2014

Does Male Circumcision Prevent Herpes Simplex Virus Type 2 in Sexually Active Males Aged 18-50?

Mary K. Macon
Philadelphia College of Osteopathic Medicine, marymac@pcom.edu

Does male circumcision prevent herpes simplex virus type 2 in sexually active males aged 18-50?

Mary K. Macon, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment Of The Requirements For

The Degree Of Master Of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 20, 2013

ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not male circumcision prevents herpes simplex virus type 2 ("HSV-2") in sexually active males aged 18-50.

STUDY DESIGN: Review of three English language primary studies published in 2009 and 2012.

DATA SOURCES: Three randomized control trials analyzing the intervention of circumcision to prevent HSV-2 in sexually active males found using Medline and PubMed.

OUTCOMES MEASURED: The main clinical outcome in all studies measured the incidence of HSV-2 defined as a sexually transmitted infection with symptoms of visible genital ulceration. The outcomes were measure by patient self-report of symptoms, nurse examination, and serum samples tested for the HSV-2 antibody utilizing the Kalon Biological assay. Mahiane et al. additionally measured the spread of HSV-2 from female to male partners, calculated via self-report of patients' sexual behavior including number of partners as a function of time and number of sexual contacts with each partner.

RESULTS: In the study by Mehta et al., circumcision was not statistically significant ($p = 0.655$) in preventing HSV-2. In the study by Tobian et al., statistical significance was proven ($p= 0.008$) in the intervention group receiving circumcision. In the study by Mahiane et al., circumcision was also found to be statistically significant in preventing HSV-2 per sex act ($p= 0.005$) and per partnership ($p=0.001$).

CONCLUSIONS: The results of two RCTs show circumcision to be an effective intervention in the prevention of HSV-2. Because one trial does not reach statistical significance, the overall results are inconclusive. In order to improve further research, a larger age and geographical population should be recruited.

KEY WORDS: Circumcision, HSV-2, males

INTRODUCTION

Herpes simplex virus type 2 ("HSV-2") is a sexually transmitted infection that is one of the main causes of genital lesions[8]. These lesions present in various stages ranging from vesicles to painful erythematous ulcers[3]. Transmission can occur during sexual contact from either those who have visible sores or those who have subclinical viral shedding when sores are not visible[1]. Because transmission can occur when ulcerations are not visible, a high percentage of the population is unknowingly HSV-2 positive[7].

Because of high prevalence of HSV-2, physician assistants in a variety of specialties will encounter HSV-2 patients. The Center for Disease Control ("CDC") estimates that 776,000 new cases of HSV-2 occur per year resulting in twenty-five percent of the United States population having serologic evidence of infection with HSV-2[7]. Although there are no specific estimates targeting HSV-2 alone, the CDC estimates the financial burden of treating eight of the most common sexually transmitted infections including HSV-2 contracted in one year is fifteen billion dollars[7]. In addition to the cost, the CDC reports that in 2010 there were approximately 232,000 healthcare visits regarding HSV-2[7].

HSV-2 is spread via exposure to mucosal surfaces or abraded skin sites permitting the entry of the virus and the initiation of viral replication[3]. Symptoms of HSV-2 primary infection include painful genital ulcers, dysuria, fever, and tender inguinal lymphadenopathy[3]. Other symptoms include burning, stinging, and neuralgia preceding accompanying attacks[1]. Lesions most often occur on the vermillion border of the lips, the penile shaft, the labia, the perianal skin, and the buttocks[3]. As compared with Herpes simplex virus type 1 ("HSV-1"), HSV-2 has a higher genital recurrence rate and the seroprevalence of the virus increases with sexual activity[4].

The combination of pain, cost, and impaired quality of life place a heavy burden on the infected patient.

Currently, no definitive cure for HSV-2 exists. Medications used to treat herpes simplex outbreaks are anti-viral drugs including Acyclovir, Famciclovir, and Valacyclovir. These medications simply act to decrease pain during an outbreak, shorten the course, and decrease viral shedding[1]. Patients may use these medications on an episodic basis and are advised to take the medication at the onset of prodromal symptoms such as tingling and pruritus[1]. If taken daily, antiviral treatment can reduce transmission of HSV-2 from partner to partner[7]. Consistent latex condom use can also help reduce the spread of HSV-2; however, transmission can still occur in genital areas that the condom does not cover[1]. Patient education and abstinence are among the limited options to reduce transmission, as well[1]. Male circumcision may be used as an alternative to oral antiviral medication. This paper evaluates three randomized control trials comparing the efficacy of male circumcision to prevent HSV-2.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not male circumcision prevents herpes simplex virus type 2 in sexually active males aged 18-50.

METHODS

A set of criteria was selected to perform the research needed for this topic. The criteria included a population of male patients aged 18 to 50 who are sexually active. Each study selected used the intervention of male circumcision. Comparisons were made in one article between groups of males who underwent immediate circumcision and those who had a delayed circumcision of twenty-four months. The other two randomized controlled trials compared circumcised males to uncircumcised males. Outcomes measured the spread of HSV-2 from

female to male partners and the incidence of HSV-2, which is defined as a sexually transmitted infection with symptoms of visible ulceration in the selected population.

All three studies were randomized control trials published in the English language. The articles selected were all published in peer reviewed journals found in Medline and PubMed data bases. Key words utilized in the research of this topic included “circumcision,” “HSV-2,” and “males.” Articles were selected on the basis of the classification of the study (RCT), clinical relevance, and specific patient oriented outcomes that matter (“POEMS”). All three studies maintained the baseline inclusion criteria of uncircumcised males. Age groups varied but each fell into the broader category range of 18-50. Other studies specified HIV status, residency, and hemoglobin levels (See Table-1). Exclusion criteria differed between each study (See Table-1). A summary of the statistics reported or used in the trials include p-values, RRR, ARR, and NNT. Table 1 displays the demographics and characteristics of the included studies.

Table 1: Demographics & Characteristics of Included Studies

Study	Type	# Pts	Age (yrs)	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Mahiane (2009)	RCT	2787	18-24	Males aged 18-24 Uncircumcised		0	Male circumcision
Mehta (2012)	RCT	2044	18-24	Males aged 18-24; Uncircumcised HIV negative Sexually active in the last 12 months; Hemoglobin more than 9.0 mmol/l; Reside in the Kisumu district	Foreskin covering less than half of the glans; Bleeding disorder; Keloid formation; Other conditions that might unduly increase the risks of elective surgery; Medical indication for circumcision; Participants with sexually transmitted infections were deferred until treated	0	Medical male circumcision (MMC)
Tobian (2009)	RCT	5534	15-49	Males aged 15-49 HIV negative Uncircumcised	Preexisting positive or indeterminate HSV-2 status	0	Male circumcision

OUTCOMES

All outcomes measured were POEMS, each varying by the subjective and objective tools related to the particular study. All three studies measured the incidence of HSV-2 defined as a sexually transmitted infection with symptoms of visible ulceration, while other articles measured additional outcomes.

Mahiane, et al. ("Mahiane"), measured the incidence of HSV-2 defined as a sexually transmitted infection with symptoms of visible ulceration. Mahiane measured this outcome by a genital examination performed by a clinically trained nurse and by collecting plasma samples that were tested using a HSV-2 specific IgG assay to detect HSV-2 antibodies (Kalon HSV-2 gG2 assay). In addition, the spread of HSV-2 from female to male partners was calculated via self-report of patient's sexual behavior including number of partners as a function of time, number of sexual contacts with each partner, reported condom use, and age of each partner.

In contrast, Mehta, et al. ("Mehta"), and Tobian, et al. ("Tobian") only measured the incidence of HSV-2 defined as a sexually transmitted infection with symptoms of visible ulceration. Mehta utilized patient's self-reported symptoms, physical exam findings, and serum specimens to measure this outcome. Patient's self-reports included the presence of painful or painless sores occurring in the genital region in the past six months and at the current visit. Physical exam findings looked at the presence or absence of genital ulcers and the location and number of genital ulcers. Trained clinicians performed all genital exams and "clinicians were instructed to record any epithelial defect in the skin or mucosa of the genitalia."[6] Both groups underwent STI and HIV risk reduction counseling and were provided unlimited supplies of free condoms[6]. Serum specimen tests were collected at baseline, 6, 12, 18, and 24 months from randomization[6]. Specimens were tested for the HSV-2 antibody (Kalon HSV-2 IgG ELISA)[6].

Tobian calculated the incidence by patient's self-reported symptoms of sexually transmitted infection including genital ulceration, urethral discharge, and dysuria[8]. Patients were tested at baseline, 6, 12, and 24 months and were subject to physical exams and interviews[8]. All subjects at each visit were offered HIV testing and counseling, health education, and condoms[8].

In addition, HSV-2 testing was performed with the use of an enzyme-linked immunosorbent assay (ELISA Kalon Biological)[8].

RESULTS

Two of the studies included in this report utilized dichotomous data. Mahiane utilized continuous data that could not be converted to dichotomous values. All three studies used circumcision as the primary and only intervention, but Mehta and Tobian both included the variable of time to differentiate between the intervention group (immediate circumcision) and the control group (delayed circumcision), while Mahiane only differentiated control and intervention by circumcised or uncircumcised.

The first randomized control trial by Mehta utilized immediate circumcision as the intervention group (n= 1931) compared to delayed circumcision after a 24 month follow up period as the control group (n= 1393) and assessed by HSV-2 testing and medical examinations during follow ups at 1, 3, 6, 12, 18, and 24 months. This study only included the specific age group of 18-24 year old males and had specific inclusion and exclusion criteria as noted in Table-1. This study looked at circumcision status and incidence of HSV-2, syphilis, and HIV infection. Each group was analyzed separately then HIV incidence was adjusted for HSV-2 status and genital ulcer disease.

Table 2: Mehta Results

CI	P-Value	RRR (%)	ARR (%)	NNT
[0.7-1.25]	0.655	5.2	0.3	1/0.003=334

All patients were analyzed in the group they were originally assigned. Results were considered statistically significant at a p value of ≤ 0.05. Based on the p value, the treatment

effect of this intervention is not clinically significant. The results of this RCT showed a numbers needed to treat ("NNT") of 334; meaning one must treat 334 patients with male circumcision in order to prevent HSV-2 in one more patient when compared to no circumcision. The absolute risk reduction ("ARR") shows males who underwent immediate circumcision had a 0.3 times absolute decrease in HSV-2 infection rate. In addition, the cumulative incidence of HSV-2 was 5.8 per 100 person-years among circumcised men and 6.1 per 100 person-years among uncircumcised men[6]. The combination of the statistical insignificance, low ARR, and large treatment size show that circumcision was not effective in providing protecting from acquiring HSV-2 in this study.

Tobian enrolled 3393 uncircumcised, HSV-2 negative, male subjects between the ages of 15-49. Of the 3393 participants, 1684 were assigned immediate circumcision (intervention) while 1709 were assigned to undergo circumcision 24 months later (control). Differences between the intervention and control groups included higher condom use in the intervention group at 6 months, more non-marital sexual relationships in the intervention group, and higher rates of alcohol use with sexual intercourse in the control group. In addition, the frequency of genital ulcer disease was higher at six months, twelve months, and twenty four months in the control group. This study also looked at the effect of male circumcision on the incidence of HPV and syphilis infections in addition to HSV-2. Each group was analyzed separately for efficacy and HSV-2 and HIV reduction were more broadly touched on.

All persons whose data was collected in Rakai, Uganda were analyzed in the groups they were assigned originally. The treatment effects show a negative NNT. This value correlates for every 40 men treated with circumcision immediately, there was 1 fewer incidence of HSV-2 than in the group that was delayed by 24 months. In addition, based on a p-value of ≤ 0.05 considered

statistically significant, the p-value shows that circumcision for the prevention of HSV-2 is statistically significant. The narrow confidence interval further supports the precision of our NNT value. Table 3 shows treatment effect as well as p-value and confidence intervals.

Table 3: Tobian Results

CI	P-Value	RRR (%)	ARR (%)	NNT
[0.56-0.92]	0.008	-24.3	-2.5	1/-0.025=-40

The final study by Mahiane analyzes the effects of male circumcision to prevent HSV-2 per-sex-act female to male transmission probabilities. Mahiane enrolled 3,274 uncircumcised males and randomized participants into two groups; circumcision as the interventional group and non-circumcision as the control group. Data was analyzed via mathematical models of HSV-2 statuses as functions of time used to estimate the female to male transmission probabilities. Male circumcision's protective effect against HIV transmission was also analyzed separately and in relation to HSV-2.

Unlike the previous two studies, sexual behavior information was collected including number of partners as a function of time, number of sexual contacts with each partner, reported condom use, and age of each partner. The 95% CI of the female to male transmission probabilities and relative risks were estimated using the bootstrap re-sampling method with 2000 replications of the trial data. Based on a p-value of ≤ 0.05 indicating statistical significance, male circumcision's protective effect against HSV-2 was considered statistically significant for both HSV-2 transmission per sex act ($p= 0.005$) and per partnership ($p=0.001$).

DISCUSSION

The aim of this systematic review was to see if male circumcision was a preventative option against HSV-2. Both Mahiane's and Tobian's studies proved this prevention option is statistically significant.

Male circumcision is one of the most common surgical procedures in the United States[2]. This procedure is more commonly performed at birth[2]. Circumcision is proven to decrease rates of urinary tract infections, penile cancer, penile inflammation, penile dermatoses, and lower rates of sexually transmitted infections[2]. In a study with older adults, twenty-three percent of lifetime urinary tract infections are due to being uncircumcised[2]. In the United States, circumcision is an elective process, and parents begin to receive counseling regarding the procedure during pregnancy[2].

Decreased risk of sexually transmitted infections, including HIV, HPV, and HSV-2, has been proven in various studies[2]. HIV risk reduction is attributed to the removal of the inner mucosa of the foreskin, which has an increase in HIV-1 receptors versus the glans[2]. The inner mucosa of the foreskin is also lightly keratinized which may facilitate the access of HSV-2 and HPV to underlying epithelial cell in uncircumcised men[2].

Circumcision on adolescents and adults is associated with more adverse effects than circumcision on a newborn. It is linked with greater risks and cost, a longer recovery period, and more pain and discomfort after the procedure[2]. In addition adolescents who are sexually active will not reap the protective benefits of circumcision against sexually transmitted infections.

Each study reviewed contained limitations. Limitations to all three RCTs include a lack of discussion of safety of medical male circumcision or significant side effects due to the

procedure. When searching for these articles, it was difficult to find all three articles focusing on the prevention of HSV-2 as the sole sexually transmitted infection in the given time frame.

In the Mehta article, the Kalon test used to analyze serum specimens was found to have a lower sensitivity (92%) and specificity (79%) in the Kisumu study. This study had a small age range of 18-24 and only used males residing in the Kisimu district of Kenya. These specific parameters limit the generalizability of the study.

The Mahiane study lists that the male population aged from 18-24 was not representative of the general male population. The majority of this population was unmarried and reflected a short duration of partnerships and low number of sexual contacts. Because the population age range was so limited for both Mehta and Mahaine, these studies had a low generalizability to the age group in my question.

Finally, in the Tobian study, the article lists that older subjects were likely to be currently or previously married, had a higher number of sexual partners in the previous year, and a higher rate of alcohol use with sex in the previous six months. These findings limited the study and may have skewed results[8].

CONCLUSION

In conclusion, two of the three studies reviewed demonstrated male circumcision was effective in the prevention of HSV-2. Due to the fact that one study of the three did not find the intervention in question to be effective, the overall evidence is inconclusive. Mehta proved that HSV-2 was not prevented by male circumcision and the large numbers needed to treat to have any significant impact further supported that finding.

In order to improve the clinical outcomes and in efforts to improve further research, future studies should reflect a larger geographical population, recruit a larger age range, and

should have a standard guideline of evaluating genital ulcerations. First, a larger geographic sample will have a greater world wide effect if studies took place in other countries. It is difficult to compare this research and findings to the United States where the majority of circumcision is performed at a younger age. Next, a larger age range of uncircumcised men should be recruited. In two of the three studies the age range of 18-24 greatly limited the generalizability to the population in question of 18-50. Finally, all studies should create a standard guideline when evaluating circumcision to explore possible adverse effects. By including a pain scale for circumcision, more data would be available for a numbers need to harm analysis.

HSV-2 affects over 200,000 Americans and is continuing to be a burden on health care workers and the health care system. The genital ulceration as a result of HSV-2 is painful and overall decrease the patient's quality of life. As research continues to grow on the subject, male circumcision may become a leader in preventative measures against HSV-2.

REFERENCES

1. Albrecht, M. Treatment of genital herpes simplex infection. UptoDate website. http://www.uptodate.com/contents/treatment-of-genital-herpes-simplex-virus-infection?source=search_result&search=hsv-2+and+circumcision&selectedTitle=21~137 Accessed December 19, 2013
2. Baskin L, Lockwood C, Bartlett J, Wilcox D. Neonatal Circumcision: risks and benefits. UptoDatewebsite. http://www.uptodate.com/contents/neonatal-circumcision-risks-and-benefits?source=search_result&search=circumcision&selectedTitle=2~75 Accessed December 19, 2013.
3. Corey L. Chapter 179. Herpes Simplex Virus Infections. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. Harrison's Principals of Internal Medicine. 18th ed. New York: McGraw-Hill. 2012.
4. Herpes 1 & 2. CMDT. http://www.accessmedicine.com/content.aspx?aID=17073&searchStr=human+herpesvirus+2 Accessed December 19, 2013.
5. Mahiane S, Legeai C, Taljaard D, Latouche A, Puren A, Peillon A, Bretagnolle J, Lissouba P, Nguema E, Gassiat E, Auvert B. Transmission probabilities of HIV and herpes simplex virus type 2, effect of male circumcision and interaction: a longitudinal study in a township of South Africa. *AIDS*. 2009; 23(3):377-383.
6. Mehta S, Moses S, Parker C, Agot K, Maclean I, Bailey R. Circumcision status and incident of herpes simplex virus type 2 infection, genital ulcer disease, and HIV infection. *AIDS*. 2012; 26:1141-1149.
7. Center for Disease Control and Prevention. Sexually Transmitted Diseases (STDs): Genital herpes. http://www.cdc.gov/std/herpes/STDFact-Herpes.htm Accessed September 17, 2013.
8. Tobian A, Serwadda M, Quinn T, Kigozi G, Gravitt P, Laeyendecker O, Charvat B, Ssempijja V, Riesdal M, Oliver A, Nowak R, Moulton L, Chen M, Reynolds S, Wawer M, Gray R. Male circumcision for the prevention of HSV-2 and HPV infections and syphilis. *N Engl J Med*. 2009; 360(13):1298-309.