Single Hydrogen Peroxide Vaginal Douching *versus* Single-Dose Oral Metronidazole for the Treatment of Bacterial Vaginosis : A Randomized Controlled Trial

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Abstract

Objective : To compare the effectiveness of single hydrogen peroxide vaginal douching and a single oral dose of metronidazole for the treatment of bacterial vaginosis.

Method : A randomized trial was performed at the outpatient clinic in King Chulalongkorn Memorial Hospital. 142 patients diagnosed as having bacterial vaginosis were randomly allocated into two groups. The subjects in the first group were douched with 20 milliliters of 3 per cent hydrogen peroxide and received an oral placebo. The subjects in the second group received oral metronidazole 2 grams orally and were douched with a placebo. The cure rate in each group was assessed using Amsel's criteria 2 weeks after treatment.

Result : The cure rate in the subjects treated with hydrogen peroxide douching was lower than the cases who received oral metronidazole (62.5% *versus* 78.6%, p-value = 0.036). Rate of gastro-intestinal side effects in metronidazole group was higher than in the hydrogen peroxide group (48.6% *versus* 13.9%, p-value < 0.001).

Conclusion : Single hydrogen peroxide vaginal douching was less effective than a single oral dose of metronidazole in the treatment of bacterial vaginosis.

Key word : Hydrogen Peroxide, Metronidazole, Bacterial Vaginosis, Randomized Controlled Trial

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Bacterial vaginosis is the most common cause of abnormal vaginal discharge in reproductive aged women[1]. It results from a shift in bacteria in the vagina from the normal peroxide-producing lactobacilli to a polymicrobial group consisting of anaerobes, Gardnerella vaginalis and Mycoplasma hominis[2,3]. Recent studies have confirmed its association with several obstetric and gynecologic complications, including acute pelvic inflammatory disease, posthysterectomy infection and preterm labor[4-10]. Standard treatment regimens for bacterial vaginosis include a 7 days course or single- oral dose of metronidazole, oral clindamycin, clindamycin vaginal cream and metronidazole vaginal gel[1,11]. Topical formulations have the advantage of reduced systemic side effects but are significantly more expensive compared to metronidazole[11].

Hydrogen peroxide (H_2O_2) production has been proposed as a mechanism by which lactobacilli may inhibit the growth of other vaginal organisms[12]. Studies on the association between vaginal microflora and bacterial vaginosis supported the hypothesis that H_2O_2-producing vaginal lactobacilli protect against acquisition of bacterial vaginosis[13]. One study reported the efficacy of using a single vaginal washout with 3 per cent H_2O_2 for the treatment of bacterial vaginosis[14], however, it was not a controlled trial. For testing the effectiveness of single 3 per cent H_2O_2 vaginal douching in the treatment of bacterial vaginosis, the present randomized study was conducted to compare the effectiveness between single 3 per cent H_2O_2 vaginal douching and single oral dose of metronidazole.

MATERIAL AND METHOD

This study was carried out as a randomized double-blind controlled trial. The protocol was approved by the Institutional Review Board and conducted at the outpatient gynecologic clinic in King Chulalongkorn Memorial Hospital, Bangkok, Thailand. Patients who were diagnosed as having bacterial vaginosis and aged between 15 and 45 years were required to give written consent prior to entry into the study. For diagnosis of bacterial vaginosis, it required at least three signs of the Amsel criteria[15]. The criteria include: 1) having homogeneous vaginal discharge; 2) vaginal pH greater than 4.5; 3) positive fishy odor when 10 per cent potassium hydroxide was added to vaginal secretion; and 4) presence of clue cells more than 20 per cent of epithelial cells on a saline wet mount. The subjects who met one or more of the following criteria were excluded from the study: 1) history of H_2O_2 or metronidazole allergy; 2) having taken antibiotic treatment within two weeks prior to trial entry or required antibiotics for other diseases; 3) pregnancy; 4) immuno-compromised included HIV-infected; 5) diabetes mellitus; 6) current use of intrauterine device; 7) menopause; and 8) vaginal or cervical ulceration or coinfections.

A computer-generated random number was used to allocate the subjects who met the eligibility criteria into two groups to receive H_2O_2 vaginal douche or oral metronidazole. Investigators and subjects were blinded to treatment. Because of the difference in route of drug administration, double dummies were used for blinding the treatment arm. Metronidazole used in this study was a 500 mg tablet (B.J. Limited, Thailand). The oral placebo, produced by the same company, had a similar color and shape as metronidazole. This study used either 3 per cent H_2O_2 or placebo for douching the subjects. Clean water was used as placebo.

The eligible patients were randomly allocated into two groups. The subjects in the first group received oral placebo and were douched with H_2O_2 while the second group received oral metronidazole and were douched with placebo. They had to take 4 tablets of oral medications (metronidazole or visually identical placebo) at the clinic. Vaginal douching was performed by the investigators by inserting a vaginal speculum and use of 20 milliliters of fluid (3%H_2O_2 or clean water) in a sterilized syringe while the patient was in the lithotomy position. After douching, the subjects had to wait about three minutes before changing position.

To avoid co-intervention and contamination, the subjects were instructed not to take any other antibiotics and not to use other vaginal preparations during the study period. They were followed-up at 2 weeks after treatment for outcome measurement. The patients were instructed to avoid sexual intercourse and to observe any symptoms related to the side effects that occurred before the follow-up visit. The primary outcome was the cure rate. Cure was assessed by the investigators who did not know the treatment arm and measured by using Amsel's criteria. To be defined as "cure", the absence of at least three of Amsel's criteria was needed[16]. Symptoms after treatment were measured for evaluation of the side effects. Gastrointestinal side effects included nausea, vomiting and unpleasant taste. The subjects who had symptoms that reduced eating or had vomiting were

defined as having gastrointestinal side effects. For vaginal irritation symptoms, the subjects who did not require treatment were defined as having mild vaginal irritation while the subjects who required treatment were defined as having severe vaginal irritation.

Descriptive statistics were used for demographic and baseline data and summarized as mean or proportion with 95 per cent confidence interval. The outcome variables were described as proportion with 95 per cent confidence interval and compared between groups using Z-test for proportion. Intention-to-treat analysis was applied in analyzing the outcome variables. Statistical tests were 2-tailed and considered significant only if p-value < 0.05.

RESULTS

There were a total of 142 patients enrolled in the study, 72 cases in the H_2O_2 group and 70 cases in the metronidazole group. The demographic data of the patients is shown in Table 1. The baseline characteristics of the two groups were comparable with respect to age, marital status, parity, sexual activity and contraceptive methods.

All cases presented with increasing vaginal discharge but none of them had gastrointestinal symptoms before treatment. Details of symptoms and signs in the subjects before treatment are presented in Table 2.

The outcomes and clinical signs at follow-up visit are summarized in Table 3. The cure rate for treatment of bacterial vaginosis was 62.5 per cent (45 in 72 patients) in H_2O_2 group and 78.6 per cent (55 in 70 patients) in the metronidazole group. The result was considered statistically significant (p-value = 0.036) with difference of cure rate was equal to 16.1 per cent (95% CI, 1.3, 30.8). The patients in the metronidazole group had statistically significantly higher gastrointestinal side effects than the patients in the H_2O_2 group (48.6% and 13.9%, p-value < 0.001) resulting in a difference equivalent to 34.7 per cent (95% CI, 20.5, 48.9). Most of the patients had mild degree of nausea for a few days after taking the medication. No patient who had vaginal irritation needed treatment. Mild irritation found during the douching process was statistically significantly higher in the H_2O_2 group than in the metronidazole group (33.3%

Table 1. Demographic characteristics.

Characteristics	H_2O_2 group (n = 72)	Metronidazole group (n = 70)
Age (yr)*	31.2 (29.6, 32.9)	30.9 (29.4, 32.4)
Marital status**		
Single	6.9 (1.0, 12.8)	7.1 (1.1, 13.1)
Married	86.1 (78.1, 94.1)	
Divorced/Separated	6.9 (1.0, 12.8)	5.7 (0.3, 11.1)
Parity (time)**		
0	31.9 (21.1, 42.7)	30.0 (19.3, 40.7)
1	27.8 (17.5, 38.1)	27.1 (16.7, 37.5)
2	23.6 (13.8, 33.4)	34.3 (23.2, 45.4)
3	16.7 (8.1, 25.3)	5.7 (0.3, 11.1)
4	0.0	2.9 (0, 6.8)
Sexual activity (time/wk) **		
None	30.6 (19.9, 41.2)	22.9 (13.1, 32.7)
1-3	62.5 (51.3, 73.7)	68.6 (57.7, 79.5)
4-6	1.4 (0, 4.1)	8.6 (2.0, 15.2)
> 6	5.6 (0.3, 10.9)	0.0
Contraception **		
None	34.7 (23.7, 45.7)	32.9 (21.9, 43.9)
Pills	9.7 (2.9, 16.5)	21.4 (11.8, 31.0)
Injectable	0.0	1.4 (0, 4.2)
Norplant	2.8 (0, 6.6)	1.4 (0, 4.2)
Tubal resection	30.6 (19.9, 41.2)	12.0 (10.6, 29.4)
Condom	16.7 (8.1, 25.3)	17.1 (8.3, 25.9)
Vasectomy	5.6 (0.3, 10.9)	5.7 (0.3-11.1)

* Values are expressed in mean and (95% confidence interval).

** Values are expressed in per cent and (95% confidence interval).

Table 2. Symptoms and signs before treatment.

Symptoms and Signs	H_2O_2 group (n = 72)	Metronidazole group (n = 70)
Symptoms*		
Increased discharge	100.0	100.0
Vaginal malodor	87.5 (79.5, 95.1)	85.7 (77.5, 93.9)
Vaginal irritation	56.9 (45.5, 68.3)	42.9 (31.3, 54.5)
Nausea and vomiting	0.0	0.0
Signs*		
Homogeneous	95.8 (91.2, 100)	100.0
pH > 4.5	97.2 (93.4, 100)	94.3 (88.9, 99.7)
Whiff test positive	79.2 (69.8, 88.6)	71.4 (60.8, 81.9)
Clue cell	97.2 (93.4, 100)	97.1 (93.2, 100)

* Values are expressed in per cent and (95% confidence interval).

Table 3. Summary of outcome.

	H_2O_2 group (n = 72) %	Metronidazole group (n = 70) %
Cure	62.5	78.6
Side effects		
Gastrointestinal	13.9	48.6
Vaginal irritation	33.3	14.3
Signs after treatment		
Homogeneous	30.6	21.4
pH > 4.5	48.6	27.1
Whiff test positive	26.4	15.7
Clue cell	36.1	25.7

versus 14.3%, p-value = 0.008) resulting in a difference equivalent of 19.0 per cent (95% CI, 5.4, 32.7).

DISCUSSION

The standard treatment of bacterial vaginosis includes one of the following regimens: 1) oral metronidazole 500 mg twice daily for 7 days; 2) a single oral dose of metronidazole 2 grams; 3) oral clindamycin 300 mg twice daily for 7 days; 4) 2 per cent clindamycin vaginal cream once daily for 7 days; and 5) 0.75 per cent metronidazole vaginal gel twice daily for 5 days[1,11]. Topical antimicrobial therapy has similar efficacy as oral medications but has fewer systemic side effects. However, it is more expensive than oral metronidazole[1] and not available in Thailand.

Winceslaus et al[14] conducted a study using a single vaginal washout with 3 per cent H_2O_2 for treatment of recurrent bacterial vaginosis. Twenty-three symptomatic women with clinically confirmed bacterial vaginosis were recruited. After treatment, 78 per cent (18/23) of the subjects who had symptoms were completely cleared and the laboratory findings confirmed the efficacy. There were no side effects observed in this report.

For testing the effectiveness of single 3 per cent H_2O_2 vaginal douching in the treatment of bacterial vaginosis, the authors conducted the presented randomized controlled clinical trial. A single oral dose of metronidazole was selected as the control because it is one of the standard treatments, has low cost and is taken only once[17]. The authors could avoided the compliance problem because both experimental and control treatments were completed at the initial visit. The present trial demonstrated that the cure rate of treatment of bacterial vaginosis with single 3 per cent H_2O_2 vaginal douching was significantly less than with a single oral dose of metronidazole. The difference in the cure rate was 16.1 per cent with a 95 per cent confidence interval of 1.3 to 30.8. The cure rate with single 3 per cent H_2O_2 vaginal douching in the present study was only 62.5 per cent which is not appropriate for clinical application. The reason may be either 3 per cent H_2O_2 vaginal douching is not effective for the treatment of bacterial vaginosis or a single douche is not adequate. The result (62.5%) was lower than the previous study (78%)[14], which was not a controlled study. It may be because of different populations and using different criteria for outcome measurement. The effectiveness of a single oral dose of metronidazole, for the treatment of bacterial vaginosis, achieved a cure rate of 78.6 per cent in the pre-

sent trial. The result is similar to previous studies with cure rates between 67 per cent and 87 per cent[18-21].

The findings support the previous study[14] that no serious adverse effects occur after douching the vagina with 3 per cent H_2O_2. No patient who participated in this study had severe vaginal irritation. Mild irritation, found during the douching process, occurred in the H_2O_2 group significantly more frequently than in the metronidazole group (33.3% *versus* 14.3%, p-value = 0.008). The subjects in the metronidazole group had more gastro-intestinal side effects than those in the H_2O_2 group with statistical significance (48.6% and 13.9%, p-value < 0.001). This is the disadvantage of oral metronidazole, however, most of the patients only had nausea and the symptoms cleared within two days.

In conclusion, a single H_2O_2 vaginal douching is less effective in-terms of cure rate than a single oral dose of metronidazole in the treatment of bacterial vaginosis. However, the patients who received metronidazole had more gastro-intestinal side effects.

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การสวนล้างช่องคลอดด้วยไฮโดรเจนเพอร์ออกไซด์ครั้งเดียวเปรียบเทียบกับการรับประทานยาเมโทรนิดาโซลครั้งเดียวในการรักษาภาวะแบคทีเรียลวาไจโนสิส : การศึกษาแบบสุ่ม

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วัตถุประสงค์ : เพื่อเปรียบเทียบประสิทธิผลของการสวนล้างช่องคลอดด้วยไฮโดรเจนเพอร์ออกไซด์ครั้งเดียวกับการรับประทานยาเมโทรนิดาโซลครั้งเดียว ในการรักษาภาวะแบคทีเรียลวาไจโนสิส

วิธีการศึกษา : ได้ศึกษาแบบสุ่มที่คลินิกผู้ป่วยนอก โรงพยาบาลจุฬาลงกรณ์ ในผู้ป่วยซึ่งได้รับการวินิจฉัยเป็นภาวะแบคทีเรียลวาไจโนสิส จำนวน 142 ราย แบ่งผู้ป่วยโดยการสุ่มเป็น 2 กลุ่ม กลุ่มแรกได้รับการรักษาโดยการสวนล้างช่องคลอดด้วยไฮโดรเจนเพอร์ออกไซด์ความเข้มข้นร้อยละ 3 ปริมาณ 20 มิลลิลิตร และรับประทานยาหลอกครั้งเดียว กลุ่มที่สองได้รับการรักษาโดยการสวนล้างช่องคลอดด้วยยาหลอกและรับประทานยาเมโทรนิดาโซลขนาด 2 กรัมครั้งเดียว ประเมินอัตราการหายโดยใช้ Amsel's criteria หลังการรักษา 2 สัปดาห์

ผลการศึกษา : อัตราการหายในผู้ป่วยที่ได้รับการรักษาด้วยการสวนล้างช่องคลอดด้วยไฮโดรเจนเพอร์ออกไซด์ครั้งเดียว ต่ำกว่าในผู้ป่วยที่รับประทานยาเมโทรนิดาโซลครั้งเดียว (ร้อยละ 62.5 ต่อ ร้อยละ 78.6, p-value = 0.036) และพบอัตราผลข้างเคียงต่อระบบทางเดินอาหารในผู้ป่วยที่รับประทานยาเมโทรนิดาโซลสูงกว่า (ร้อยละ 48.6 ต่อ ร้อยละ 13.9, p-value < 0.001)

สรุป : การสวนล้างช่องคลอดด้วยไฮโดรเจนเพอร์ออกไซด์ครั้งเดียว มีประสิทธิผลในการรักษาภาวะแบคทีเรียลวาไจโนสิส ต่ำกว่าการรับประทานยาเมโทรนิดาโซลครั้งเดียว

คำสำคัญ : ไฮโดรเจนเพอร์ออกไซด์, เมโทรนิดาโซล, ภาวะแบคทีเรียลวาไจโนสิส, การศึกษาแบบสุ่ม

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