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# Comparative study of efficacy of cefotaxime sodium versus ampicillin plus gentamicin for the treatment of postcesarean endomyometritis

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Objective : *The purpose of this study was to evaluate the efficacy and safety of cefotaxime compared with the combination of ampicillin and gentamicin in the treatment of postcesarean endomyometritis.*

Setting : *Department of Obstetrics and Gynecology, Sing Buri Hospital, Sing Buri Province.*

Design : *Prospective, randomized study.*

Patients : *Sixty-five patients with endomyometritis following cesarean section from January 1995 to December 1997 were treated with cefotaxime and ampicillin plus gentamicin, 32 patients received cefotaxime intravenously and 33 patients received ampicillin plus gentamicin intravenously.*

Method : *Demografic, clinical laboratory, and response information data was analyzed by the $X^2$ test, Student's t test, or Fischer's exact test where appropriate. A p-value of $\leq 0.05$ was interpreted as significant.*

Results : *Among the 32 patients treated with cefotaxime there were therapeutic cured in 31 patients (96.88%) one had therapeutic failure and no side effect failure. Among the 33 patients treated with ampicillin plus gentamicin group, there were therapeutic cure in 26 patients (78.79%), seven had therapeutic failure and no side effect failure. The therapeutic cure rate in cefotaxime group*

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*was higher than ampicillin plus gentamicin group significantly ($P \leq 0.05$). There were no significant differences in duration of postoperative hospital stay but there was significant differencence in number of wound infection ($P \leq 0.05$).*

**Conclusion** : *Cefotaxime was more effective than ampicillin plus gentamicin in successful treating postcesarean endomyometritis. Both regimens had good cure rate and safe.*

**Key words** : *Cefotaxime, Endomyometritis, Wound infection.*

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**ประยงค์ สุริย์จามร. การศึกษาเปรียบเทียบประสิทธิผลการใช้ยาเซฟโฟตาซีมกับยาแอมพิซิลินร่วมกับเจนตาไมซินในการรักษามดลูกอักเสบหลังผ่าตัดคลอดบุตร. จุฬาลงกรณ์เวชสาร 2543 ส.ค; 44(8): 595 - 605**

**วัตถุประสงค์** : *เพื่อศึกษาประสิทธิผลและความปลอดภัยของยาเซฟโฟตาซีมกับยาแอมพิซิลินร่วมกับเจนตาไมซินในการรักษามดลูกอักเสบหลังผ่าตัดคลอดบุตร*

**สถานที่ที่ทำการศึกษา** : *กลุ่มงานสูติ-นรีเวชกรรม โรงพยาบาลสิงห์บุรี จังหวัดสิงห์บุรี*

**รูปแบบการวิจัย** : *การศึกษาไปข้างหน้า แบบแรนดอมไมล์*

**ผู้ป่วยที่ได้ทำการศึกษา** : *ผู้ป่วยมดลูกอักเสบหลังผ่าตัดคลอดบุตรในระหว่างมกราคม พ.ศ. 2538 ถึงธันวาคม พ.ศ. 2540 จำนวน 65 ราย ได้รับยาเซฟโฟตาซีมหรือยาแอมพิซิลินร่วมกับเจนตาไมซิน โดยมีผู้ป่วยได้รับยาเซฟโฟตาซีมทางหลอดเลือดดำ จำนวน 32 ราย และได้รับยาแอมพิซิลินร่วมกับเจนตาไมซินทางหลอดเลือดดำ จำนวน 33 ราย*

**วิธีการศึกษา-วัดผล** : *ข้อมูลลักษณะทั่วไป ผลทางห้องปฏิบัติการและผลการรักษานำมาวิเคราะห์โดยใช้สถิติ $X^2$ test, Student's t test หรือ Fischer's exact test ตามความเหมาะสม ค่าของ p-value เท่ากับ หรือน้อยกว่า 0.05 ถือว่ามีนัยสำคัญทางสถิติ*

**ผลการศึกษา** : *ผู้ป่วยที่รักษาด้วยยาเซฟโฟตาซีม จำนวน 32 ราย พบว่าหายป่วย จำนวน 31 ราย หรือร้อยละ 96.88 โดยรักษาไม่ได้ผล จำนวน 1 ราย และไม่พบการรักษาล้มเหลวจากอาการข้างเคียงของยา ส่วนผู้ป่วยที่ได้รับการรักษาด้วยยาแอมพิซิลินร่วมกับเจนตาไมซิน จำนวน 33 ราย พบว่าหายป่วย จำนวน 26 ราย หรือร้อยละ 78.79 โดยรักษาไม่ได้ผล จำนวน 7 ราย และไม่พบการรักษาล้มเหลวจากอาการข้างเคียงของยา ผลการวิเคราะห์พบว่ายาเซฟโฟตาซีม ให้ผลการรักษามดลูกกเสบหลังผ่าตัดคลอดบุตรสูงกว่ายาแอมพิซิลินร่วมกับเจนตาไมซินอย่างมีนัยสำคัญที่ระดับนัยสำคัญ 0.05 ส่วนระยะเวลาอยู่ในโรงพยาบาลภายหลังผ่าตัดไม่มีความแตกต่างกันอย่างมีนัยสำคัญในทั้งสองกลุ่มแต่จำนวนผู้ป่วยเกิดแผลติดเชื้อมีความแตกต่างกันอย่างมีนัยสำคัญที่ระดับนัยสำคัญ 0.05*

**สรุป** : *ยาเซฟโฟตาซีมให้ผลการรักษามดลูกอักเสบ หลังผ่าตัดคลอดบุตรดีกว่ายาแอมพิซิลินร่วมกับเจนตาไมซิน โดยทั้งสองกลุ่มให้ผลการรักษาที่ดีและมีความปลอดภัย*

**คำสำคัญ** : *เซฟโฟตาซีม มดลูกอักเสบ แผลติดเชื้อ*

Endomyometritis remains the most common infective complication associated with cesarean delivery with potential sequelae[1-3] that include abscess formation, septic pelvic thrombophlebitis, sepsis, sterility, and death. Antibiotic therapy[4-6] of these infections, which is usually effective in preventing complication must be directed against a wide variety of aerobic and anaerobic organism.[1,7]

One commonly used antibiotic regimen is ampicillin[5,6,8] in combination with an aminoglycoside.[1,5,8-13] Previous therapy studies have the cure rates with penicillin-aminoglycoside of 70-80%[1,4-6,8] but aminoglycosides can cause eighth-nerve injury and impair renal function.[9,14]

Cefotaxime sodium[15-17] is a newer cephalosporin and had a bactericidal, it is effective against many pathogens, including those recovered from women with pelvic infections after cesarean section.[17] Clinical success was 97.5% for women given parenteral cefotaxime.[17]

The purpose of this study was to evaluate the safety and efficacy of cefotaxime compared with combination of ampicillin and gentemicin in treating postcearean endomyometritis.

## Material and Methods

The investigation, conducted between January 1995 and December 1997, included postcesarean section patients at Sing Buri Hospital. Patients who were at least 18 years old and gave informed written consent were enrolled in the study if they met the following criteria: (1) two oral temparatures greater than $100.4^0$ F ($38.0^0$ C) at least 24 hours from the time of cesarean section, measured on two occasions at least six hours apart, or a temperature greater than $101^0$ F ($38.4^0$ C); (2) abnormal uterine tenderness; (3) leukocytosis (> 12,000 cells/cu mm) or a 10% increase in immature leukocytes; (4) uterine subinvolution; (5) purulent or foul-smelling lochia; (6) the absence of any other foci of infection.

Patients with preexisting amnionitis or other initially identifiable sources of infection were excluded. Allergy to any of the study antimicrobials or compromised renal function were also excluded. Other exclusions included patients with a high probability of death within 48 hours despite intensive therapy; patients receiving antibiotic prophylaxis or treatment other than the study antibiotic within 24 hours of enrollment; patients with infected devices, eg, heart valves; and patients who required concomitant therapy with probenicid.

Eligible patients were then prospectively randomized to receive either (1) cefotaxime 2.0 gm in 150 ml of 5% dextrose in water by intravenous infusion over 30 minutes every 12 hours, or (2) ampicillin 1 gm intravenously every 6 hours, and gentamicin sulfate 1.0 mg/kg body weight in 100 ml of 5% dextrose in water by intravenous infusion over 30 minutes every 8 hours.

At the time of diagnosis, a hematocrit, leukocyte count and differential, and serum electrolytes including blood urea nitrogen and creatinine were determined. Cultures of blood, urine, and the intra-uterine content were obtained before therapy. Aerobic and anaerobic blood cultures, urine culture obtained by sterile catheterization and intra-uterine contents were obtained by an unprotected sterile cottontipped applicator.

Patient responses were judged to be a therapeutic cure, a therapeutic failure; or a side effect failure. A therapeutic cure was defined as a resolution

of signs and symptoms such as fever and uterine tenderness with in 72 hours after the start of therapy. The response was considered to be a therapeutic failure when there was no resolution of the above signs and symptoms within this period. A side effect failure resulted when adverse reactions led to cessation of therapy.

When there was a cure, the regimen was continued until the patient remained afebrile with resolution of signs and symptoms for 48 hours. Oral antibiotic were administered upon discontinuation of intravenous medication women were discharged on oral cephalexin or ampicillin 500 mg every six hours to complete a 12 to 14 day course of therapy.

When there was a therapeutic failure or side effect failure, the patient was reevaluated and the therapy was modified or altered according to clinical judgements and culture results.

Data were analyzed by the $X^2$ test, Student's t test, or Fischer's exact test where appropriate. A p-value of $\leq 0.05$ was interpreted as significant.

**Results**

During the study period, there were 5,098 deliveries and 962 patients (18.87%) undergoing cesarean section. The overall postcesarean endomyometritis was found in 98 patients (10.19%) and 68 patients were enrolled. Of these 68 patients, 3 patients were excluded: two because of inadequate inclusion criteria and one because of receiving antibiotic for treatment other than the study antibiotic within 24 hours of enrollment. Thus, 65 postcesarean section patients with endomyometritis were studied, 32 patients received cefotaxime and 33 patients received ampicillin plus gentamicin. Characteristic of the two groups are shown in Table 1. There were no statistical difference between the cefotaxime and the ampicillin plus gentamicin groups.

**Table 1.** Characteristics of the groups receiving the two regimens in study patients.

| Characteristics | Cefotaxime (N = 32) | Ampicillingentamicin (N = 33) | P-value |
|---|---|---|---|
| Age (yr) | 23.2 ± 5.3 | 22.9 ± 48 | NS |
| Parity (mean ± SD) | 2.0 ± 1.3 | 2.3 ± 1.5 | NS |
| Weight (kg) (mean ± SD) | 64.2 ± 16.3 | 63.8 ± 15.8 | NS |
| Gestational age (wk) (mean ± SD) | 39.3 ± 2.5 | 39.8 ± 2.3 | NS |
| Membrane ruptured | 12 (37.6%) | 13 (39.5%) | NS |
| Rupture of membrane to delivery (hr) (mean ± SD) | 8.3 ± 7.9 | 8.9 ± 8.3 | NS |
| In labor | 25 (78 %) | 27 (81.8%) | NS |
| Labor (hr) | 9.3 ± 8.2 | 9.1 ± 8.0 | NS |
| Vaginal examination (mean ± SD) | 5.7 ± 4.8 | 5.4 ± 4.6 | NS |
| Cesarean section | | | |
| Primary | 26 (81.2 %) | 26 (78.8 %) | NS |
| Repeat | 6 (18.8 %) | 7 (21.2 %) | NS |

Table 1. Countinues.

| Characteristics | Cefotaxime (N = 32) | Ampicillin-gentamicin (N = 33) | P-value |
|---|---|---|---|
| Tubal ligation performed | 5 (15.6 %) | 5 (15.2 %) | NS |
| Indication | | | |
| Cephalopelvic disproportion | 20 (62.5 %) | 19 (57.6 %) | NS |
| Fetal distress | 3 (9.4 %) | 4 (12.1 %) | NS |
| Malpresentation | 3 (9.4 %) | 3 (9.1 %) | NS |
| Repeat | 6 (18.8 %) | 7 (21.2 %) | NS |
| Anesthesia | | | |
| Regional | 4 (12.5 %) | 3 (9.1 %) | NS |
| General | 28 (87.5 %) | 30 (91.9 %) | NS |
| Operative time (min) (mean ± SD) | 63.3 ± 20.8 | 64.8 ± 21.1 | NS |
| Temperature at enrollment ($^{O}$F) | 102.1 ± 0.8 | 102.0 ± 0.7 | NS |
| Hematocrit < 33 | 5 (15.6 %) | 6 (18.2 %) | NS |
| Luekocyte > 15,000 cells/cu mm | 12 (37.6 %) | 12 (36.4 %) | NS |

Table 2 shows the culture results in five patients (7.69%) with positive urine culture and three patients (4.62%) with bacteremia at the time of enrollment. The distribution of bacterial isolates in urine and blood specimens between the cefotaxime and ampicillin plus gentamicin groups is shown in table 2.

Table 3 shows bacterial isolates from intra-uterine contents which were similar kinds in both groups Results of susceptibility testing are shown in Table 4.

Table 2. Bacterial isolates from urine and blood specimens.

| Urine and Blood cultures | Cefotaxime (N = 32) | Ampicillin-gentamicin (N = 33) |
|---|---|---|
| Urine culture | | |
| Group B streptococcus | 1 | 1 |
| Escherichia coli | 1 | 1 |
| Enterococcus | 0 | 1 |
| Blood culture | | |
| Group B streptococcus | 1 | 1 |
| Staphylococcus aureus | 0 | 1 |

Table 3. Bacterial isolates from intrauterine contents.

| Species or group of bacteria | Cefotaxime (N = 32) | Ampicillin-gentamicin (N = 33) |
|---|---|---|
| Aerobes : | | |
| Escherichia coli | 19 | 18 |
| Group B streptococci | 13 | 12 |
| Proteus mirabilis | 6 | 8 |
| Klebsiella species | 6 | 6 |
| Other gram-negative rods | 8 | 10 |
| Enterobactor species | 5 | 7 |
| Staphyllococcus epidermidis | 2 | 3 |
| Staphyllococcus aureus | 1 | 1 |
| Enterococci | - | 2 |
| Pseudomonas aeruginosa | 1 | - |
| Anaerobes : | | |
| Bacteroides bivius | 10 | 12 |
| Bacteroides fragilis group | 4 | 3 |
| Other bacteroides species | 6 | 6 |
| Gram-positive cocci | 8 | 8 |
| Fusobacterium species | 2 | 1 |
| Clostridium species | 1 | 1 |

The outcome of treatment of the patients is shown in Table 5. The cefotaxime and ampicillin plus gentamicin group had therapeutic cure rate of 96.88% and 78.79%, respectively. These therapeutic cure rates were significantly different ($P \leq 0.05$). There were no adverse effects requiring cessation of therapy in any of the study population. The therapeutic failure in the cefotaxime group were attributed to a resistant group B streptococcus plus wound infection in one patient. Of those seven therapeutic failures in ampicillin plus gentamicin group, there were apparent explanations for three (isolation of a resistant enterococcus, bacteroid fragilis and staphylococcus aureus). In the other four cases, there was no apparent cause. Inadequate dosage of gentamicin may be suggested as a possible cause of therapeutic failure, especially in patients with marginally susceptable isolates or with weights greater than 80 kg. Of the one patient in the cefotaxime group with bacteremia had cures. Of the two patients in the ampicillin plus gentamicin group with bacteremia, one had cures, and one had a failure.

Table 4. Susceptibility to protocol antibiotics of bacteria isolated from intrauterine contents.

| Species or group of bacteria | Cefotaxime | Ampicillin | Gentamicin |
|---|---|---|---|
| Aerobes : | | | |
| Escherichia coli | 37/37 | 26/37 | 36/37 |
| Group B streptococci | 24/25 | 20/25 | 21/25 |
| Proteus mirabilis | 14/14 | 9/14 | 12/14 |
| Klebsiella species | 12/12 | 6/12 | 12/12 |
| Other gram-negative rods | 17/18 | 11/18 | 15/18 |
| Enterobactor species | 9/12 | 2/12 | 4/12 |
| Staphyllococcus epidermidis | 5/5 | 4/5 | 0/5 |
| Staphyllococcus aureus | 2/2 | 1/2 | 0/2 |
| Enterococci | 0/2 | 1/2 | 1/2 |
| Pseudomonas aeruginosa | 1/1 | 0/1 | 0/1 |
| Amaerobes : | | | |
| Bacteroides bivius | 22/22 | 11/22 | - |
| Bacteroides fragilis group | 7/7 | 0/7 | - |
| Other bacteroides species | 11/12 | 6/12 | - |
| Gram-positive cocci | 15/16 | 12/16 | - |
| Fusobacterium species | 3/3 | 2/3 | - |
| Clostridium species | 2/2 | 2/2 | - |

Table 5. Outcome of antibiotic treatment in study patients.

| Outcomes | Cefotaxime (N = 32) | Ampicillin-gentamicin (N = 33) | P value |
|---|---|---|---|
| Therapeutic cure | 31 (96.88%) | 26 (78.79%) | $\leq 0.05$ |
| Therapeutic failure | 1 (3.12%) | 7 (21.21%) | $\leq 0.05$ |
| Side-effect failure | 0 | 0 | - |
| Wound infections | 1 | 6 | $\leq 0.05$ |
| Pelvic abscess / septic pelvic thrombophlebitis | 0 | 0 | - |
| Postoperative stay (day, (mean $\pm$ SD) | $7.2 \pm 2.3$ | $8.1 \pm 2.5$ | NS |

In this study, there were one patients receiving cefotaxime who developed wound infection and associated with a therapeutic failure. There were six patients receiving ampicillin plus gentamicin who developed wound infection. There was statistically significant difference in the number of wound infection between two group ($P \leq 0.05$). Furthermore the postoperative hospital stay were similar. No patients showed nephrotoxicity.

## Discussion

Patient developing endomyometritis following cesarcan section have many of the serious infective complications seen on an obstetric-gynecologic service. In view of the high incidence of bacteremia antibiotic therapy need to be initiated before culture results are available. The availability of new antibiotics has caused a reassessment of therapy for female genital tract infection.[4-6]

In this study, we compared ampicillin plus gentamicin, often considered to be the standard therapy for such infection to cefotaxime, a newer cephalosporins. To range of activity includes those pathogens commonly isolated in postcesarean endomyometritis, such as escherichia coli, klebsiela pnuemoniae, proteus sp, bacteriodes sp, group B and D streptococci, peptococci, and peptostreptococci. Cefotaxime[17] appears to be free of major toxicity and has lower rate of adverse reactions compared with penicillin. Previous report[17] indicated that cefotaxime was well suited for single-agent parenteral therapy for this polymicrobial pelvic infection and reported a 97.5% cure rate in postcesarean endomyometritis.

In this study, the two treatment groups had similar clinical characteristics and bacterial isolates in urine, blood and intra-uterine contents. The overall bacterial isolates from intra - uterine contents are similar to those previously reported.[4,11,12,13,17] Some differences are evident probably because of differences in population and technique. The therapeutic cure rate was higher for cefotaxime ($P \leq 0.05$). There were no significant differences in duration of postoperative hospital stay but significant difference in number of wound infection ($P \leq 0.05$). No cases of abscess or presumed septic pelvic thrombophlebitis were diagnosed. There were no cases of side effects failures in both regimens.

The therapeutic cure rate of cefotaxime (96.88%) and ampicillin plus gentamicin (78.79%) is similar to previous study that found therapeutic cure rate in cefotaxime of 97.5%[17], ampicillin of 81%[6] and penicillin plus gentamicin of 70-76%.[1,4,5,8]

In this study, a large percentage of patients with endomyometritis also developed abdominal wound infection (7/65, 10.77%) which is similar to previous study (29/198, 15%).[11]

A major concern about the use of gentamicin is its narrow margin of safety. In our population of young women, there were no instances of nephrotoxicity. Among patients on medical wards, who are likely to have more risk factors, nephrotoxicity has been reported in 5%.[14]

The cost of cefotaxime (4 gm/day) was 256 baht, whereas the cost of ampicillin (4 gm/day) plus gentamicin (3 mg/kg/day) was approximately 68 baht. However, the nursing cost for drug preparation should be considered in the ampicillin plus gentamicin regimen due to seven-doses versus two doses of cefotaxime.

## Conclusion

In this comparative randomized trial, the cefotaxime regimen had fewer therapeutic failures and efficacy better than those of ampicillin plus gentamicin for the treatment of postcesarean endomyometritis. Both regimens had good cure rate and safe.

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