Gynecology; *and Gynecological Oncology*

Dequalinium Chloride is it an Effective Alternative for Local Treatment of Vaginal Infections?

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OBJECTIVE: To assess the efficiency of dequalinium chloride for treatment of vaginal infections of varying etiology.

STUDY DESIGN: 100 women applying to gynecology outpatient clinic with vaginal discharge complaints and accompanying symptoms were enrolled prospectively into the study. All of the patients had a clinical and a microbiological diagnosis before the treatment. Patients were treated only with 10 mg dequalinium chloride vaginal tablet once a day for 6 days. 10 days after the treatment, patients were re-examined and control cultures were taken for microbiologic examination. Clinical diagnosis, microbiologic results and symptoms of patients before and after the treatment were compared. McNemar test and descriptive statistical analysis tests were applied for statistical analysis and significance level was accepted as $p<0.05$.

RESULTS: 91 patients had a clinical vaginitis diagnosis before the treatment, 51 of them were cured with the dequalinium treatment ($p<0.0001$). Sixty patients had a microbiological diagnosis before the treatment, 46 of them were cured with the dequalinium treatment ($p<0.001$). Also, patients' symptoms (bad odor, itching, burning, dysparonia) and vaginal discharge complaints were improved significantly after the treatment ($p<0.001$).

CONCLUSION: Dequalinium chloride with its broad antimicrobial spectrum constitutes a valuable alternative to other vaginal anti-infective therapies.

Key Words: Dequalinium, Vaginitis

Gynecol Obstet Reprod Med 2012;18:16-20

Introduction

Vaginal discharge complaint accounts for more outpatient visits than any other reason that women seek health care over the world.[1] Vaginal complaints are usually diagnosed as "vaginitis", a general term that refers to inflammation of the vaginal wall usually caused by one of three disorders: fungal infections, bacterial vaginosis, and trichomoniasis.[2,3]

Although specific anti-infective agents are available for treatment of most common vaginal infections, it is still necessary and desirable to broaden the selection of therapeutic possibilities. Less specific antiseptic agents have the advantages that a) resistance of pathogens is not expected due to their mechanism of action, b) they can be used for treatment of disturbed flora due to their wide spectrum of antimicrobial activity, c) they are appropriate for pre- and post-operative prophylaxis.[4]

The wide antibacterial activity of dequalinium in vitro was reported by Babbs in 1956. They found that dequalinium is capable of inhibiting the growth of all of 21 species of pathogenic bacteria tested, including Gram-positive, Gram-negative, penicillin-resistant, and acid-fast bacteria; and some fungi.[5] The mechanism of its action is mainly based on the destruction of the microbial cytoplasmic membrane.[4]

Dequalinium chloride is a well-known antiseptic agent, which is used frequently for skin and pharyngeal infections. The benefit of vaginally applied dequalinium chloride has been published in many studies.[6] However, most of these studies were conducted between 1958 and 1980, and were uncontrolled design. Dequalinium chloride preparations for vaginal usage spread to the market again after 2000s. Clinical studies to assess the efficacy and safety of dequalinium chloride are lacking so far.

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Submitted for Publication: *26. 12. 2011*
Accepted for Publication: *10. 04. 2012*

The aim of this prospective clinical study was to assess the efficacy of dequalinium chloride for treatment of vaginal infections of varying etiology.

Material and Method

This study was conducted at Dr. Lutfi Kirdar Kartal Education and Research Hospital, gynecology outpatient clinic between November 2009 and Augst 2010. The study protocol was approved by the local ethics committee. All premenopausal women applying to our gynecology outpatient clinic with vaginal discharge complaint were enrolled prospectively into the study after a written informed consent was obtained.

Exclusion criteria were; presence of vaginal bleeding, pregnancy, history of antibiotic usage within last month. Application of other local or systemic antibiotics or antiseptics, vaginal douches, local contraceptives containing 9-nonoxinol were not allowed during the study period.

Clinically, each patient underwent an evaluation including a standard history and vaginal examination that includes direct observation and evaluation of vaginal secretions for color, viscosity, and homogeneity. Samples of vaginal secretion were taken with cotton tipped swab and transported in Amies' modified Stuart medium to the microbiology laboratory for diagnostic tests (cultures and gram stain). Then, two more swab samples were obtained for clamydia rapid antigen test and clinical diagnostic tests (wet mount examination and whiff test). Lastly, pH testing of vaginal secretions with color-pH indicator strip was performed.

Description of Clinical Tests;

- Wet mount examination: Vaginal secretions diluted with normal saline solution and 10% KOH slide preparations were examined under x10 and x40 magnification of a bifocused, phase contrast microscope. Findings (lactobacilli, leukocytes, clue cells, motile trichomonas parasite, yeast buds or hyphae) were recorded.

- Whiff test: It was done with exposure of vaginal secretions to 10% KOH solution and considered positive if amine odor was detected.

- Clamydia rapid antigen test (which is a rapid chromatographic immunoassay for qualitative detection of Chlamydia Trachomatis in female cervical swab, ulti med products, Deutschland, GmbH, Chlamydia Test 004A170): Cervical swab was first treated with reagent A (0.2M NaOH) and then treated with reagent B (0.2N HCL) as instructed. Then 3 drops of extracted solution was added on test device and examined after 10 minutes. Test was accepted positive if two distinct colored lines appeared on the test device.

Clinical Diagnostic Criteria;

The clinical diagnosis was based on combinations of symptoms and office-based tests that included observation of discharge character on speculum examination, wet mount examination, whiff test, vaginal ph and Chlamydia rapid antigen test.

- Clinical diagnosis of yeast infection was made by presence of either typical discharge and itching or direct observation of yeast buds or hyphae on wet mount.

- Clinical diagnosis of trichomonas infection was made by observing motile trichomonads on wet mount and typical grayish vaginal discharge together with strawberry cervix.

- Clinical diagnosis of bacterial vaginosis was made by Amsel's criteria, which is presence of three or more of the following criteria; a homogeneous discharge, a vaginal pH> 4.5, positive whiff test, and identification of clue cells on wet mount.

- Clinical diagnosis of clamydial infection was made by clamydia rapid antigen test positivity.

- Clinical diagnosis of gonorrheal infection was made by symptoms, characteristic vaginal discharge and suspicious wet mount findings.

- Clinical diagnosis of mixed infection was made by combinations of two or more clinical diagnosis e.g. presence of both fungal infection and clamydial infection.

Microbiologic Diagnostic Criteria;

For the microbiological diagnosis, material in Amies' modified Stuart medium was transported immediately to the microbiology laboratory for culture inoculation and Gram stain. Sabouraud agar for yeast infection, HBt medium for Gardnerella vaginalis and blood-chocolate agar for other microorganisms were used. All procedures were performed and the results were evaluated by the same microbiologist.

Intervention and Assessment;

All of the patients had a clinical and a microbiological diagnosis. Patients were treated only with 10 mg dequalinium chloride vaginal tablet once per day for 6 days. 10 days after the end of treatment patients were reexamined clinically with office-based tests and vaginal samples were sent to the microbiology laboratory for control cultures. Clinical diagnosis, microbiologic results and patients' symptoms before and after the treatment were compared at the end of the study.

Statistical Analysis;

One hundred fifteen patients were enrolled into the study initially but, 12 of them lost to follow up and three patients withdrew due to an unrelated concurrent disease. One hundred patients who completed study were included into the statistical analysis.

Data were entered into a database and analyzed with SPSS

statistical software (SPSS release 13; Inc, Chicago, Ill). McNemar test and descriptive statistical analysis tests were applied for statistical analysis and significance level accepted as $p< 0.05$

Results

The mean age of the study population was 31.9±8.1. Among participants, 70 % had history of previous vaginal infection and 61% had been treated before.

At the beginning of the study, we clinically diagnosed any kind of vaginal infection in 91% of patients. After the treatment, only 40 % of patients still had a clinical diagnosis of vaginal infection. The difference before and after the treatment was remarkable ($p<0.0001$) (Table1).

The distribution of clinical diagnoses before and after the treatment was shown on table 2.

Notably, clinical diagnoses of fungal infections and bacterial vaginosis were improved considerably after the treatment. Although there were improvements in clinical diagnoses of clamydial, trichomonial, gonorrheal and mixed infections after the treatment, they were not statistically significant.

The percentage of patients who took a microbiological diagnosis before treatment was 60 % whereas it was 14% after the treatment. The difference before and after the treatment was statistically significant ($p< 0.001$) (Table 1).

The distributions of infections on the basis of microbiological diagnoses before and after the treatment were shown on Table 3. There were statistically significant improvement in microbiological diagnoses of candida, gardnerella and coliform bacterial infections.

Also, all accompanying symptoms of the patients (bad odor, itching, burning, dysparonia) were improved significantly after the dequalinium treatment ($p<0.0001$) (Table 4).

Table 1: Comparison of all clinical and microbiological diagnoses before and after the treatment

	Before treatment	After treatment	p
Number of patients with any clinical diagnosis	91	40	0.0001
Number of patients with any microbiological diagnosis	60	14	0.0001

Table 2: Distribution of clinical diagnoses before and after the treatment.

Clinical Diagnosis	Before treatment (n)	After Treatment (n)	p
Physiologic discharge (no clinical infection)	9	60	0.0001
Fungal infection	25	6	0.0001
Bacterial Vaginosis	26	6	0.0001
Chlamydial infection	9	3	0.07
Trichomonial infection	5	2	0.45
Gonorrheal infection	3	2	1
Mixed infection	23	21	0.77
Total	100	100	

Table 3: Distribution of microbiological diagnoses before and after the treatment

Microbiological Diagnosis	Before Treatment (n)	After Treatment (n)	p
Normal flora	40	86	0.0001
Candida species	21	2	0.0001
Gardnerella vaginalis	19	2	0.0001
Coliform bacteria	5	0	0.0001
Escherichia Coli	4	2	0.62
Staphilococcus aerus	4	3	1
Streptococcus species	3	1	0.5
Proteus mirabilis	4	4	1
Total	100	100	

Table 4: Distribution of patients' symptoms before and after the treatment

Patients' symptoms	Before Treatment(n)	After Treatment(n)	p
Bad odor	59	12	0.0001
Itching	41	8	0.0001
Burning	54	8	0.0001
Dysparonia	36	10	0.0001

Discussion

Dequalinium chloride is a well-known antiseptic agent and is used for different topical applications in the treatment of dermal, buccal, and pharyngeal infections.[5,7] First clinical reports of dequalinium for its local antibacterial action have been published by Trotter in 1956 and by Fowler & Jones in 1957. Trotter used dequalinium chloride in gelatin sponge as a bacteriostatic and haemostatic dressing after dental extractions in over 900 patients. He found it effective in counteracting and preventing sepsis and promoting healing.[5] Fowler and Jones used a powder containing dequalinium chloride 0.1% as a wound dressing in veterinary practice.[5] In another study, dequalinium, has been used on 241 patients suffering from various skin conditions and was found to have considerable value in monilial, pyococcal infections of the skin notably impetigo and neonatal staphylococcal infections. Non-infective conditions did not respond, but were not made worse.[7] No irritant or toxic properties were observed, and it was reported that it could be used on the mucous membranes and on the skin of infants.[7] In our study, we did not encounter any side effect related with the use of dequalinium chloride vaginal tablet as well.

It has also been applied in the treatment of vaginal infections such as bacterial vaginosis, aerobic vaginitis, vulvovaginal candidiasis and trichomoniasis since four decades. Dequalinium chloride has been discussed as being of less damaging on lactobacillus flora comparing to other anti-infective therapies but, unequivocal data are still missing. In our study, we treated 100 women with vaginal discharge complaint by using dequalinium chloride vaginal tablets (Donaxyl 10 mg tablet, Abdi Ibrahim, Turkey). We assessed the efficacy of dequalinium by comparing both clinical and microbiological diagnoses before and after the treatment. We found out that, both clinical and microbiological diagnoses were improved significantly after the dequalinium treatment ($p<0.0001$).

The mechanism of action of dequalinium chloride is primarily based on its effects on bacterial cell permeability and bacterial proteins. It is absorbed by the bacterial cell surface and diffuses through cell wall. Having entered the cell, dequalinium chloride leads to the denaturation of proteins involved in the respiratory chain and glycolisis, causing discontinuation of protein synthesis. Depending on the concentration, dequalinium may lyses the cell wall because of osmotic imbalance.[8] Overall, gram-positive bacteria were more sensitive to dequalinium chloride than gram-negative species. This is likely to be explained by the differences in cell wall structures and hydrophobicity between gram-positive and gram-negative bacteria, the cell wall of the latter possibly reducing the surface activity of the agent.

Administration of a 10 mg dequalinium chloride vaginal tablet results in local concentration of 4000 to 2000 μg/ml assuming that the vagina contains 2.5 to 5 ml fluid to dissolve the active substance, respectively.[9] These concentrations are well above the MIC values found for all tested species except Proteus mirabilis. An anti-infective effect is ensured if the concentration of the active agent at the site of action is 2-4 times higher than the MIC for 20 min up to 2 hours. In consequence, wide ranging antimicrobial activity of dequalinium chloride against all leading germs of vaginal infections is indicated.[9] Both clinical and microbiological improvement with the use of dequalinium in our study, confirms this literature.

Importantly, abuse of over-the-counter antimycotics as well as widespread prescription of systemic azoles, result in the spread of resistant Candida species. The activity of dequalinium chloride against Candida species is similar to the activity of clotrimazole reported in the literature.[9,10] In our study, diagnosis of fungal infection fell down from 25% to 6% clinically and from 21% to 2% microbiologically with dequalinium treatment.

Moreover, dequalinium chloride showed activity against metronidazole resistant Trichomonas vaginalis strain which should be taken into consideration for the treatment of resistant cases in clinical practice.[9] In our series, there were five cases that have the diagnosis of trichomanas infection clinically before treatment whereas it was only 2 patients after the treatment. We could not verify trichomonas infections microbiologically due to the limited technical equipment of our laboratory, which was the main drawback of our study.

Another limitation of our study was related with the clinical diagnosis of gonorrheal infections. Because of our inadequate clinical settings, we could make the diagnosis of gonorrhea only by symptoms, characteristic vaginal discharge and suspicious wet mount findings that was not efficient enough.

Vaginal infections in pregnancy (e.g. bacterial vaginosis) have been linked to pregnancy complications like preterm delivery. Particularly with respect to vaginal infections during pregnancy and the phenomenon of increasing drug resistance, agents showing low toxicity and wide range of antimicrobial activity are desirable. Mild antiseptics with wide antimicrobial

spectrum like dequalinium chloride might thus be a valuable alternative during pregnancy.

In conclusion, dequalinium chloride with its broad antimicrobial spectrum constitutes a valuable alternative to other vaginal anti-infective therapies. It might be a particular interest especially if, the cause of the vaginal infection is not well defined. In addition, therapy with dequalinium chloride might be useful due to its broad antimicrobial spectrum and its low risk of evoking microbial resistance.

Dekualinium Klorid; Vajinal Enfeksiyonların Lokal Tedavisinde Gerçekten Etkin Bir Alternatif midir?

AMAÇ: Dekualinium kloridin değişik etyolojili vajinal enfeksiyonların tedavisindeki etkinliğinin araştırılması.

GEREÇ VE YÖNTEM: Jinekoloji polikliniğimize vajinal akıntı ve eşlik eden semptomlarla başvuran 100 kadın prospektif olarak çalışmaya dahil edildi.Tüm hastaların tedavi öncesi hem klinik hem mikrobiyolojik tanısı kondu. Hastalar sadece 10 mg dekualinium klorür vajinal tablet ile günde bir kez 6 gün tedavi edildi. Tedaviden 10 gün sonra hastalar tekrar muayene edildi ve kontrol kültürleri alındı. Klinik tanılar, mikrobiyolojik tanılar ve semptomlar tedavi öncesi ve sonrası karşılaştırıldı. Tanımlayıcı istatistiksel testler, Mc Nemar testi kullanıldı ve istatistiksel anlamlılık düzeyi p< 0,05 olarak kabul edildi.

BULGULAR: Tedavi öncesi 91 hasta klinik olarak vajinit tanısı almışken bunları 51 tanesi dekualinium ile iyileşti (p<0,0001). Tedavi öncesi 60 hasta mikrobiyolojik olarak tanı almışken bunların 46 tanesi dekualinium ile iyileşti (p<0,0001). Ayrıca hastaların semptomları (kötü koku, kaşıntı, yanma, disparoni) ve akıntı şikayetleri de tedavi sonrası istatistiksel olarak anlamlı ölçüde düzeldi (p<0,001).

SONUÇ: Dekualinium klorid geniş antimikrobiyal spektrumu ile diğer vajinal antienfektif tedavilere iyi bir alternatiftir.

Anahtar Kelimeler: Dekualinyum, Vajinit

References

1. Landers DV, Wiesenfeld HC, Heine RP, Marijane A. Predictive value of the clinical diagnosis of lower genital tract infection in women. Am J of Obstet Gynecol 2004; 190:1004-10.
2. Karasz A, Anderson M. The vaginitis monologues: women's experiences of vaginal complaints in a primary care setting. Soc Sci Med 2003;56:1013-21.
3. Dünder İ, Kahraman K, Sarı E. Vulvavaginitis. Turkiye Klinikleri J Gynecol Obst-Special Topics 2008;1:40-7.
4. Petersen EE, Weissenbacher ER, Hengst P, Spitzbart H, Weise W, Wolff F, et al. Local treatment of vaginal infections of varying etiology with dequalinium chloride or povidone iodine. Arzneim Forsch Drug Res 2002;52: 706-15.
5. Hugo WB, Frier M. Mode of Action of the Antibacterial Compound Dequalinium Acetate. Appl Microbiol 1969; 17:118-27.
6. Levinson DR. Dequalinium in the treatment of trichomoniasis in women. Practitioner 1959;183:195-7.
7. Colles RB, Grubb C, Mathuran-Ayagam D, Wilkinson DSR. Trial of dequalinium for skin infections. Br Med J, 1958;25:2;1014-6.
8. Merianos J. Querternary ammonium antimicrobial compounds. Disinfection, Sterilisation and Preservation. Block SS, 4th ed. Lea & Febiger, Philadhelphia- London, 1991. pp 225-255, 9- Della Casa V, Noll H, Gonser S, Grob P, Graf F, Pohling G. Antimicrobial activity of dequalinium chloride against leading germs of vaginal infections. Arzneim Forsch Drug Res 2002;52:699-705.
10. Schmidt A. In vitro activity of clotrimazole for candida strains isolated from recent patient samples. Arzneim Forsch Drug Res 1995;45:1338-40.