Published in final edited form as:
J Acquir Immune Defic Syndr. 2004 February 1; 35(2): 138–143.

Tolerance and Safety of Different Concentrations of Chlorhexidine for Peripartum Vaginal and Infant Washes: HIVNET025

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Abstract

Background—There is a continuing need to evaluate sustainable interventions for prevention of mother-to-child transmission (MTCT) of HIV type 1. We evaluated different concentrations (0.25%, 1%, and 2%) of chlorhexidine (CHX) for perinatal maternal and infant washes to identify the maximum tolerable concentration of CHX for such an intervention.

Methods—Women were enrolled during their third trimester at the maternity unit of the Chris Hani Baragwanath Hospital in Soweto, South Africa, and perinatal maternal and infant washes were completed. Subjective maternal symptoms as well as infant examinations were used to assess tolerability of the washes.

Results—The 0.25% concentration of CHX was well tolerated by the mothers (n = 29). Ten of 79 women (13%) with 1% CHX washes complained of mild vaginal area burning or itching, and washes were stopped in 5 (6%). Twenty-three of 75 women (31%) in the 2% CHX wash group had subjective complaints, and the washes were stopped in 12 (16%). There were no clinical indications of toxicity of the CHX washes among infants.

Conclusion—A 1% solution of CHX appears to be a safe and tolerable concentration of CHX for consideration in an MTCT prevention trial.

Keywords

vertical transmission; chlorhexidine; peripartum microbicide washes

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An estimated 600,000 children worldwide were infected with HIV type 1 in 2001.[1] The majority of these infections occurred through mother-to-child transmission (MTCT) of HIV during pregnancy, around the time of labor and delivery, or through breast-feeding.[2] An estimated 95% of MTCT took place in developing countries, where the resources to prevent and manage these infections are limited. In the highly endemic areas of southern Africa, seroprevalence of HIV among women of childbearing age typically ranges from 10% to 40%, and estimates of rates of MTCT vary from 25% to 45%. Although several interventions have been developed for prevention of MTCT of HIV,[3] including antiretroviral prophylaxis,[4] cesarian delivery before labor and before ruptured membranes,[5,6] and avoidance of breast-feeding,[7] most of these interventions will take years to implement satisfactorily in resource-limited settings. Thus, the need continues to evaluate simple low-cost strategies for the prevention of MTCT. Peripartum cleansing with chlorhexidine (CHX) represents such a possible intervention, and it has the potential additional benefit of reducing overall maternal and infant morbidity and mortality.[8]

CHX is a biguanide antiseptic that has been in widespread use since the late 1940s. There is extensive dental, obstetric, and surgical scrub literature on the use of CHX in specialized settings.[9] CHX is poorly absorbed across mucosal surfaces, is only minimally absorbed percutaneously, and is generally considered to be quite safe.[9,10] CHX in various preparations has been used extensively in obstetrics and peripartum perineal and vaginal washes, with concentrations as high as 4% being well tolerated.[11–14] In addition, safety studies in newborn infants exposed to CHX washes in various concentrations demonstrated no evidence of toxicity, including cases in which percutaneous absorption may have taken place.[15–18] Inadvertent intravenous CHX administration resulted in no serious long-term toxicities.[11]

Two randomized clinical trials done in Malawi[19] and Kenya[20] evaluated the efficacy of CHX peripartum washes in reducing MTCT of HIV, with neither study demonstrating overall efficacy. The concentrations of CHX in these studies were relatively low (0.25%–0.4%), however. A remaining question is thus whether higher concentrations of CHX might prove a useful tool for prevention of MTCT of HIV. The objective of this study was to assess the safety and tolerability of higher concentrations of CHX used for peripartum maternal and infant washes so as to identify the highest tolerated concentration of CHX for potential use in a peripartum intervention.

Methods

Study Population

Pregnant women receiving care in the antenatal clinic at the Chris Hani Baragwanath Hospital in Soweto, South Africa, were eligible for enrollment if they consented to HIV counseling and testing, they were at least in the 36th week of gestation as estimated by the dates of their last menstrual period and by fundal height on obstetric examination, and they had no major medical conditions (eg, tuberculosis, diabetes) or were not scheduled for an elective or planned cesarian delivery. Both HIV-infected and -uninfected women were enrolled. Study procedures and intent were explained, and informed consent was obtained, as overseen by the Committee for Research on Human Subjects and Ethics of the University of Witwatersrand, Johannesburg, South Africa. Women who tested positive for HIV received peripartum zidovudine prophylaxis for prevention of MTCT per local standard of care.

Once enrolled, women could be excluded from the intervention if any of the following occurred: a severe complication of pregnancy such as placenta previa, antepartum hemorrhage of any cause, or severe preeclampsia; obvious genital ulcerations at the time of presentation in labor; facial presentation of the neonate at delivery; and receipt of prostaglandin tablets

intravaginally at presentation in labor. If a mother was excluded from the study after enrollment, the CHX washes were still offered to her newborn.

Enrollment into different CHX concentration groups was accomplished in a sequential manner. The initial design of the study was to evaluate CHX at 0.25%, 2%, and 4% concentrations sequentially based on previous studies. Once the intolerance of the 2% CHX concentration was identified, the protocol was revised and the 1% CHD concentration was evaluated. Thus, there was sequential enrollment of an initial 25 mothers into a 0.25% CHX cohort, followed by the enrollment of the 2% CHX and 1% CHX groups between January and October of 2000.

Chlorhexidine Solutions

Commercially available CHX gluconate was purchased as a 5% stock solution diluted water without other additives. The pharmacist of the Perinatal HIV Research Unit of Chris Hani Baragwanath Hospital made dilutions in the pharmacy off site. Solutions were aliquoted and stored as 1-L bottles for single use of 1 bottle for each mother and her infant(s). Bottles were protected from light, and solutions were stored at 20°C to 25°C.

Peripartum Interventions

Each woman was given a card at enrollment to identify her as a study participant at presentation in labor. Maternal washing with CHX solution was initiated at the first examination subsequent to admission to the labor ward for active labor. Approximately 3 oz of solution was poured onto 2 to 3 large cotton balls in a sterile basin for each wash. The study protocol called for washing to be repeated at each subsequent maternal examination, at least every 4 hours, and with at least 1 wash to be attempted once cervical dilation of 8 cm occurred. Washing was performed using sterile gloves and holding a CHX-soaked cotton ball and rotating the examining fingers in a circumferential manner to cover the entire cervix, vagina, and external genitalia. Washing was performed in a standardized manner by study staff who had undergone on-site training for this study, and regular retraining was done for quality assurance.

Infant interventions consisted of suctioning of the nasal and oral passages and washing with CHX of the same concentration as that used for the mother's washes. Infant washing was initiated within 10 minutes after delivery, or as soon after birth as possible, with a warmed CHX solution and warmed towels. Approximately 8 oz of CHX solution was poured onto 8 to 10 cotton balls in a sterile basin. Washing of the entire infant except for the periorbital areas was performed using sterile gloves and was superficial, leaving most of the vernix intact. Infants were dried and swaddled immediately after washing.

Evaluations

Mothers were interviewed to ascertain if specific symptoms were experienced at the time of presentation in labor, at the time of each antenatal examination and wash, and then at 24 to 48 hours postpartum. The specific items queried were itching, vaginal discharge, irritation, burning, tenderness, and swelling, and the responses were categorized as none, mild, moderate, or severe using standardized criteria. Vaginal speculum examinations were performed for any severe or persistent complaints. Infants were examined at 24 to 48 hours after birth for rashes, redness, tenderness, swelling, or mucosal surface discharge. All interviews and examinations were performed by study physicians after on-site training, and regular retraining was done for quality assurance. Serum samples for determination of CHX concentrations were obtained from 20 infants (10 in the 1% CHX group and 10 in the 2% CHX group).

Statistical Analysis

All data analyses were conducted at the HIVNET statistical center in Seattle using SAS, version 8.2, for Unix.[21] Summary statistics (means, medians, and proportions) were computed across the 3 CHX groups. Pearson χ^2 tests of independence were used to test for a difference in proportions between women who had complaints and those who did not.

Chlorhexidine Levels

Blood samples collected for CHX levels were separated within 8 hours of collection, and the serum was frozen at −20°C and shipped frozen to the United States for laboratory analysis. Testing was completed in the Mass Spectrometry Facility of the Comprehensive Cancer Center of the University of Alabama at Birmingham. Multiple preparation procedures were tested for quantitative recovery of CHX in spiked human sera samples. For final sample analysis, serum samples were diluted 1:4 with deionized distilled water. Samples were analyzed by high-performance liquid chromatography (HPLC) using an Aquapore C-18 RP-300 4.6-mm × 100-mm reverse-phase column that was networked with an API III PE Sciex Triple Quadrapole Electrospray Ionization Mass Spectrometer. Samples were analyzed in the positive multiple reaction monitor (MRM) mode using 80% methanol with 0.1% HCOOH at an isocratic flow rate of 1 mL/min. Samples were analyzed in duplicate, and results were quantitated using a curve established with known concentrations of CHX. The lower limit of detection using this methodology was 5 ng/mL of CHX.

Results

Of the 273 women screened for the study, 271 (99%) were eligible and agreed to enroll. Of these 271 women, 205 (76%) were known to have delivered their infants at Chris Hani Baragwanath Hospital and the others presumably delivered at a district hospital or at home. Of these 205 confirmed deliveries, 183 received peripartum CHX washes; the remaining 22 women were not identified at presentation in labor and were not washed. Twenty-nine women received 0.25% CHX washes, 79 were washed with 1% CHX, and 75 were washed with 2% CHX. Characteristics of these 183 women are shown in Table 1. The median age of the participants was 28 years, and approximately half in each group were married or living with their partner. The majority had completed secondary education, and 70% to 75% were multigravida. The proportion that was HIV infected in the 0.25% group reflects the general demographics of the local population presenting for antenatal care. The proportions that were HIV infected in the 1% CHX and 2% CHX groups (66% and 60%, respectively) represent overselection of eligible HIV-infected women. Nearly all (97.1%) HIV-infected subjects were on zidovudine prophylaxis at the time of delivery. Most of the deliveries were vaginal in each CHX wash group; however, 16 women (20%) in the 1% CHX group and 10 women (13%) in the 2% CHX group had washes initiated but subsequently delivered by cesarian delivery.

The intrapartum histories related to the CHX washes for each group are given in Table 2. Subjects in the 0.25% and 1% CHX groups received a median of 3.2 washes, whereas those in the 2% CHX group received a median of 3.0 washes. Washes were stopped before delivery in similar proportions of each CHX wash group. In the 0.25% and 1% groups, the most common reason for stopping washes was cesarian delivery, whereas in the 2% group, the washes were more commonly stopped due to complaints or refusal of further washes. The most common complaints related to the CHX washes were vaginal or vulvar/perineal burning or itching. The distinction between burning and itching was difficult in the languages used for the interviews (Sesotho and Zulu); thus, we considered these complaints together in the analysis. The rates of complaints were 13% in the 1% CHX wash group (95% confidence interval [CI]: 0.053–0.20) and 31% in the 2% CHX wash group (95% CI: 0.202–0.411). The only complaint considered to be severe occurred in the 2% CHX wash group. The proportion of those subjects

with complaints who requested that the washes be discontinued was 50% (5 of 10 subjects with complaints) in the 1% CHX wash group and 52% (12 of 23 subjects with complaints) in the 2% CHX wash group.

Selected features of the pregnancy and delivery histories are compared for subjects who had complaints associated with the 1% and 2% CHX washes in Table 3. In both the 1% and 2% CHX wash groups, rates of complaints with the washes were similar in women who had a history of recurrent itchy vaginal discharge or an abnormal vulvar examination at presentation compared with those women who did not have these findings. The cesarian delivery rates were similar for those women who had complaints with washes versus those who had no complaints in both the 1% and 2% wash groups. There were no clear associations with duration of labor or rupture of membranes (ROM) and complaints with the CHX washes in either the 1% or 2% wash groups (data not shown).

There were a total of 197 newborns who received CHX washes as part of this study: 27 received washes with 0.25% CHX, 82 with 1% CHX, and 88 with 2% CHX (Table 4). All births were singleton. All admissions to the intensive care nursery as well as all recorded adverse events (n = 10) were common neonatal complications (eg, transient tachypnea, perinatal asphyxia, meconium aspiration, hypoglycemia). All infants who were not well on discharge were recovering from common neonatal complications. There were no indications that the CHX washes caused any skin problems or other adverse reactions.

Of the 20 infants with serum CHX concentrations measured, CHX was detected in 1 of 10 infants in the 2% CHX wash group (serum concentration: 26.7 ng/mL; birth weight: 3000 g) and in 3 of 10 infants in the 1% CHX wash group (serum concentrations: 13.5, 20.3, and 26.2 ng/mL; birth weights: 2900, 3500, and 4100 g, respectively). There were no signs or symptoms recorded for any of these infants in whom CHX was detected.

Discussion

The objective of this study was to assess the safety and tolerability of higher concentrations of CHX for maternal and infant peripartum washes than had previously been used in clinical trials of CHX for prevention of MTCT of HIV. The 1% concentration of CHX was tolerated well by the women in this study; however, the 2% concentration had an unacceptably high rate of maternal complaints, in our judgment, to be considered for future general use. Both the 1% and 2% concentrations of CHX were well tolerated by the infants; although there was evidence of some absorption of CHX in the infants, no untoward adverse effects were noted.

There is a continuing need to develop and evaluate simple interventions for prevention of MTCT of HIV with applicability to resource-limited settings. CHX peripartum washes are inexpensive and can be delivered without universal counseling and testing for HIV, which, although an important goal, may not be universally achievable in the near future. In addition, there is demonstrated benefit of CHX peripartum cleansing in reducing overall morbidity and mortality for both mothers and infants.8 Thus, CHX washes could be an important public health intervention even if the reduction of HIV MTCT with this intervention were only modest.

In vitro studies have evaluated the effect of CHX on HIV replication. In one study, viral inactivation was observed at a concentration of 0.2%, with no effect observed with 0.02% (other concentrations between these 2 extremes were not evaluated).[22] In another study, exposure of free virus to a solution of 1% CHX for 1 minute reduced the rate of replication of HIV by 80% to 100%.[23] Exposure of HIV to 0.5% CHX for as little as 30 seconds has been observed to reduce infectivity to undetectable levels as measured by a plaque reduction assay.[24] Together, these studies strongly support the virucidal activity of CHX when the

concentration "seen" by the HIV viral particles is high enough (ie, beyond a threshold of approximately 0.2%).

The 1% concentration of CHX is 2.5 to 5 times greater than the CHX concentrations previously used in Malawi and Kenya in clinical trials evaluating CHX washes or lavages for prevention of MTCT of HIV.[19,20] The lower concentrations of CHX used in those studies (0.2%–0.4%) were near the threshold of the concentrations needed to inhibit HIV in vitro replication. In addition, subgroup analyses in both the Malawi and Kenyan studies suggested possible effects of CHX cleansing in prevention of MTCT of HIV. In Malawi, where a 0.25% CHX concentration was used, a post hoc subgroup analysis of data regarding infants born more than 4 hours after ROM showed an apparent 40% reduction of MTCT in the CHX group compared with the placebo group (transmission rates of 25% vs. 39.4%; relative risk [RR] = 0.6; 95% CI: 0.4–0.9).[19] In Kenya, where 0.2% and 0.4% concentrations were used as vaginal lavage, in the group receiving 0.4% lavage before ROM, there was a reduced rate of HIV transmission (adjusted OR = 0.1; 95% CI: 0.0–0.9).[20] Although these subanalyses suggest that a CHX peripartum wash intervention could be efficacious for prevention of MTCT if the CHX concentration were increased and/or the frequency of administration were increased, such post hoc subgroup analyses are unreliable and should be interpreted with caution.

CHX is a cationic molecule that binds avidly to any negatively charged organic substrates, including cotton, and its activity is based on disruption of molecular function.[9] CHX is also known for its substantivity, or ability to have a prolonged biologic effect related to its sustained environmental presence associated with its binding characteristics.[9] As such, delivering a higher effective concentration would be expected to have a greater antimicrobial effect.

The reasons for the intolerance to the 2% CHX washes in our study are not readily apparent. Peripartum washes with CHX concentrations of up to 4% were previously well tolerated in populations in North America.[11–13] The self-reported history of prior recurrent itchy vaginal discharge was higher among those subjects receiving the 2% CHX concentration washes compared with those washed with 1% CHX in our study. In neither wash group, however, was this self-reported history associated with complaints after the washes were initiated. Given the high rates of maternal complaints among those who were washed with the 2% CHX concentration, this concentration of CHX seems impractical for further testing in this geographic setting.

Low levels of CHX were found in 4 of 20 infants whose sera were assayed as part of this study. Extensive studies on the safety of CHX in neonates were done when the compound was first being used in the 1950s, particularly because its release and testing were occurring in the posthexachlorophene era. Previous studies also have demonstrated CHX levels in sera of infants[16–18]; in 1 study, these levels were more likely to be found in the infants who were born preterm or when the CHX was in an alcohol-based solution.[15] CHX binds strongly to human skin,[16] and in each of these studies where CHX was detected, there were discussions of contamination of the serum samples from percutaneous sampling. This also could be a consideration with the results reported here. CHX has been in widespread use in a number of settings and concentrations since the 1950s and has an admirable safety profile. Although anecdotal hypersensitivity responses have been reported, no other untoward effects have been routinely noted with extended oral or cutaneous use.

In summary, our data suggest that a 1% concentration of CHX is well tolerated when used for peripartum maternal and infant washes. There are a number of reasons for testing this higher concentration of CHX in an efficacy trial to reduce MTCT of HIV, including the suggestion of efficacy at lower concentrations, low cost, and global health benefits of delivering this

intervention as well as the potential additive effect with any of the proven interventions for lowering MTCT of HIV-1.

Acknowledgments

The authors acknowledge the dedication of the staff of the antenatal and obstetric wards and the Perinatal HIV Research Unit of the Chris Hani Baragwanath Hospital and thank the subjects who volunteered for this study. They also gratefully acknowledge Landon Wilson of the University of Alabama at Birmingham Cancer Center Mass Spectrometry Shared Facility for work on the standardization and performance of the CHX concentration assays.

Supported by the HIV Network for Prevention Trials (HIVNET) and sponsored by the US National Institute of Allergy and Infectious Diseases (NIAID), National Institute of Child Health and Human Development (NICHD), National Institutes of Health (NIH), Department of Health and Human Services (DHHS) through contract N01-AI-35173 with Family Health International; contract N01-AI-45200 with Fred Hutchinson Cancer Research Center; and subcontracts with the University of Alabama at Birmingham (N01-AI-35173-414) and the Perinatal HIV Research Unit, Chris Hani Baragwanath Hospital, Soweto, South Africa (N01-AI-35173-418). In addition, this work was supported by the HIV Prevention Trials Network (HPTN) and sponsored by the NIAID, NICHD, National Institute on Drug Abuse, National Institute of Mental Health, and the Office of AIDS Research of the NIH, DHHS (5 U01 AI46749).

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Table 1

Maternal Characteristics of 183 Women Who Received Chlorhexidine Peripartum Washes

	0.25%		1%		2%	
Chlorhexidine %	**n**	**%**	**n**	**%**	**n**	**%**
Subjects receiving washes at specified concentration	29	100	79	100	75	100
Demographic characteristics						
Marital status	29		79		75	
Never married	13	45	37	47	37	49
Married/living with partner	16	55	40	51	38	51
Separated, divorced, widowed	0		2	2	0	
Education	29		77		74	
No schooling/primary only	5	17	14	18	19	26
Secondary	24	83	63	80	54	72
Postsecondary	0		0		1	1
Multigravida	20	69	57	72	58	77
HIV-positive	6	21	52	66	45	60
Pregnancy history	29		79		75	
Hypertension	4	14	12	15	12	16
Anemia	10	34	8	10	16	21
Cough for >2 weeks in last month	1	3	16	20	8	11
Recurrent itchy vaginal discharge	11	38	13	16	30	40
Admitted to hospital in last 12 months	6	21	11	14	10	13
Delivery history	29		79		75	
Spontaneous membrane rupture	26	90	71	91	66	88
Therapeutic labor induction used	11	38	22	28	20	27
Vaginal delivery	24	83	62	79	65	87
Cesarian delivery	5	17	16	20	10	13

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Table 2

Intrapartum History Related to Chlorhexidine Washes

	0.25%		1%		2%	
Chlorhexidine %	**n**	**%**	**n**	**%**	**n**	**%**
Total receiving at least 1 CHX wash	29		78		75	
Number of washes received						
1	4	14	18	23	10	13
2	10	34	24	31	23	31
3	5	17	11	14	16	21
4	10	34	25	32	26	35
Washes stopped early (total)	5	17	19	25	18	24
Cesarian delivery	5	17	14	18	6	8
Refusal	0	0	0	0	3	4
Complaints	0	0	5	6	9	12
At least 1 complaint before washes (total)	0	0	3	4	3	4
Vaginal itching	0	0	2	3	3	4
Other	0	0	1	1	0	0
New or worsening complaint after a wash (total)	1	3	10	13	23	31
Vulvar/perineal itching	0	0	2	3	4	5
Vaginal itching	0	0	7	9	13	17
Vulvar/perineal burning	0	0	1	1	1	1
Vaginal burning	0	0	1	1	11	15
Other	1	3	0	0	3	4

Table 3

Associations of Maternal Clinical Conditions and Incidence of Maternal Complaints With Chlorhexidine Washes

	1% Wash (n = 79)			2% Wash (n = 75)		
	Complaints			Complaints		
	n (%)	Yes (%)	No (%)	n (%)	Yes (%)	No (%)
Had recurrent itchy vaginal discharge						
Yes	13 (16)	1 (7.7)	12 (92.3)	30 (40)	10 (33)	20 (66)
No	66 (84)	9 (14)	57 (86)	45 (60)	13 (29)	32 (71)
Abnormal vulvar examination at delivery						
Yes	6 (7.6)	2 (33)	4 (66)	7 (9.3)	3 (43)	4 (57)
No	73 (92.4)	8 (11)	65 (89)	68 (90.7)	20 (29)	48 (71)
Had an emergency cesarian delivery						
Yes	15 (19)	3 (20)	12 (80)	9 (12)	5 (57)	4 (43)
No	64 (81)	7 (11)	57 (89)	66 (88)	18 (27)	48 (72)

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Table 4

Neonatal Characteristics of Infants Receiving Chlorhexidine Washes

	0.25%		1%		2%	
Chlorhexidine %	**n**	**%**	**n**	**%**	**n**	**%**
Number of infants washed	27	100	82	100	88	100
Low birth weight (<2500 g)	3	11	5	6	1	1
Gender						
Female	11	41	46	56	47	53
Male	16	59	36	44	41	47
Infant admitted to intensive care nursery	0	0	6	7	4	5
Infant well on discharge	27	100	80	98	85	97