Effectiveness of Cefoxitin on Preventing Endometritis after Uterine Curettage for Spontaneous Incomplete Abortion: A Randomized Controlled Trial Study

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Background: There are only few studies concerning the usage of antibiotics in preventing endometritis after uterine curettage for spontaneous first trimester incomplete abortion and no conclusion can be demonstrated.

Objective: To investigate the effectiveness of prophylactic cefoxitin in preventing endometritis after uterine curettage for spontaneous first trimester incomplete abortion.

Material and Method: Eighty-four women with spontaneous first trimester incomplete abortion were randomly allocated into two groups using a computer-generated random number list and the allocation concealment was maintained using a sealed opaque envelope. The patients in the study group were given 1 g of cefoxitin while the patients in the control group were given 0.1 ml of vitamin B complex intravenously 20 minutes prior to curettage. Uterine curettage was performed after intravenous sedation and analgesic drugs were administered. The patients were evaluated on the first, third and seventh day after uterine curettage.

Results: Seventy-nine cases had completed the study protocol. There were no statistically significant differences in demographic data and details of uterine curettage between both groups. Two cases of endometritis were found in the control group but none in the study group. However, the difference did not reach the statistical significance (p = 0.241).

Conclusion: Prophylactic cefoxitin is not effective in preventing endometritis after uterine curettage for spontaneous first trimester incomplete abortion.

Keywords: Endometritis, Cefoxitin, Spontaneous incomplete abortion, Prophylaxis

The reported incidence of spontaneous abortion varies from country to country. In USA, it occurs in 15% of pregnant women[6]. Statistics from Siriraj Hospital in 2009 showed that of 9,842 hospitalized pregnant patients, 353 patients had spontaneous abortion, of which 84.70% were diagnosed with spontaneous incomplete abortion[6].

Uterine curettage is the standard treatment for incomplete abortion. The method is done by inserting a curette through the cervical canal into the uterine cavity to remove the remaining product of conception. This procedure is at risk for development of endometritis.

There are various pathogens causing endometritis. The common ones are *Escherichia coli* and anaerobic bacteria. *Chlamydia* and *gonococcus* can cause the infection, but only when they already exist in the vaginal canal[6].

Cefoxitin is a second-generation cepharosporin with a half-life of 45 to 60 minutes. It reaches the peak of therapeutic level in only 20 to 30 minutes after intravenous injection. Its bactericidal action results from inhibition of bacterial cell wall synthesis. Cefoxitin’s activity spectrum includes a broad range of covering both gram-negative and gram-positive bacteria including anaerobes that cause the endometritis[6].

From literature review, there have been only three studies of prophylactic antibiotic for spontaneous incomplete abortion. The first one was performed by Prieto et al, which was methodologically sound revealed no difference between the patients who did or did not receive prophylactic antibiotics. However, too many patients were lost to follow-up and this made the results unreliable[6]. The second one was Ramin's. It studied the effectiveness of doxycycline in
comparison to placebo in preventing endometritis after uterine curettage for the patients whose diagnosis was spontaneous incomplete abortion. It showed no different effectiveness\(^{(6)}\). The third study was Seeras’s. It studied the effectiveness of prophylactic tetracycline versus placebo in preventing endometritis after uterine curettage. The study found the same results as the two studies mentioned above\(^{(7)}\).

Since there are only a few studies concerning the usage of antibiotics in preventing endometritis after uterine curettage for spontaneous first trimester incomplete abortion and no conclusion can be drawn from these studies, the authors set out to investigate the effect of antibiotics in this aspect.

**Material and Method**

The present study was approved by the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital, Mahidol University before commencing the project and was supported by the Siriraj Research Development Fund.

Between November 14, 2008 and October 15, 2010, pregnant women in Siriraj Hospital faced with spontaneous first trimester incomplete abortion that gave their informed consent were recruited to participate in this triple blind clinical trial. However, the patients with conditions of cephalosporin allergy, penicillin allergy, diabetes mellitus, Acquired immunodeficiency syndrome, anemia and hypovolemic shock were excluded from the present study.

Eighty-four pregnant women were involved in the present study. After receiving the details of the study by the trained nurse at the septic labor room, all the patients were randomly allocated into two groups, study group, and control group. The randomization was done via a computer-generated random number list. Allocation concealment was maintained using a sealed opaque envelope. The study group received 1 g of cefoxitin diluted in 10 ml of sterile water, while the control group received 0.1 ml of vitamin B complex diluted in 10 ml of sterile water, which will create a light yellow coloration similar to the cefoxitin preparation. All the preparations mentioned above were prepared by the nurse who allocated the patients. These drugs were intravenously injected 20 minutes prior to uterine curettage by the second year resident physicians who did not know the type of the medications they were giving. Similarly, the patients were not informed about type of medication used. Uterine curettage was performed after intravenous sedation and analgesic drugs were administered. The details of the process were then recorded in the case record forms. The patients who had any complications during or after the procedure such as uterine perforation or hypovolemic shock would be excluded from the present study and would receive medical care accordingly. After the procedure, all the patients who had no complications were hospitalized for one day to be assessed for the development of endometritis and would be discharged on the next day if negative findings were found. The patients were asked to come back on the third and seventh day after the procedure for re-examinations and reassessment by the second year resident physicians who did not know which treatment the patients received prior to the appointment. The details of the reassessment were recorded in the case record forms.

Endometritis would be diagnosed if the patients met at least three of the following criteria as described in Seeras’s study\(^{(7)}\): 1) history of fever, headache or pelvic pain, 2) body temperature exceeded 38 degrees Celsius, 3) tenderness on one or both sides of the abdomen, 4) positive cervical excitation test, or 5) presence of a foul smelling vaginal discharge.

The patients who were diagnosed as having endometritis would be further evaluated and received medical care according to standard treatments.

**Sample size determination**

Since the present study wanted to compare two proportions of outcome, the authors used this formula for the estimation of sample size\(^{(8)}\).

\[
N = \left[ \frac{Z_\alpha^2 P_0 Q_0 + Z_\beta^2 P_1 Q_1 + P_2 Q_2}{(P_1 - P_2)^2} \right]^2
\]

Where \(N\) = required samples

\(P_0 = (P_1 + P_2)/2\)

\(Q_0 = 1 - P_0\)

\(Q_1 = 1 - P_1\)

\(Q_2 = 1 - P_2\)

\(Z_\alpha = 1.64\) at Type I error = 0.05

\(Z_\beta = 0.842\) at Power = 80%

\(P_1\) was the incidence of endometritis in the control group which was found to be 25% from the extensive review of Strahan TW et al\(^{(9)}\). Therefore, in this study, we used \(P_1 = 0.25\)

\(P_2\) was the incidence of endometritis in the study group, which was interested in clinical benefit if it was found to be 5%. Therefore, we used \(P_2 = 0.05\)
Then

\[ N = \left( \frac{L}{d^2} \right)^2 \times \left[ \frac{1}{2} \times \frac{0.25 + 0.05}{0.25} \times (1 - 0.25) + 0.05 + 0.05 \times (1 - 0.05) \right] \]

\[ = 38 \text{ cases for each group} \]

Ten percent of cases were added to the calculated number for expected loss of follow-up of the patients. Therefore, the total number was \((38 \times 2) + 8 = 84\) cases.

**Statistical analysis**

All the collected data were reviewed using the SPSS 11.5 (statistical package for the social science/personal computer plus). The demographic data was presented as mean ± standard deviation and Unpaired t-test was used for comparison. The Mann Whitney U-test was used to compare the outcomes of median between the two groups. The non-parametric data was presented as percentage using Fisher’s exact test for comparison. The result was considered statistically significant if the p-value was less than 0.05.

The summary of the research intervention is shown in Fig. 1.

**Results**

During the experiment, from 84 women who enrolled in the present study, five patients were excluded, one patient was allergic to cefoxitin, two patients had abnormal pathological reports (one with clear cell metaplasia, and the other had complete hydatidiform mole). In addition, two patients did not show up at the scheduled appointments. Thus, there were 79 patients (94.05%) left in the experiment. The study group consisted of 40 patients and the control group consisted of 39 patients.

There were no statistically significant difference in age, BMI, gestational age (Table 1) and details of uterine curettage between both groups (Table 2). Two cases of endometritis were found in the control group but none in the study group (Table 3). The pathologic agents for these two cases were *Escherichia coli* and *Chlamydia trachomatis*. However, the difference did not reach the statistical significance \((p = 0.241)\).

**Discussion**

Endometritis is a complication that could occur after procedure such as vaginal delivery, caesarean delivery, or uterine curettage. It could also cause further serious complications that have long-term damages, for instance sepsis, infertility, or ectopic

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**Table 1.** Demographic data of the patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cefoxitin (n = 40) mean ± SD</th>
<th>Placebo (n = 39) mean ± SD</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>29.15 ± 6.97</td>
<td>27.79 ± 8.60</td>
<td>0.44</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.42 ± 3.75</td>
<td>21.80 ± 3.60</td>
<td>0.55</td>
</tr>
<tr>
<td>&lt; 18.5</td>
<td>5 (12.5%)</td>
<td>2 (5.1%)</td>
<td></td>
</tr>
<tr>
<td>18.5-23.4</td>
<td>23 (57.5%)</td>
<td>30 (76.9%)</td>
<td></td>
</tr>
<tr>
<td>23.5-28.4</td>
<td>10 (25.0%)</td>
<td>3 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>&gt; 28.5</td>
<td>2 (5.0%)</td>
<td>4 (10.3%)</td>
<td></td>
</tr>
<tr>
<td>Gestational age (weeks)</td>
<td>9.94 ± 2.19</td>
<td>9.73 ± 2.32</td>
<td>0.68</td>
</tr>
</tbody>
</table>

*p* Unpaired t-test
pregnancy. Hence, the prevention of endometritis will become advantageous in forestalling any sequelae that may be followed.

Cefoxitin can cover most pathogens including *Escherichia coli* and anaerobic bacteria, the two common pathogens of endometritis. It is also easy to administer. Furthermore, it has a few side effects, has low cost, and is generally used as an endometritis prophylaxis in cesarean section. Additionally, it has already been investigated for the effectiveness to prevent endometritis after uterine curettage for spontaneous incomplete abortion. Therefore, the authors chose this medication for the present study(4).

This study was carried out as an experimental study that compared the two groups of patients, 1) a study group that received 1 g cefoxitin, and 2) a control group that received 0.1 ml vitamin B complex. To decrease the chance of bias as much as possible, the researchers used a triple blind study that concealed the physicians who performed uterine curettage, the patients, and the physicians who followed-up from knowing what medication was given to the patients. To conceal the chosen medication, vitamin B complex was used as a placebo, since 0.1 ml of the substance diluted in 10 ml of sterile water makes it become light yellow, which is very similar to cefoxitin solution. This would make it difficult to distinguish one from the other.

The above technique helped eliminate confounding factors and decreased research prejudice. There was no statistically significant differences between the two groups in term of both demographic data of patients and details of uterine curettage. The results of the research were only based on the prophylactic antibiotic.

Another important factor is the variation in experience of the physician performing the procedure. For example, the longer the uterine curettage procedure lasts, the more chances it is to be infected. Therefore, in the present study, the researchers tried to eliminate this factor by selecting the second year resident physicians to perform uterine curettage. This is because they are the physicians that have gone through uterine curettage training. Therefore, they had similar capability in performing the procedure. Subsequently, in the present study, the authors found that the operative time of uterine curettage and estimated blood loss from the operation of the patients in both groups had no statistically significant differences. Additionally, there were no complications, such as uterine perforation. This further supported that the outcome of treatment in both groups was the consequence of medication, not the method of uterine curettage.

In the present study, two patients (5.1%) in the control group developed endometritis while there was none in the study group. There was no statistically significant differences between both groups of patients (p = 0.241). It could be concluded that cefoxitin is not effective in preventing endometritis after uterine curettage for spontaneous first trimester incomplete abortion.

There have been few studies about using antibiotics against endometritis due to spontaneous incomplete abortion. Seeras’ study(7) looked into the use of antibiotics in preventing infections similar to the present study. Using a randomized controlled trial, the study compared 140 spontaneous incomplete abortion patients who were randomized into two groups: a control group that received a placebo, and a test group that received 1 g cefoxitin intramuscularly to prevent endometritis. After 7 days, the incidence of endometritis was 5.7% in the control group and 2.8% in the test group. This study concluded that cefoxitin is effective in preventing endometritis due to spontaneous incomplete abortion.

Table 2. Amount of tissue from the uterine curettage, the operative time, and the estimate blood loss of the patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cefoxitin (n = 40)</th>
<th>Placebo (n = 39)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tissue from curettage (g)</td>
<td>20 (10, 30)</td>
<td>20 (10, 40)</td>
<td>0.40</td>
</tr>
<tr>
<td>Operative time (mins)</td>
<td>10 (10, 15)</td>
<td>15 (10, 15)</td>
<td>0.79</td>
</tr>
<tr>
<td>Estimate blood loss (ml)</td>
<td>20 (10, 30)</td>
<td>20 (10, 30)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

* Mann Whitney U-test

Table 3. Incidence of endometritis after uterine curettage of the patients

<table>
<thead>
<tr>
<th>No endometritis</th>
<th>Cefoxitin (n = 40)</th>
<th>Placebo (n = 39)</th>
<th>Total</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>number (%)</td>
<td>40 (100%)</td>
<td>37 (94.9%)</td>
<td>77 (97.5%)</td>
<td>0.241</td>
</tr>
<tr>
<td>Endometritis</td>
<td>0 (0%)</td>
<td>2 (5.1%)</td>
<td>2 (2.5%)</td>
<td></td>
</tr>
</tbody>
</table>

* Fishers exact test
abortion patients who were hospitalized at Harare Central Hospital in 1985. These participating patients were divided into two groups. The study group had 62 patients, each was treated with 500 mg of tetracycline, four times a day for one week after uterine curettage. On the other hand, each patient in the control group, consisting of 78 patients, was treated with placebo pills. Twenty-five patients (40.32%) from the control group and 23 patients (29.5%) from the study group got post-abortal sepsis, which was not statistically significant difference. However, Seeras’ study found that 82.6% of the patients in the study group that were infected after a uterine curettage did not consume a specified amount of medication. This was probably an important reason why more patients in the group that received antibiotics were infected after uterine curettage than in the group that received placebo pills. The weakness of Seeras’ study was the poor compliance of the patients, which led to less reliable conclusions.

Ramin et al(6), using a randomized double-blind controlled trial, studied 289 spontaneous incomplete abortion patients hospitalized at Parkland Memorial Hospital between November 1992 and June 1993. They divided the patients into two groups. Each patient in the study group was given 200 mg of doxycycline 30 to 60 minutes before uterine curettage, while the patients in the control groups were given placebo. Results showed that one patient in the study group and four patients in the control group got endometritis, which was not statistically significant different ($p = 0.22$), similar to Seeras’s and the present study.

In the present study, the authors did not have a problem with patient compliance because the drug the authors used was a single dose of intravenously injected cefoxitin. In addition, every patient in the analyzed population came to their scheduled appointments. However, the result was still similar to Seeras’s and Ramin’s. There were no differences between the study group and the control group. This may be because tetracycline, doxycycline, and cefoxitin are not effective in preventing endometritis after spontaneous incomplete abortion. Nonetheless, it was noticeable that among the patients who received cefoxitin, no endometritis occurred at all.

**Conclusion**

Cefoxitin is not effective in preventing endometritis after uterine curettage for spontaneous first trimester incomplete abortion.

**Acknowledgement**

The researchers would like to thank the Siriraj Research Development Fund who kindly approved a research fund, which contributed to the success of the present study.

**Potential conflicts of interest**

None.

**References**

2. Annual statistical report 2009. Bangkok: Division of Obstetric and Gynecologic Registry, Department of Obstetrics and Gynecology, Faculty of Medicine Siriraj Hospital, Mahidol University; 2009.
ประสิทธิผลของ cefoxitin ในการป้องกันภาวะเยื่อบุโพรงมดลูกอักเสบหลังการขูดมดลูกเพื่อรักษาภาวะแท้งไมครบที่เกิดเองในไตรมาสแรกของการตั้งครรภ์: การศึกษาแบบสุ่มอิสระ

วิทยา อนิสาพันธุ์, พนิดา เชิดชูเกียรติ

อุปมัธยม: การขูดมดลูกเพื่อรักษาภาวะแท้งไมครบที่เกิดเองในไตรมาสแรกของการตั้งครรภ์เป็นหัตถการที่มีการกระทํากันอยู่เป็นประจำ แต่มีการศึกษาหน่วงเล็กน้อยเกี่ยวกับประโยชน์ของการใช้ยาปฏิชีวนะเพื่อป้องกันภาวะเยื่อบุโพรงมดลูกอักเสบจากหัตถการดังกล่าว และจนถึงปัจจุบันยังยังไม่มีข้อสรุปที่ชัดเจนเกี่ยวกับวัตถุประสงค์นี้ วัตถุประสงค์: เพื่อดำเนินการศึกษาประสิทธิผลของ cefoxitin ในการป้องกันภาวะเยื่อบุโพรงมดลูกอักเสบหลังการขูดมดลูกเพื่อรักษาภาวะแท้งไมครบที่เกิดเองในไตรมาสแรกของการตั้งครรภ์

วัสดุและวิธีการ: สตรีที่มีภาวะแท้งไมครบที่เกิดเองในไตรมาสแรกของการตั้งครรภ์จะถูกแบ่งออกเป็น 2 กลุ่ม คือ กลุ่มศึกษาและกลุ่มควบคุม โดยใช้วิธีสุ่มคัดเลือกผู้ป่วยด้วยคอมพิวเตอร์และปกปิดผลการคัดเลือกโดยใช้ซองจดหมายทึบปกปิดกลุ่มศึกษาจะได้รับ cefoxitin ขนาด 1 กรัม ผสมในน้ำกลั่นบริสุทธิ์ปริมาณ 10 มิลลิลิตร และฉีดเข้าหลอดเลือดด้วยหลอดเลือดเดี่ยวที่มีหัวฉีดต่ำๆ 20 นาที ส่วนกลุ่มควบคุมจะได้รับ vitamin B complex ขนาด 0.1 มิลลิกรัม ผสมในน้ำกลั่นบริสุทธิ์ปริมาณ 10 มิลลิลิตร และฉีดเข้าหลอดเดี่ยวในทันทีหลังจากการขูด ผู้ป่วยที่ได้รับยาและผู้ประเมินผลของการใช้ยา ไม่มีผู้ใดทราบว่าผู้ป่วยได้รับยาชนิดใด จากนั้นทำการขูดมดลูกหลังจากการขูดมดลูกให้ใช้ยาปฏิชีวนะแบบมีการฉีดยาปฏิชีวนะในวันที่ 1, 3 และ 7 หลังจากการขูดมดลูก ผลการศึกษา: มีกลุ่มที่มีภาวะแท้งไมครบที่เกิดเอง 79 ราย ที่เข้าร่วมโครงการจนเสร็จสมบูรณ์ ซึ่งพบว่าข้อมูลที่สำคัญต่างๆ BMI อายุครรภ์ และข้อมูลเกี่ยวกับการขูดมดลูกของทั้ง 2 กลุ่ม ไม่แตกต่างกันทางสถิติ ผลการศึกษาพบว่าไม่มีการเกิดภาวะเยื่อบุโพรงมดลูกอักเสบในกลุ่มศึกษา แต่ไม่พบผลที่มีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติ (p = 0.241) สรุป: จากการศึกษาในที่นี้จะเห็นว่าการให้ cefoxitin ในการป้องกันการเกิดภาวะเยื่อบุโพรงมดลูกอักเสบหลังการขูดมดลูกในสตรีที่มีภาวะแท้งไมครบที่เกิดเองในไตรมาสแรกของการตั้งครรภ์