision method.

Vice clamp surgical assist circumcision device

The vice clamp[2] surgical assist device is based on the Gomco surgical assist device extensively used for paediatric circumcision and tried in adults in a study in Mozambique. The device provides a firm and extended (at least five minutes) crush of the foreskin, sufficient to prevent bleeding. In adults in Mozambique cyanoacrylate tissue adhesive and a firm adhesive bandage applied after device removal were sufficient to control post-operative bleeding. Problems with reuse of the Gomco devices and mismatching of parts led to the concept of a single-use disposable device, subsequently strengthened to increase the crushing force. This device – version #2 – was evaluated in a series of five studies in South Africa with a total of 543 clients, 127 of whom were adolescents ages 10–15 years (Table 2).

Table 2. Clinical data on vice clamp surgical assist device version #2

Study	Design (location and period)	Number	Remarks
Unicirc Study 2	Case series (Cape Town, South Africa, 2013)	50	First study with modified version #2 device
Unicirc Study 3	Field study (3 sites in South Africa, 2014)	110	
Unicirc Study 4	Randomized controlled trial (2 sites, South Africa, 2015)	50	Plus control arm with 25 conventional surgical circumcisions (with injectable anaesthesia. All vice clamp clients received topical anaesthesia.)

[1] Tetanus and voluntary medical male circumcision: risk according to circumcision method and risk mitigation. Report of the WHO Technical Advisory Group on Innovations in Male Circumcision – consultative review of additional information, 12 August 2016. Geneva, World Health Organization, 2016. https://apps.who.int/iris/handle/10665/250146.

[2] Unicirc™

Unicirc Study 5	Adolescent study (1 site, South Africa, 2016)	82	Adolescents ages 10–15 years
Registry	Circumcision at 1 site (South Africa, 2016–17)	251	Including 45 adolescents ages 10–15 years
Total		**543**	**Including 127 ages 10–15 years**

The totality of clinical data over the five studies was assessed according to the evaluation criteria established for assessing other circumcision method innovations:

- **Eligibility** – There were no exclusions to use of the vice clamp surgical assist device beyond those considered exclusions to circumcision by any method.
- **Efficacy** – 541 of 543 clients (99.6%) were successfully circumcised with the device alone. The two failures were due to operator error (neglected to fully tighten device, addressed by training and revised instructions for use) and mismatched parts (addressed by ensuring that all parts are presented in a single package).
- **Safety** – No severe AEs and 27 moderate AEs (5.0% [95% CI 3.3% to 7.2%]), which included moderate bleeding (13 cases, 2.4% [95% CI 1.3% to 4.1%]), haematoma (5 cases, 0.9% [95% CI 0.3% to 2.1%]) and infection (9 cases, 1.7% [95% CI 0.8% to 3.1%]). All bleeding cases occurred before discharge from the clinic after the procedure and were managed with sutures or pressure.
- **Pain** – Sufficient pain control was obtained with use of topical anaesthesia applied for at least 25 minutes before starting the procedure (topical pain control protocol used in all but the first study with 50 men [Unicirc Study 2], where injectable anaesthesia was used). The majority of clients experienced at most mild pain when the clamp was tightened to its maximum pressure.
- **Wound healing** – 264 of 279 clients followed to four weeks (94.6% [95 CI 91.3% to 97.0%]) were fully healed by four weeks after circumcision.
- **Cosmetic result** at four weeks:
  - 40 of 43 clients (93%) had a smooth, regular cosmetic result following Unicirc circumcision, compared with two of 21 clients (9%) following conventional surgical circumcision in the direct randomized comparison. The remaining clients had irregular or scalloped healing wounds.
  - Over all studies 273 of 277 clients (98.6% [95% CI 96.3% to 99.6%]) had a regular final cosmetic result following circumcision with the vice clamp surgical assist device. All other results – three irregular and one scalloped appearance – were associated with interventions to manage AEs and were expected to resolve spontaneously.