Efficacy and Safety of Parenteral Amoxycillin/ Clavulanate for Prevention of Surgical Site Infection Following Abdominal Surgery

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Objective: *The aim of the present study was to evaluate the efficacy and safety of parenteral amoxycillin/ clavulanate for the prevention of surgical site infection (SSI) following intra-abdominal surgery.*
Material and Method: *This prospective opened non-comparative clinical trial was conducted in the Department of Surgery, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand between 1 April 2004 and 30 September 2004. Prophylactic amoxycillin/clavulanate (Cavumox®) at a dose of 1.2 gram was given intravenously to all patients who underwent emergency or elective intra-abdominal procedures. All patients were scheduled to follow-up visits at 7, 14 and 30 days post operatively for monitoring the occurrence of SSI.*
Results: *Thirty emergency appendectomies (85.7%) and other 5 elective surgical procedures (14.3%) were performed in 35 patients including 14 males and 21 females with a mean age of 37 (range, 18-72) years. No SSI or drug allergy was observed.*
Conclusion: *Parenteral amoxycillin/clavulanate is a safe and effective antibiotic as the monotherapy for prevention of SSI following intra-abdominal surgery.*

Keywords: *Prophylactic antibiotics, Monotherapy, Surgical site infection, Abdominal surgery*

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Surgical site infections (SSI) are infections of tissues, organs or spaces exposed to contaminated environment, surgical equipment, personal or even their own flora while performing the invasive procedures or operations. SSI occurs when endogenous flora are translocated to a sterile site. Up to 2%-5% of patients undergoing clean extra-abdominal operations and up to 20% undergoing intra-abdominal operations could develop SSI[1]. SSI is associated with considerable morbidity and mortality as well as substantial health care costs and patient dissatisfaction[2]. In addition to good surgical technique, the use of prophylactic antibiotics could reduce the incidence of SSI rates during certain types of procedures. The antimicrobial activity should be effective against bacteria that are likely to be encountered during the particular type of operation being performed and should certainly be safe for patients.

For this reason, in May 2004, the National Surgical Infection Prevention Project of the United States had the consensus on antimicrobial prophylaxis for surgery. They concluded that infusion of the first antimicrobial dose should be administered within 60 min before surgical incision. In addition, prophylactic antimicrobials should be discontinued within 24 hrs after the end of surgery[3]. SSI, such as wound infection and intra-abdominal abscess, is one of the common complications following intra-abdominal operation. As it is associated with considerable morbidity and mortality, prevention of SSI is essential. Antibiotics have been used for both prevention and treatment of SSI[3]. The appropriate antibiotics should contain antibacterial activity against intestinal flora and common pathogens. Nowadays, various regimens of

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mono-therapy and combined therapy of antibiotics have been administered as the prophylactic intention for SSI. Concerning mixed aerobic and anaerobic bacterial domination, combined therapy such as ceftriaxone and metronidazole has been commonly used as the first line prophylactic and empirical agents. However, if the number of administration is a concerning issue, due to busy ward work and lack of nurse staff, monotherapy is favorable. One of the most widely used antimicrobial agents as monotherapy regimen for SSI prophylaxis is beta-lactam plus beta-lactamase inhibitor such as amoxycillin/clavulanate. Excellent efficacy and safety of parenteral amoxycillin/clavulanate for SSI prophylaxis were reported in many literatures[4,5]. However, these studies were conducted in western populations whose pharmacokinetics of antibiotics may be different from Thai patients. The aim of the present study was to evaluate the efficacy and safety of parenteral amoxycillin/clavulanate for the prevention of SSI following abdominal surgery.

Material and Method

After obtaining ethical approval from our institute's ethical committee, a prospective opened non-comparative clinical trail was conducted in the Department of Surgery, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand between 1 April 2004 and 30 September 2004. Thirty-five patients were enrolled with the following inclusion criteria: age between 18 and 80 years, ASA class I-III, underwent intra-abdominal operations for elective or emergency surgery. Patients were excluded by one of the following criteria: previous administration of antibiotics within 2 weeks, previous history of hypersensitivity or allergy to penicillin or its derivatives, pregnancy, lactation, renal insufficiency, hepatic impairment and consent refusal.

All patients underwent intra-abdominal operations under balanced general anesthesia. All of the operations were classified as clean-contaminated type. The detail of operative procedures depended on diagnosis and intra-operative finding. Appendectomy for acute appendicitis was the most predominant. Pus or tissue culture would be collected from the surgical site if present and sent for aerobic bacterial identification and sensitivity test. Intravenous amoxycillin/clavulanate (Cavumox®, Siam Pharmaceutical, Thailand), 1.2 grams, was given to all patients by anesthesiologists at the time of anesthetic induction (approximately 30 minutes before the operation). Subsequently, amoxycillin/clavulanate at the dose of 1.2 gram was administered intravenously by nursing staffs every eight hours until 24 hours post-operatively. Additional oral amoxycillin/clavulanate (1 gram twice a day for at least 7 days) would be prescribed if patients developed symptoms and signs of SSI. SSI was diagnosed following the Centers for Disease Control (CDC) criteria 1992[6].

The patients were discharged from the hospital if they had no fever, normal bowel function, good ambulation and no sign of infection. All patients were scheduled for follow-up at 7, 14 and 30 days post-operatively.

Results

This prospective opened non-comparative clinical study was conducted in 14 males (40%) and 21 females (60%) of 18-72 years old (mean age 37.2 $\pm$ 14.3 years). Nine patients (25.7%) had one of the following underlying diseases: diabetes mellitus, hypertension, ischemic heart disease, valvular heart disease, pulmonary tuberculosis or cirrhosis. Thirty emergency appendectomies (85.7%) and 5 elective

Table 1. Early postoperative complications

Adverse grug reaction	n	Totally no symptoms n (%)	Symptoms for 1 day P.O.	Symptoms for 2 days P.O.	Symptoms for 3 days P.O.	Symptoms for 4 days P.O.
Nausea	35	17 (48.5)	15 (42.9)	3 (8.6)	-	-
Vomiting	35	21 (60.0)	14 (40.0)	-	-	-
Diarrhea	35	26 (74.3)	9 (25.7)	-	-	-
Constipation	35	23 (65.6)	9 (25.7)	1 (2.9)	1 (2.9)	1 (2.9)
Anorexia	35	22 (62.8)	12 (34.3)	1 (2.9)	-	-

P.O. = postoperation

surgical procedures (14.3%) such as gastrectomy and laparoscopic cholecystectomy were performed. Mean of length of hospital stay was 3.2 $\pm$ 2.5 days (range, 2-17 days). Early postoperative complications are shown in Table 1. No SSI or drug allergy was detected in any patients during the follow-up period.

Discussion

In the present study, the authors used parenteral amoxycillin/clavulanate as the antimicrobial prophylaxis of choice for SSI because it targets the most likely organisms while avoiding broad-spectrum that may result in development of antimicrobial resistance. The fact is that amoxycillin is benzyl penicillin with bacteriocidal activity against sensitive organisms during the stage of active multiplication by the inhibition of biosynthesis of cell wall mucopeptide. Clavulanate is an irreversible inhibitor of beta-lactamase that was produced in penicillin-resistant organisms. Amoxycillin/clavulanate, therefore, is effective against a wide range of gram-positive and gram-negative bacteria including *Staphylococcus aureus, Staphylococcus epidermidis* (including penicillin-resistant and some methicillin-resistant strains), *Streptococcus pneumonia, Streptococcus faecalis, Hemophilus influenza, Escheichia coli, Klebsiella, Proteus, Enterobacter* and some anaerobic bacteria including *Bacteroides*. These microorganisms are among the most common causes of surgical site infection found following intra-abdominal surgery. Moreover, this antimicrobial bears such a high serum and tissue levels exceeding the minimum inhibitory concentration (MIC) of susceptible organisms. Its half life was also long enough to achieve adequate MIC covering the duration of operation up to 4 hours. Although the combinations of beta-lactam and beta-lactamase inhibitor have often been used as antibiotics of choice for surgical prophylaxis, the awareness for adverse drug reaction should be concerned. The medical history should be seriously taken to determine if patients had any previous allergy (*e.g.*, urticaria, pruritus, angioedema, bronchospasm, hypotension, or arrhythmia) or serious adverse drug reaction (*e.g.*, drug-induced hypersensitivity syndrome, drug fever, or toxic epidermal necrolysis)[7].

In the present study, high incidence of postoperative anorexia, nausea and vomiting was found (34.3, 42.9 and 40.0% respectively) within the first 24 hours. This finding probably could be the consequences following the anesthetic event as well as narcotics administration for postoperative pain control. However, these symptoms stayed shortly and were dramatically improved on the next day. Only symptomatic treatment using antiemetic agents such as intravenous metoclopramide and ondansetron could satisfy most of the patients. Diarrhea and constipation found as high as 25.7% within the first 24 hours could either be the real adverse drug reaction or early post-operative sequences. Diarrhea also disappeared after 24 hours. Only one patient (2.9%) had continuing constipation, probably an adverse drug reaction resulting in antibiotic-induced disturbance of normal gut flora. No drug-induced hypersensitivity syndrome or serious adverse reaction was demonstrated in the present study. At the end of the present study, absence of SSI among all 35 patients may confirm the excellent efficacy of antimicrobial prophylaxis using parenteral amoxycillin/clavulanate (Cavumox®). Comparing the track record from the Siriraj Infectious Control Unit during the same period of time at the same surgical wards which showed 2.5% overall incidence of SSI, the present study seemed to support the magnificent outcome of using beta-lactam/beta-lactamase inhibitor for the prevention of surgical site infection following an intra-abdominal operations. In addition, use of parenteral amoxycillin/clavulanate as a single prophylactic agent provides more convenience for drug administration compared to the commonly used combination of ceftriaxone and metronidazole.

Conclusion

Parenteral amoxycillin/clavulanate(Cavumox®) is a safe and effective antibiotic used as a single agent for the prevention of the surgical site infection following intra-abdominal surgery.

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ประสิทธิผลและความปลอดภัยของยาฉีด อะมอกซิซิลิน/คลาวูลาเนต ในการป้องกันการติดเชื้อของแผลผ่าตัดภายหลังการผ่าตัดช่องท้อง

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วัตถุประสงค์*: เพื่อประเมินประสิทธิผลและความปลอดภัยในการใช้ยาฉีด อะมอกซิซิลิน/คลาวูลาเนต ในการป้องกันการติดเชื้อของแผลผ่าตัดภายหลังการผ่าตัดช่องท้อง*

วัสดุและวิธีการ*: รูปแบบงานวิจัยที่ใช้ คือ การวิจัยชนิดเปิดที่มีการวางแผนล่วงหน้า และปราศจากการเปรียบเทียบ กระทำการศึกษาในผู้ป่วยที่รับไว้ให้การรักษาในภาควิชาศัลยศาสตร์ คณะแพทยศาสตร์ศิริราชพยาบาล ระหว่างวันที่ 1 เมษายน พ.ศ. 2547 ถึง 30 กันยายน พ.ศ. 2547 โดยใช้ยาอะมอกซิซิลิน/คลาวูลาเนต (คาวูม็อก®) ขนาด 1.2 กรัม หยดเข้าหลอดโลหิตดำ ให้แก่ผู้ป่วยที่ได้รับการผ่าตัดช่องท้องทั้งชนิดฉุกเฉินและไม่ฉุกเฉิน โดยผู้ป่วยทุกรายได้รับการติดตามผลการรักษาภายหลังการผ่าตัดนาน 7 วัน 14 วัน และ 30 วัน ตามลำดับเพื่อสังเกต และเฝ้าติดตามอัตราการ ติดเชื้อของแผลผ่าตัดที่เกิดขึ้น*

ผลการศึกษา*: ผู้ป่วยเข้าร่วมการศึกษาทั้งสิ้น 35 ราย โดยเป็นผู้ป่วยที่เข้ารับการผ่าตัดรักษาไส้ติ่งอักเสบเฉียบพลัน จำนวน 30 ราย (85.7%) และผู้ป่วยที่ได้รับการผ่าตัดช่องท้องจากสาเหตุอื่น 5 ราย (14.7%) แบ่งเป็น ชาย 14 ราย และหญิง 21 ราย โดยมีอายุเฉลี่ย 37 ปี (18-72 ปี) ผลการศึกษาปรากฏว่าไม่พบผู้ป่วยรายใดเกิดการติดเชื้อที่ตำแหน่งแผลผ่าตัด รวมถึงไม่พบการแพ้ยาแต่ประการใด*

สรุป*: การให้ยาอะมอกซิซิลิน/คลาวูลาเนตหยดเข้าหลอดโลหิตดำ มีความสะดวก ได้รับประสิทธิผล และความปลอดภัยเพียงพอในการป้องกันการติดเชื้อของแผลผ่าตัดภายหลังการผ่าตัดช่องท้อง*