ระยะเวลาในการให้ยาปฏิชีวนะในการบาดเจ็บของช่องท้องแบบทะลุ

นายเดือง ทรอง เฮียน

THE DURATION OF ANTIBIOTIC ADMINISTRATION IN PENETRATING ABDOMINAL TRAUMA

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Title : The Duration of Antibiotic Administration

In Penetrating Abdominal Trauma

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Field study : Health Development

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Duong Trong Hien : ระยะเวลาในการให้ยาปฏิชีวนะในการบาดเจ็บของช่องท้องแบบทะลุ (The duration of antibiotic administration in penetrating abdominal trauma) อ.ที่ปรึกษา ศ.นพ.จิตร สิทธิอมร, อ.ที่ปรึกษาร่วม : นพ.อภิชาต พลอยสังวาลย์, 77 หน้า ISBN 994-03-0766-3

วัตถุประสงค์ของการศึกษานี้คือ
ทดสอบสมมุติฐานที่ว่า การใช้ยาปฏิชีวนะในเวลา 24 ชั่วโมง เพียงพอที่จะลดอุบัติการของการติดเชื้อในการบาดเจ็บของช่องท้องชนิดแทงทะลุ

รูปแบบงานวิจัย : เป็นการศึกษาไปข้างหน้าชนิดการทดลองทางคลีนิคแบบสุ่ม

สถานที่ศึกษา : โรงพยาบาลเวียดดัคและเซนต์พอลในฮานอย เวียดนาม

ผู้ป่วย : ผู้ป่วย 320 คน ที่ได้รับบาดเจ็บทางช่องท้องชนิดแทงทะลุ โดยมาถึงห้องฉุกเฉินในเวลาน้อยกว่า 12 ชั่วโมง และผู้ป่วยไม่มีภาวะบกพร่องของภูมิคุ้มกันรวมทั้งไม่แพ้ยา cefradin จะทำการสุ่มแยกผู้ป่วยออกเป็น 2 กลุ่ม กลุ่มที่ 1 จะได้รับยา cefradin เป็นเวลา 24 ชั่วโมง กลุ่มที่ 2 จะได้รับยาเป็นเวลา 5 วัน โดยในห้องฉุกเฉิน ผู้ป่วยจะได้รับยา 2 กรัมเป็นขนาดแรกและต่อไปจะให้ทุก 6 ชั่วโมง

การวัดผล : จะวัดผลการติดเชื้อที่เกิดขึ้น โดยยึดตามศูนย์ป้องกันและควบคุมโรค นอกจากนี้จะวัดระยะเวลานอนโรงพยาบาลของผู้ป่วยด้วย

ผลการศึกษา : ผู้ป่วยทั้งสิ้น 320 คน ไม่มีผู้ป่วยเสียชีวิตหลังผ่าตัด ระยะเวลาของการใช้ยาปฏิชีวนะ ไม่มีผลต้องการเกิดการติดเชื้อ ในทั้งสองกลุ่มที่ทำการศึกษา ผลต่างของการติดเชื้อในทั้งสองกลุ่ม อยู่ในช่วงของความเท่ากันที่ได้ตั้งไว้ (ช่วงความเชื่อมั่น 95% คือ –0.06-0.09) การติดเชื้อในช่องท้องก็ไม่แตกต่างกัน เช่นเดียวกัน (ช่วงความเชื่อมั่น 95% คือ –0.03-0.03) ระยะเวลาในการนอนโรงพยาบาลก็ไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ (ค่า P คือ 00.1) ผู้ป่วยจะมีการติดเชื้อมากถ้าได้รับเลือดมากกว่า 750 มิลลิลิตร, มีจำนวนอวัยวะในช่องท้องได้รับอันตรายมากกว่า 1 อวัยวะ และการบาดเจ็บของลำไส้ใหญ่ การได้รับเลือดมากกว่า 750 มิลลิลิตร และการมีการบาดเจ็บของหลอดเลือดเป็นปัจจัยที่ทำให้มีการนอนโรงพยาบาลนานขึ้น

สรุป การใช้ยา cefradin ฉีดเข้าหลอดเลือดใน 24 ชั่วโมง จะให้ผลในการป้องกันการติดเชื้อไม่ต่างจากการให้ยาเป็นเวลา 5 วัน รวมทั้งระยะเวลาในการนอนโรงพยาบาลก็ไม่แตกต่างกัน การติดเชื้อจะเกี่ยวข้องกับการเสียเลือด, จำนวนอวัยวะในช่องท้องที่ได้รับบาดเจ็บ, และการบาดเจ็บของลำไส้ใหญ่ การนอนอยู่โรงพยาบาลนานจะเกี่ยวข้องกับการเสียเลือดและการบาดเจ็บของหลอดเลือด

หลักสูตร ___การพัฒนาสุขภาพ___ ลายมือชื่อนิสิต.......................................

สาขาวิชา ___การพัฒนาสุขภาพ___ ลายมือชื่ออาจารย์ที่ปรึกษา...

ปีการศึกษา ___2544___ ลายมือชื่ออาจารย์ที่ปรึกษาร่วม...............................

Objectives of the study: The purpose of this study was to test the hypothesis that 24 hours of antibiotic therapy remains sufficient to reduce the incidence of surgical site infection in penetrating abdominal trauma

Design: This is a prospective, randomized equivalence clinical trial

Setting: VietDuc and Sainpaul Hospital in Hanoi Vietnam

Patients: Three hundred and twenty consecutive adult patients with penetrating abdominal trauma were recruited for this study. They were diagnosed penetrating abdominal trauma at emergency room with time from accident to hospital less than twelve hours and without immune depression or allergy to cefradin. They were stratified by colon injury and then randomly assigned into two treatment groups

Intervention: The patients received intravenous (IV) cefradin twenty-four hours or five days respectively group I and II. At first, the patient was given 2g dose in the emergency department (ED) immediately after the determination of requirement for laparotomy, followed by q6 h administration for total of four doses or twenty doses. Cefradin is not redosed intraoperatively during prolonged surgery unless indicated by original q6h dosing interval.

Main outcome measurements: The development of surgical site infection as defined by the Centers for Disease Control and Prevention was recorded. Hospital length of stay was a secondary endpoint.

Results: Three hundred and twenty patients were valuable. There was no postoperative mortality. The duration of antibiotic had no influence on the rate of surgical site infection. The difference in surgical site infection rate between two groups was within the range of equivalence set up (95%C.I:-0.06 to 0.09). The equivalent of intra-abdominal infection between treated groups was also confirmed (95%C.I: -0.03 to 0.03). There was no statistically significant difference in overall length of hospitalization between groups (p=0.1). Patients were more likely to develop SSI when blood transfusion were more than 750 ml (OR: 3.5; 95%C.I: 1.45-8.48;p=0.005) or number of intra-abdominal organ injuries more than one (OR: 6.57; 95%C.I: 3.45-12.5;p<0.001) and colon injury (OR: 2.66; 95%C.I: 1.1-6.4;p=0.03). Blood transfusion more than 750 ml (p=0.001), vascular (0.006), Solid organ (p=0.036) and colon injuries (0.006) which were independent contributors to prolongation of hospital stay.

Conclusion: Twenty four hours of intravenous cefradin versus five days of therapy made no difference in the prevention of surgical site infection or length of hospitalization. However, need further study to validate short course treatment on high risk patients such as colon, vascular or several organs injuries. Infection was associated with blood loss, number of intra-abdominal organs injured, and colon injury. Prolonged hospitalization was associated with blood loss, vascular, solid organ and colon injury.

Programme: Health Development   Student's signature…..………………………………….

Field of study: Health Development   Advisor's signature ……………………………………..

Academic year: 2001   Co-advisor's signature ……………………………….

ACKNOWLEDGEMENT

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CHAPTER I

BACKGROUND AND RATIONALE

Trauma is one of the leading causes of death and disability during the most productive years of life. After the acute phase of injury has been treated, infection is the most prevalent cause of morbidity and mortality. The overall incidence of infection in large series of trauma patients is between 15 % and 25 % [1, 2], with infections divided about equally between minor infections (e.g., urinary tract, drain site) and those that cause major morbidity (pleural -pulmonary or intra –abdominal infection). Penetrating abdominal trauma carries a high risk of serious infection because of immune-suppression from hemorrhaged shock and transfusion and the high likelihood of intestinal injury. For example, the incidence of small bowel injury is approximately 29- 45 % in abdominal stab and gunshot wounds, respectively, and that of colon injury is approximately 18- 38 % [3]. Reducing the incidence of sepsis requires expeditious resuscitation and operation after wounding. Rapid control and repair of vascular injuries and appropriate drainage of pancreas, liver, and kidney injuries are of key importance in operative management. The adjunctive measure of antibiotic therapy continues to be the only supportive measure for the immune system to eradicate invasive bacteria. However, the inappropriate administration of antimicrobial agent, the most commonly used in hospital practice,

plagues all medical specialties. There are multiple reasons for "antimicrobial inappropriate" use such as administration in the absence of infection, poor choice of drug (bacteriological, pharmacologically, or both), wrong dosage, excessive duration, and misguided prophylaxis. Excessive duration, however, appear to be the main reason for "inappropriateness" in current surgical practice. The prevailing trend to continuous antibiotic therapy when, in fact, it could have been stopped has been, and still is, observed in most any surgical ward or critical care unit. Particularly, antibiotics have been used empirically for victims of penetrating trauma; their use is not always based on the actual defined risk of infection. Although most principles of antibiotic usage in surgical patients have been fairly well elucidated, appropriate usage in penetrating abdominal trauma in somewhat unclear. Basic principles for prophylaxis require that antibiotics are given before contamination and that administration is limited to no more than 24 hours after the operation. The first of these principles is violated in penetrating trauma. Further, therapeutic agents are continued for several days in the scenario of invasive infection, but invasive infection is not the case with gastrointestinal contamination after penetrating wound. Thus, a major question concerns the optimal duration of antibiotic treatment in patients sustaining penetrating abdominal wound. The role of antimicrobial agent in penetrating abdominal trauma is well established. There are some studies, which have given sound evidence of role prophylaxis antibiotic in patients with penetrating abdominal trauma[4].In none of these has prolonged therapy beyond 24 hours been shown to be more effective than short-course treatment. Excessive, long duration of antibiotic

treatment and prophylaxis in current clinical practice needs to be addressed to reduce cost, to reduce adverse reactions such as direct toxicity or impairment of immune defense mechanism, and in theoretically to reduce induction of resistance or selection of resistant bacteria. Beside those reasons, there is an evidence of pharmacodynamics supporting for shorter duration of antibiotic prophylaxis in current clinical practice. In the laboratory, inoculate sites of 10^5 -10^7 organisms per milliliter are used to assess concentrations. That will inhibit bacterial growth (minimal inhibitory concentration = MIC) or that will kill 99% of the bacteria (minimal bacterial concentrations = MBC). Laboratory data with standardized bacterial inoculate suggest that bacteria need to be exposed to either the MIC or the MBC for only 16-24 hours to inhibit growth or to kill 99.9% of bacteria, respectively. Therapeutically, physician administered antimicrobial that yield tissue compartment concentrations in excess of the MIC or MBC, therefore, may be equally effective and eliminate bacteria within 16- 24 hours, once operative therapy has reduced the bacterial inoculums to testing condition. Pharmacodynamic units, such as the time about MIC, that expresses a certain antibiotic -microbial–time relationship become important. The duration of administration, therefore, must be tailored by clinical judgment to the magnitude of the remaining bacterial inoculums and the condition of the patient. From a pharmacokinetic standpoint, treatment courses can be shortened substantially. If antibiotic effectively eliminates bacteria in the laboratory within 16-24 hours, the same efficacy should be possible in tissue, if the antimicrobial concentration sustained in the tissue exceed the MIC or MBC. Since the magnitude of tissue

concentration is the mostly proportional to the dose given, higher doses of antibiotics are preferred to guarantee sufficient tissue levels about the MIC or MBC. Once bacteria are dead, no further antibiotics are necessary. Sufficient pharmacokinetics models are available for guidance.

In Vietnam setting, antibiotic prophylaxis used in patients with penetrating abdominal trauma is the first generation cephalosporin, which is seen less efficacious on anaerobic enteric pathogens for patients with penetrating abdominal injury and bowel penetration. However, it is still approved by Vietnam FDA for use as antibiotic prophylaxis for patients with penetrating abdominal trauma. The inappropriate use of cefradin for an excessive duration in patient with penetrating abdominal trauma is frequently observed in many hospitals, event when patients have no sign of infection. There are reasons in term of operative characteristics including: patient characteristics, preoperative issues, intra-operative issues and postoperative issues, which make some surgeons still hesitant to administer antibiotic prophylaxis for only 24 hours of therapy. Even when it was shown to be sufficient to reduce the incidence of infection in penetrating abdominal trauma[5].

This study aims to find whether short-term treatment antibiotic prophylaxis is as efficacious as long-term treatment with presumptive antibiotic such as cefradin.

CHAPTER II

REVIEW OF RELATED LITERATURE

The role of antimicrobial agent in penetrating abdominal trauma is well - established in the studies of Stone 1976, Fullen et al 1972 and Kager 1980[6-8]. The current prevailing "antibiotic overkill" in trauma victims, which was demonstrated by Hadjiminas et al[9] and Schein, Wittmann[10]. Uninfected patients received antimicrobial agents for an average of 15 antibiotic days, while infected patients received a means of 57 antibiotic days. Such unnecessarily prolonged administration of antibiotic in patients, in whom no infection can be demonstrated, could be curtailed only if clinicians would comprehend that it has never been shown that longer administration is advantageous.

In early clinical trial, patient with penetrating abdominal trauma was treated in combination with semi-synthetic penicillin and an aminoglycoside, or an amino glycoside and clindamicin for a minimum 48 hours or for as long as seven days[11, 12]. With the advent of broad spectrum, there are some studies showing that the result of single agent can be comparable with combination antibiotics for therapy in penetrating injuries of the abdomen[4, 13, 14]. Crensaw et al[13] studied one hundred patients underwent operating for penetrating and potentially contaminated wounds of the abdomen were given cefamandole or a combination of cephalotthin-Tobramycin by a random, single blind method as preventive therapy. Results were valuable for 49 patients receiving

cefamandole for success rate of 93.9%. The 45 valuable results in the second group had a success rate of 88.9%. Those in single therapy groups also required fewer days of treatment and of hospital confinement, resulting in lower per patient cost. Hofstetter 1984[4, 13, 14] determined the best antibiotic regimen to employ in patients undergoing laparotomy for trauma, a randomized prospective study was designed comparing cefoxitin alone with triple drugs regime of an aminoglycoside, ampicillin, and clindamycin. One hundred nineteen consecutive patients sustaining abdominal trauma (97 penetrating; 22 blunt) were divided by date of admission to a 24 hour course of antibiotic. The overall infection rate was 16% with 14.5% of the cefoxitin treated patients, and 18% of the triple drug treated patients developing an infectious complication. Excluding remote site infection, the abdominal wound and intraperitoneal infection rate were 13% for cefoxitin treated patients, and 12% for triple drug treated patients. Author concluded that a 24 hours course of cefoxitin is a safe and effective prophylaxis regime in patients undergoing laparotomy for trauma. Dellinger[15]1991 review of studies more than 2,600 patients provided convincing evidence that monotherapy provided comparable efficacy to multiple drug treatment as long as anti-anaerobic coverage was sufficient.

The first study to show that multiple dose prophylaxis (for 5 days) results in more postoperative infections 6% than single dosage 3% was published in 1977[16]. The number of patients enrolled in this study, however, was insufficient to prove a statistical significance. Similar results were obtained in numerous subsequent studies comparing single dose versus multiple prophylaxis. In three well conducted, randomized and double

blinded studies comparing single dose prophylaxis (n= 201) with multiple dose prophylaxis (n=193) in colon operation the combined postoperative infection rates were 2.5% for single dose and 6.2% for multiple dose, respectively[17-19]. In a large, prospective randomized trial, a single doses prophylaxis (n=1,312) was compared to three doses (n=1,361), and fewer infection were seen in the single dose group. Although the authors were unable to show a significant difference concerning wound infection rates (p = 0.09) in the multiple dose group, significantly more patients required more operative antibiotics (p = 0.002), prolonged hospital stays (p =0.01)[20].

First generation cephalosporin, active against aerobic and anaerobic enteric gram-negative bacilli, was used as antibiotic prophylaxis in gastric, biliary and colonic surgery[7, 21]. Stone et al[7] had enrolled 400 patients into a prospective, randomized and double blind study. The result demonstrated that the incidence of wound infection could be reduced significantly by preoperative administration of antibiotic in operations on the stomach from 22% to 4%, on biliary tract 11% to 2%, and large bowel from 16% to 6%. Cefradin, a first generation cephalosporin, has subsequently and extensively been studied because of its suitable antibiotic profile and excellence record of safety. Some studies document the efficacy of first generation cephalosporin for presumptive therapy in penetrating abdominal injuries. However, today the trending to presumptive therapy with a single antimicrobial agent such as cefoxitin one second generation cephalosporin has become widespread[6, 22, 23]. Another single agent that has been used successfully is

ampicilline /sulbactam[24] which has antianearobic effect comparable with that of metronidazole.

The optimal timing of antibiotic administration in trauma has been inferred from both animal and clinical studies. Classic experiment studies of Brucke[25] and Miles et al[26] showed that antibiotic must be given within 3 hours of injury if they are to be effective. Further, Fullen et al[8] had studied 650 patients with penetrating wound of abdomen and compared group consisted of patients who received their initial antibiotic therapy in the preoperative period with the groups those receiving initial antibiotic therapy during the intra-operative period and postoperative period. He established that the antibiotic is vital in the management of penetrating abdominal wound and must be given as close as to the time of injury as possible to be effective. Antibiotics are administered "presumptive" as soon as the decision to operate is made, because, the distribution of specific organ injuries in individual case cannot be inferred from clinical examination.

In contrast to well-established indication for therapy, relatively few studies have addressed the optimal duration of treatment. Credit for popularizing the safety and efficacy of short course (24hours) single agent presumptive antibiotic therapy rightly belong to Dellinger et al[27] in study 116 patients with penetrating intestinal injuries. Twenty-one patients 18% developed trauma related infections, twenty-eight 24% any infections, and three 2.6% died. There were no significant differences between groups in any category of outcome. For the patients with penetrating intestinal or colon injury, a 12-

hour course of antibiotics is as effective as a five-day course and has the advantage of lower cost and, theoretically, fewer side effects. However, the sample size was not large enough and lacked to detect the significant difference. The concept for shortening course of antibiotic has recently gained support by forum of expert[28]. Available data indicate the longer course of antibiotic confer no advantage over a 24 hours regime. Timothy and et al[22] enrolled 515 patients with penetrating abdominal trauma use cefoxitine and cefotan to compare 24h and 5 day in 4 groups and give the conclusion: Regardless of contamination and the degree of injury, 24 h antibiotic therapy is satisfactory for all penetrating abdominal trauma. However, the study had not enough power for subgroup analysis so Timothy cannot compare the outcome of long term and short-term therapy. Even more, Timothy evaluated the outcome, which was not standardized in SSI. In recently, Bozorgzadeh[23] recruited 300 patients with penetrating abdominal trauma can give the result of 24 hours of IV cefoxitin versus 5 days of therapy made no difference in the prevention of postoperative infection. However the study had rather week power to give the conclusion about the equivalence between 24 hours of therapy comparable with longer course of treatment in the prevention of the postoperative infection, and it does not reflect the epidemiology of penetrating abdominal trauma in developing countries.

Another major problem related to surgical site infection in Vietnam setting was use the first generation of cephalosporin as one antibiotic prophylaxis in patients with penetrating abdominal trauma. This drug was less broad spectrum than the second generation cephalosporin on anaerobic enteric pathogens for patients with penetrating

abdominal injuries and bowel penetration. However, it is a cheapest antibiotic to use as surgical antibiotic prophylaxis over all district hospitals in developing countries as Vietnam. Previously no study was performed in Vietnam to contribute the role of timing used for antibiotic prophylaxis on patient with penetrating abdominal trauma. So this study was conducted in central hospitals in Vietnam with the aim to find out whether 24 hours antibiotic prophylaxis on the patients with penetrating abdominal trauma is as efficacious as antibiotic prophylaxis for a longer duration.
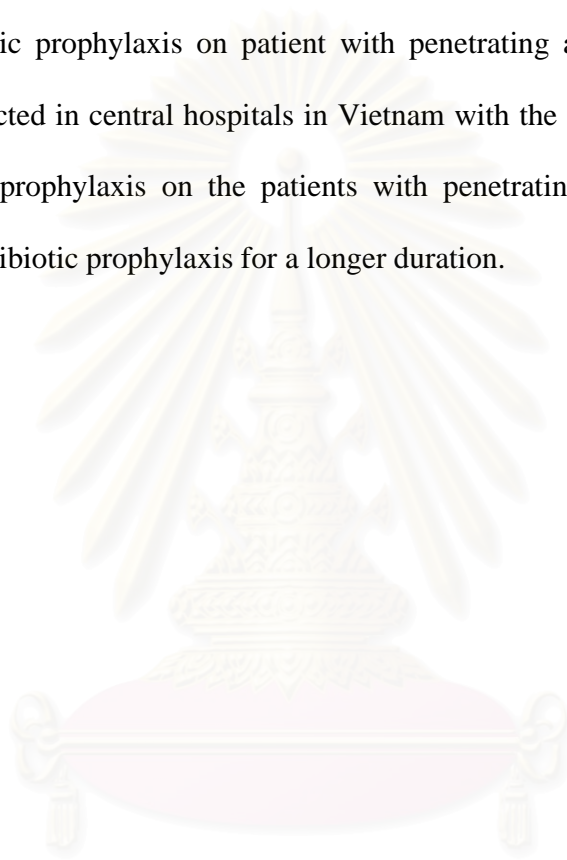
CHAPTER III

RESEARCH QUESTIONS, OBJECTIVES AND CONCEPTUAL FRAMEWORK

3.1 Research question

3.1.1 Primary research question

Does twenty-four hours of presumptive intravenous cefradin prevent SSI as efficacious as a five days treated course in patients with penetrating abdominal trauma?

3.1.2 Secondary research question

❖ Is there any difference in length hospital stay between the two treated groups?

❖ What are the risk factors associated with the surgical site infection?

3.2 Research Objective

3.2.1 General objective

1. The purpose of this study was to test the hypothesis that 24 hours of antibiotic therapy remains sufficient to reduce the incidence of surgical site infection in penetrating abdominal trauma compared to antibiotic prophylaxis for a longer duration.

2. To seek information on certain factors and to find out whether they are associated with the development of surgical site infection

3.2.2 Specific objective

1. To compare the efficacy of short course (cefradin 24 hours) in prophylaxis SSI versus five days

2. To compare the hospital admission duration between two treatment groups

3. To find out if there is any association between several risk factors and SSI on patients with penetrating abdominal trauma.

3.2.3 Hypothesis

1. Twenty-four hours of presumptive intravenous cefradin as antibiotic prophylaxis can prevent surgical site infection equality to five days of therapy in patient with penetrating abdominal trauma.

2. When compared with patients without SSI, patients with SSI are more exposed to a list of factors, which includes the type and extent of injury as: the situation of hemodynamics at emergency department (ED), colon or solid organ injury and number of organ injuries as well.

3.3 Conceptual framework
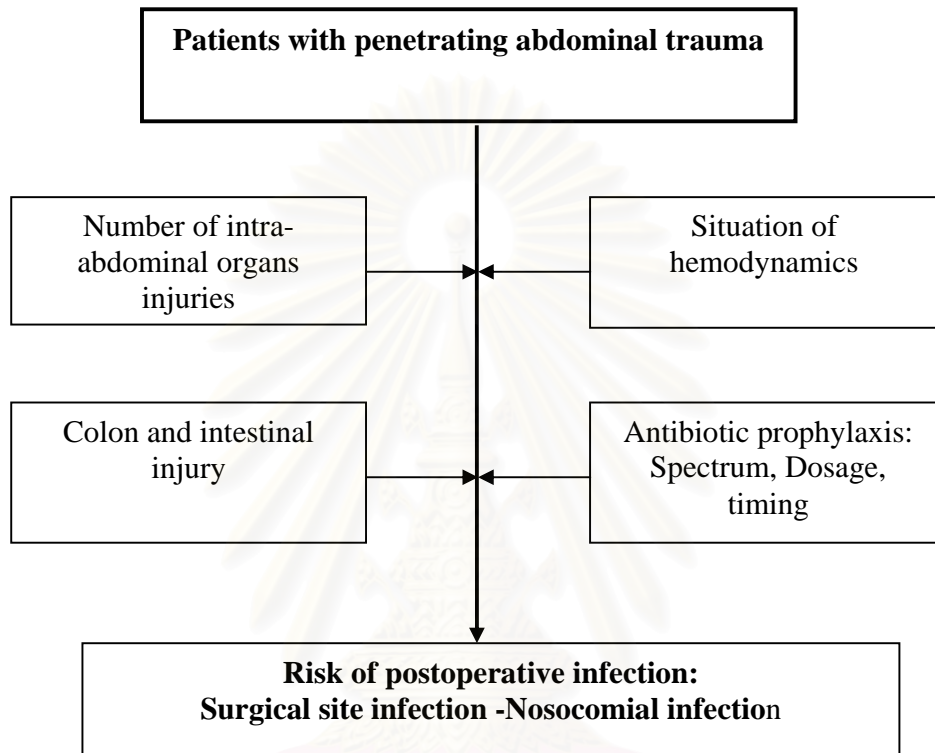
Figure 3.3   Conceptual framework of the study

Antibiotic prophylaxis is used for in patients with penetrating abdominal trauma. There are many factors affecting to surgical site infection (SSI), like type of injury as gunshot which is made more damage than stab wound. The time from accident to surgical treatment this was seen to relate to bacterial growth. Whether the hemodynamics stable or not at ED seem to be the risk factor effect immune system. The number of organ injury and type of injury as hollow viscus, solid organ injuries can affect the rate of infection

through depressed immune system and inoculated microorganism etc. The objective of antibiotic prophylaxis is to reduce the rate of surgical site infection. Clinical and laboratory experience has shown that prophylactic antibiotics may be effective in patient with penetrating abdominal trauma when the period of contamination is brief, defined and predictable. Prevention of infections has been achieved in the treatment of penetrating abdominal wounds and early wounds that can be adequately debrided and closed. The optimal selection of antibiotic and dosage were addressed in many well-documented papers. The knowledge from pharmacodynamic units, such as the time about MIC or MBC, that express a certain antibiotic-microbial–time relationship become important contribute to decision antibiotic timing. From a pharmacokinetic standpoint, treatment courses can be shortened substantially. If antibiotic effectively eliminates bacteria in the laboratory within 16-24 hours, the same efficacy should be possible in tissue, if the antimicrobial concentration sustained in the tissue exceed the MIC or MBC. Since the magnitude of tissue concentration is the mostly proportional to the dose given, higher doses of antibiotics are preferred to guarantee sufficient tissue levels about the MIC or MBC. Once bacteria are dead, no further antibiotics are necessary. Sufficient pharmacokinetic models are available for guidance. In clinical practice, the duration administration of antibiotic prophylaxis was important factor because continuing contamination is the primary reason for ineffectiveness in these situations; however prolonged use of prophylactic antibiotics only serves to make the ensuing infections antibiotic-resistant. The duration of administration, therefore, must be tailored by clinical

judgment to the magnitude of the remaining bacterial inoculums and the condition of the patient.

3.4 Operational Definition

3.4.1 Infection:

Pathogenic microorganism in normally sterile tissue with a local inflammatory host response

3.4.2 Shock:

the systolic blood pressure $\leq$ 80 mmHg

3.4.3 Criteria for defining a surgical site infection (SSI) [29]

1. Superficial incision SSI

Infection occurs within 30 days after the operation and infection involves only skin or subcutaneous tissue of the incision

And at least one of the followings:

❖ Purulent drainage, with or without laboratory confirmation from the superficial incision.

❖ Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.

❖ At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision which are deliberately opened by surgeon, unless incision is culture-negative.

Diagnosis of superficial incision SSI should be by a surgeon or an attending physician.

Do not report the following conditions as SSI:

- ❖ Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration).

- ❖ Incision SSI that extends into the fascia and muscle layers (see deep incision SSI).

2. Deep incision SSI

Infection occurs within 30 days after the operation if no implant is left in place or within one year if implant is in place. The infection appears to be related to the operation, infection involves deep soft tissues (e.g., fascia and muscle layers) of the incision and at least one of the followings:

- ❖ Purulent drainage from the deep incision but not from the organ/space component of the surgical site.

- ❖ A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38C), localized pain, or tenderness, unless site is culture-negative.

- ❖ An abscess or other evidences of infection involving the deep incision is found on direct examination, during re-operation, or by histopathology or radiological examination.

Diagnosis of a deep incision SSI should be by a surgeon or an attending physician.

Notes:

❖ Report infection that involves both superficial and deep incision sites as deep incision SSI.

❖ Report an organ/space SSI that drains through the incision as a deep incision SSI.

3. Organ/Space SSI

Infection occurs within 30 days after the operation if no implant is left in place or within one year if implant is in place. Infection appears to be related to the operation and infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation

And at least one of the following:

❖ Purulent drainage from a drain that is placed through a stab wound into the organ/space.

❖ Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.

❖ An abscess or other evidence of infection involving the organ/space That is found on direct examination, during re-operation, or by histopathology or radiological examination.

❖ Diagnosis of an organ/space SSI should be by a surgeon or an attending physician.

National Nosocomial Infection Surveillance definition: a nonhuman-derived implantable foreign body (e.g., prosthetic heart valve, nonhuman vascular graft, mechanical heart, or hip prosthesis) that is permanently placed in a patient during surgery.

If the area around a stab wound becomes infected, it is not a SSI. It is considered a skin or soft tissue infection, depending on its depth.

3.4.4 Hospital discharge

Patient discharges from hospital when the surgical wound is healed and no sign of infection.

3.5 Study drugs

Cefradin is the first generation cephalosporin; it was provided by Vietnam pharmacy and was produced by Kunwha Pharmaceutical Korea

3.6 Multi– site study

Multi-site and multi-center studies are those studies undertaken by more than one institution with the same procedure on the same protocol. The difference between the multi-site and multi-center study is the role of investigators in each site and the scientific accountability and responsibility. In multi-site studies the investigators at the site do not participate as co-investigator of the study, they are merely carrying out the study (e.g.. recruiting subjects, treating subjects and or following subjects). Meanwhile, multi-centers study, the investigators at the sites are involved as co-investigators in the planning of the study protocol and procedures, are scientifically responsible for the study results, and

participate in manuscripts and other dissemination activities. In this study, we use multi-site study.

CHAPTER IV

RESEARCH METHODOLOGY

4.1 Research design:

This is a multi-site, stratified, randomized and equivalence clinical trial

4.1.1 Research design model
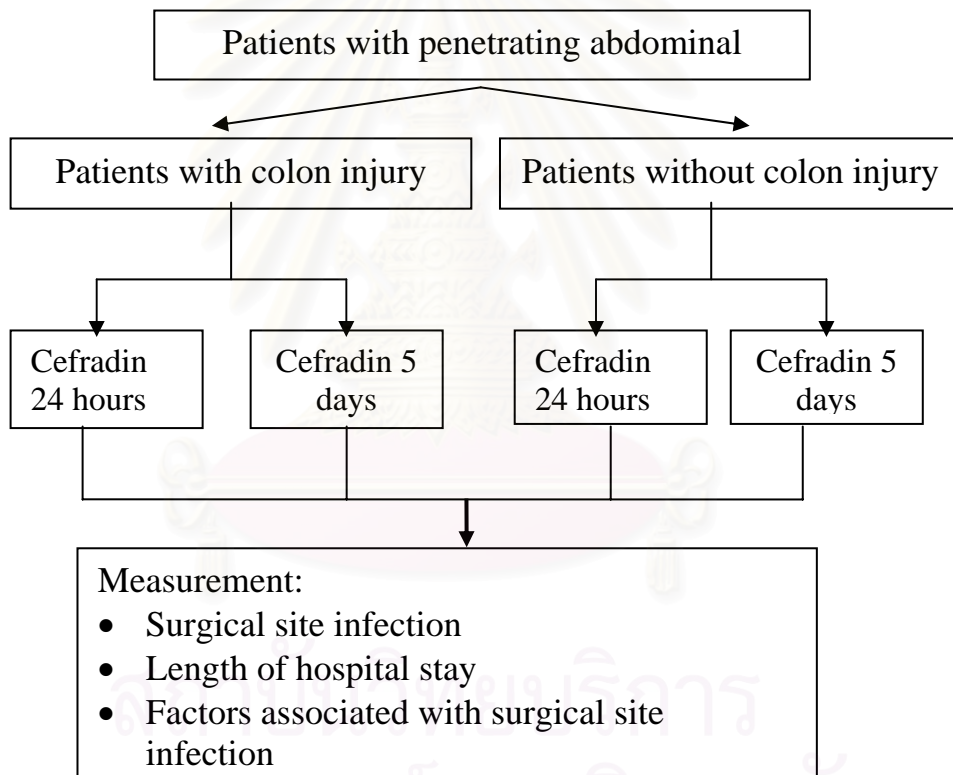
Figure 4.1   Research design model

4.1.2. Management of multi-site Study

This study was conducted as multi-sites in two hospitals in Hanoi, Vietnam. Both of them are state-owned hospitals. For enhance the quality of our research desire:

❖ **Reliability:** At first, we arranged a meeting of investigators from all centers at the planning stage to obtain agreement prior to starting the study. Secondly, for quality control in measurement and clinical observation, we made explicit the detail of outcome measurement and did intra-observer and inter observer reliability test following standard criteria of CDC before the trial began.

❖ **Validity:** At the step of data recording, we were able checking collective data regularly between study protocol and patient. If co-investigator could not verify outcome, he needed to discus with attending physician or surgeon to get agreement and in processing of data as well. Since this study was medium sample sized study, so I as principal investigator took a main responsibility in data managing to receive data and provide feedback to participating centers. At the end, frequent phone calls and contacts were made to encourage all participants who play enthusiastic and responsible role to keep in touch with proceedings of the study.

4.2 The sample

4.2.1 Target population:

All adult patients with penetrating abdominal trauma

4.2.2. Sampled population:

Patients who participated in this study and met the following eligible criteria was diagnosed penetrating abdominal trauma in two centers.

4.2.3 Eligible criteria

4.2.3.1 Inclusion criteria:

1. All the patients with penetrating abdominal trauma

2. Adults and children with age more than 13 years old. The patients with ages less than 13 years old were admitted in pediatric hospital.

4.2.3.2 Exclusion criteria:

1. The patients with time from accident to hospital more than 12 hours.

2. The patients with AIDS (HIV- positive) because this disease may affect the infection rate.

1. The patient with immune depression and allergy to cefradin

4.2.4 Sample size

Since the primary outcome is the proportion of SSI, the sample size formula for comparing two proportion of two independents groups were used

P: to be the overall percentage of infections to be expected if the treatment are equivalent

Δ: The range of equivalence for the difference in percentage

$$ n/ \text{Group} = \frac{2p(1-p)}{\Delta^2} \left\{ Z_{(1-\alpha)} + Z_{(1-\beta/2)} \right\}^2 $$

n is the sample size of each group.

P = 0.165   Δ = 0.15 (select this range follow the guideline of FDA and

CPMP) [30]

α = 0.05   β = 0.1

$$n/\text{Group} = \frac{2 \times 0.165(1 - 0.165)}{0.0225} \{1.96 + 1.645\}^2 = 158.7 \approx 160$$

4.3 Experimental maneuver

4.3.1. Stratified randomization

The patients recruited into study will be stratified into two strata aiming to balance the important characteristics without sacrificing the advantages of random allocation:

1. The patients would be stratified into two strata: patients with colon injury and non-colon injury.

2. After completing randomization list, in each stratum the patient will be randomized in block of 4. The code was kept in sealed envelopes and distributed as estimated sample size to each center. Each center received two set of envelope, the first was the set of patients with colon injury and the second was set without colon injury. (Group I: 2 cefradin within 24 hours and Group2: 2 cefradin within 5 days).

3. When eligible patients registered to the trial, the investigator picked up the envelope from each set has specified colon injury.

4.3.2 Blinding method

To avoid bias in comparison of the groups, the blinding method is desirable. In this study we used observer-blinded design, an independent evaluator who is blind to the study protocol assessed the primary outcome variable.

4.3.3. Intervention

This study was conducted in two hospitals in Hanoi. The Institutional Review Board of each hospital approved the protocol.

The procedures in this study were:

❖ One or two well -trained residents in each center conducted the study

❖ The investigator assessed the patients who fulfilled the eligible criteria.

❖ Patients or family authorized signed informed consent after proper counseling

and describing the detail of the study including side effects of the drug by one of the investigators or specified assistants.

After that, patients were stratified into 2 strata; relied on injury of colon finding in operating theatre and randomized to parallel study groups.

❖ Group I: received 24 hours of intravenous (IV) cefradin with the first 1 gram dose given in the emergency department (ED) immediately after the determination of requirement for laparotomy, followed by q6 h administration for total of four doses.

❖ Group II: patient received five days of IV cefradin, with the first 1 gram dose given in the ED immediately after the determination of requirement for laparotomy follow by q6h administration for a total of 20 doses.

Cefradin is not repeated intra-operatively during prolonged surgery unless indicated by original q6h dosing interval. The Nurse at GI department will inject drug

following the investigator prescription. Examination was performed every morning by investigators to find out the sign of SSI and do bacteria culture.

The patients who have SSI at any time could recognize as treatment failure and the investigators could adjust the treatment.

4.4 Measurement

Independent variable = Intervention given, time from injury to surgical treatment, hemodynamics, blood transfusion, number organs injuries, associated injury, P.A.T.I

Dependent variable = percentage of SSI, length hospital stay

4.4.1 Instrument and evaluators

Investigator measure the surgical site infection following the Guideline for prevention of surgical site infection 1999:

❖ Doctor, during re-operation, or abdominal X-ray and ultrasound could find the SSI on direct examination.

❖ The bacteria cultures are routinely cultured at 37° C on Luria-Bertani (LB) agar.

4.4.2 Outcome measured

1. <u>Main outcome</u> :

The primary outcome is Surgical Site Infection (SSI) include :

Superficial incision SSI: diagnosed by the surgeon

Deep incision SSI or Organ/ space SSI: found on direct examination by doctor, during re-operation, or abdominal X-ray and ultrasound.

2. <u>Secondary outcome</u> :

The hospital duration was counted from hospital admission to

the day patient back home following the hospital note.

4.5. Data collection

As this is a multi-site study, all forms were prepared and collected at the trial-coordinating center (Vietduc hospital). A principal investigator also acted as a data manager whose responsibilities were:

1. Distributed every form to each investigator before the trial started

2. Received all trial data in good shape ready for statistical analysis. We had a folder for each patient's record, being ordered by trial number.

3. Carried out a series of checks: General checks , missing data checks, range check and logical checks

4. Any problem identified during these checking processes was conveyed back to the study site so that corrections were made.

5. Actively seeking forms from the study site when they were overdue

4.6. Data analysis

4.6.1 Summarization of data

1. Compare the different surgical site infection rate between two treated groups by consideration confident interval and the range of equivalence were set up.

2. The difference hospital stays between treated groups were compared by two-tailed unpaired t-test. We found the role of certain risk factors on hospital stay by univariate analysis and multiple linear regressions.

3. The incidence of coordinate variable is compared using chi-square

analysis. This result was expressed all through the study at a level of α=0.05 (p<0,05) as significantly. A continuity correction (Yates correction) was done for chi square value, in some instances Fisher's exact test was done, if the expected value in any cell was less than five. All values had a two tailed probability.

4. This study also considered the independent variables found to be of potential significant effect on defined outcome assessed by univariate analysis. After full exploration using the simple statistical techniques, multiple logistic regression analysis was utilized. This was the appropriate test since the research involved exploration of SSI and the joint effects of number of variable.

Table 4.1   Statistical analysis for demographic data

Variables	Type of data	Data summary
Baseline and demographic data		
• Age	Continuous	Mean, SD, Range
• Sex	Categorical	Frequency , percentage
• Time from injury to surgical treatment	Continuous	Mean, SD, Range
• Type of injury	Categorical	Frequency , percentage
• The situation of Shock in emergency department	Categorical	Frequency , percentage
• Transfusion require	Continuous	Mean, SD, Range
• Number of organs injuries	Categorical	Mean, SD, Range
• Associated injuries	Categorical	Frequency , percentage
• Abdominal index score	Continuous	Mean, SD, Range

Table 4.2   Statistical analysis for outcome variable

Variable	Type of data	Data summary	Statistical test
Primary outcome -Percentage of superficial SSI	Categorical	Frequency, percentage	Chi -square test Chi- square test
-Percentage of deep SSI	Categorical	Frequency, percentage	Chi -square test
-Percentage of organ/space SSI	Categorical	Frequency, percentage	
Secondary outcome -Hospital length of stay	Continuous	Mean, SD, Range	Unpaired t-test Multiple linear regression
-Affecting development of SSI		Adjusting for confounding factors: Shock, blood transfusion, colon, solid organ, chest injury and number organs injuries	Bivariate analysis Multiple Logistic regression

4.6.2 Data presentation

The table, graph and bar chart would be presented as appropriate

4.7. Ethical consideration

1. Cefradin is the conventional antibiotic used. It is the first generation cephalosporin that has been approved by the Vietnam Drugs Council for treatment of intraperitoneal infection before this study.

2. The dose 4 grams/ 24 hours of cefradin is conventional dose in surgical antibiotic prophylaxis.

3. The patients are completely free to refuse to participate or drop out at any time. The patient will be asked to sign an informed consent before recruitment into study.

4.8. Limitation

Because cefradin was produced abroad so it is difficult to get placebo production, thus the study cannot be blind. Nevertheless, it will be unethical when patients used placebo by intravenous injection. To minimize bias it might cause, clear criteria for judging the outcomes were given. An independent evaluator who was blind to the study protocol assessed the primary outcome variable.

4.9. Benefit of the study

If a twenty four hour antibiotic prophylaxis regimen which is proven equally effective. It may have to a shorter duration of antibiotic prophylaxis in current clinical practice, a reduction in cost and adverse reactions such as direct toxicity or impairment of immune defense mechanism and in theory, a reduction in the induction of resistance or selection of resistant bacteria.

4.10. Obstacles

1. Patient's compliance: Patients in this study were all hospitalized, so were easy to be observed. Nurses following physician indication gave patients injections. The research nurse will collect the empty bottle every day; therefore could control the schedule dose of patient.

2. Missing and erroneous data: this might bias the conclusion. The residents on the ward were trained the method of patient's management for the study and also had clear understanding of operational definition of record data. The chief investigator checked the completeness and appropriateness of the data.

3. Some particular cases who died within twenty four hours of admission to hospital were excluded from the study.

4.11. Administration and Time schedule

This study took 15 months for data collection, one month for data analysis, one month for writing the thesis and another month for correction and preparation for final defense.

Preparation ………………………… …………..March –April 2000

Staff meeting ………………………… …………..April 2000

Data collection…………………………… …….April 2000 – December 2001

Analysis ………………………………… ...December 2001

Thesis writing …………………………………… January 2002

Presentation …………………………………… February 2002

CHAPTER V

RESULTS

5.1. Demographic characteristic of patients

This study was conducted in two hospitals in Hanoi from March 2000 to December 2001. Three hundred and twenty patients were enrolled in this study, 161 patients randomized into group I and 159 patients in group II. No patient withdrew from the study. The patient population included 302 males (94.4%) and 18 females (5.6%) with the mean of age of 28 ± 9.6 years (range 14 to 67 years). There was no age and gender difference between treated groups (Table 5.1). There were 292 stab wounds (91.3 %), 15 gunshot wounds (4.7%) and there were 13 patients (4.1%) with other causes. The injury mechanism was the same between treated groups (p=0.24) and stab wound was more frequently (table 5.1). 47 patients (14.7%) presented to the ED with shock. Of these, 25 patients (15.5%) were randomized to groups I, 22 patients (13.8%) was randomized to groups II. There was no difference in the incidence of shock in the ED (p= 0.67)(table 5.2). There was no difference of time from injury to surgical treatment between two treated groups (p=0.47) and over all mean of time was 2.5±2.5 hours. All patients underwent laparotomy; 276 were positive (86.2%) and 44 were negative (13.8 %) for the presence of injury. 146 patients in group I (90.7%) and 130 in group II (81.8%) had positive findings at exploration (p=0.02). There was no difference in the incidence of

gastrointestinal and hollow viscus injury proximal to the ileocecal value between both treated arms (Table4.5). 30 (9.4%) sustained an injury to the colon or rectum, and 26 (8.1%) had injuries proximal to the ileo-cecal valve and 60 (18.8%) patients with injuries of gastric and distance ileocecal valve. In all, 30 patients (9.4%) had colon injuries, 15 patients (9.3%) in the group I, 15 patients (13%) of the group II (p= 0.97). So overall hollow viscus injuries were 103 (32.2%), which distributed balance between twenty four hour course 59 (36.6%) and 44 (27.7%) with (p=0.09). 193 patient (60.3%) sustained one or more solid organ injuries with no difference in over all incidences between groups (p=0.11) (table 5.3). The most common solid organ injured was liver. The incidence of abdominal vascular injuries was equal between two groups (table 5.3). The means estimated blood transfusion require were lower in group I (172 ml versus 205 ml) but no significant difference exist between groups (p = 0.5). Qualifying the injury severity by the abdominal penetrating trauma index which was also balance between two treated groups (p=0.29)

Table 5.1   Distributions of demographic data between groups

Variable	Group I	Group II	Total	P- value
Patients: **n**	161	159	320	
Vietduc hospital: n (%)	129 (80.1)	129 (81.1)	258	0.82[a]
Sainpaul hospital: n (%)	32 (19.9)	30 (18.9)	62	
Age : mean (SD)	27.8 (9.4)	28.2 (9.7)	28 (9.6)	0.76[b]
Gender : n (%)				
Male	155 (96.3)	147 (92.5)	302(94.4)	0.15 [a]
Female	6 (3.7)	12 (7.5)	18(5.6)	
Type of injury: n (%)				0.24 [a]
Gun-shot wound or fire	6 (3.7)	9 (5.7)	15 (4.7)	
Stab wound	151 (93.5)	141 (88.7)	292 (91.3)	
Another cause	4 (2.5)	9 (5.7)	12 (4.1)	
Time from injury to surgical (hour): Mean (SD)	2.7 (2.4)	2.5 (2.7)	2.5 (2.5)	0.47 [b]
Hospital length of stay in day: Mean (SD)	9.1 (3.1)	10.1 (7.2)	9.6 (0.3)	0.1 [b]
Abdominal index score: Mean (SD)	8.9 (6.1)	8.1 (6.2)	8.5 (6.2)	0.29 [b]

a : Pearson chi square test.

b : Unpaired t -test

Table 5.2   Distributions of shock and blood transfusion required between groups

Variables	Group I	Group II	Total	P-value
Transfusion require(ml): Mean (SD)	172 (378)	205 (504)	189 (444)	0.5 [b]
The situation of Shock : n (%)	25 (15.5)	22(13.8)	47 (14.7)	0.67 [a]

a : Pearson chi square test.

b : Unpaired t -test

Table 5.3   Anatomic distribution of injuries between groups

Injuries	Group I n (%)	Group II n (%)	Total n (%)	P-value
Chest	49 (30.1)	51(32.1)	100 (31.3)	0.75 [a]
Vascular	5 (3.1)	5 (3.1)	10 (3.1)	0.98 [a]
Gastrointestinal	36 (22.4)	24 (15.1)	60(18.8)	0.09 [a]
Proximal to ileocecal value (1)	15 (9.3)	11 (6.9)	26 (8.1)	0.43 [a]
Colon / rectal(2)	15 (9.3)	15 (9.4)	30 (9.4)	0.97 [a]
Combined (1) and(2)	2 (1.2)	5 (3.1)	7 (2.2)	0.46 [a]
Solid organ	97 (60.2)	96 (60.4)	193 (60.3)	0.98 [a]
Liver	64 (39.8)	60 (37.7)	124 (38.8)	0.71 [a]
Spleen	11 (6.8)	12 (7.5)	23 (7.2)	0.80 [a]
Pancreas	3 (1.9)	3 (1.9)	6 (1.9)	0.98 [a]
Kidney	5 (3.1)	4 (2.5)	9 (2.8)	0.75 [a]
Multiple solid organ	8 (5)	5 (3.1)	13 (4.1)	0.4 [a]

a : Pearson chi square test.

Table 5.4   Numbers of abdominal organs injured

Number of organ injury	Group I n (%)	Group II n (%)
None	15 (9.3)	29 (18.2)
One organ	94 (58.4)	82 (51.6)
Two organ	37 (23)	37 (23.3)
Three organs	9 (5.6)	8 (5.0)
Four organs	6 (3.7)	3 (1.9)

5.2 Primary outcome analysis

The distribution of various types of infection is shown in (table 5.5). 63 patients (19.7%) developed infection, these included 35 patients (10.9%) developed superficial incision infection, 21 patients (6.6%) had deep incision infection and 7 patients (2.2%) developed an intra-abdominal infection.

A frequent reservation about short-term antibiotic therapy is though it might be appropriate for mild degree of injury; the more seriously injured patients should receive longer antibiotic administration. This question was answered partially by compared the 95% confident interval of difference proportion SSI between two treated groups with an equivalence range which was primary measurement setup. The range of equivalent was set at ± 15% that is $\Delta = 15\%$. The results of trial were as follows:

The proportion of general SSI in group I was: 33(20.5%)

Group II was 30 (18.9%). The difference between proportions of two groups was d = 0.016; Estimate standard error of proportion different SE (d) = 0.04 so the 95% confidence interval for true difference ranges from:

Lower limit = 0.016 – 1.96×0.04   = - 0.06

Upper limit = 0.016+ 1.96×0.04   = 0.09

So this 95% confident interval was from – 0.06 to 0.09, which included 0 and lies entirely within the range of equivalence of –0.15 to 0.15, thus equivalence is confirmed.

Similarly, we also assessed the proportion difference of intra-abdominal infection between two treated groups. The different proportion between two treated groups was 0.003 and 95% C.I. from -0.028 to 0.034. This range was also lies entirely within the range of equivalence from -0.15 to 0.15, thus the equivalence of intra abdominal infection between two treated groups was confirmed.

Some consideration for more seriously injured patients such as colon, vascular or more than one organ injuries could affect the association of treated course on SSI. We use stratified analysis to estimate the association between treated course and surgical site infection adjusted with risk factors such as colon, vascular or more than one organ injuries. No significant difference SSI between two treated groups in each layer, however, the sample size in subgroups was insufficient to conclusion the equivalent. So, it is still room for doubt in seriously injured patients should receive longer antibiotic administration.

Table 5.5   Distribution of infection between groups

Variable	Group I n (%)	Group II n (%)	Total n (%)	P-Value
Any infection episode	33 (20.5)	30 (18.9)	63 (19.7)	0.71 [a]
Superficial incision SSI	21 (13)	14 (8.8)	35 (10.9)	0.23 [a]
Deep incision SSI	9 (5.6)	12 (7.5)	21 (6.6)	0.48 [a]
Organ/space	3 (1.9)	4 (2.5)	7 (2.2)	0.69 [a]

a : Pearson chi square test.

5.3 Secondary outcome analysis

One of clinical interesting is the length of hospital stay, physician need to know whether it is difference between treated groups. The average hospital stay in group I and II were 9.1 ± 3.1 days and 10.1 ± 7.1 days respectively as shown in (table 5.1). Although the hospital stay is longer in group II than group I around one day, but the length of hospital stay was not statistical significance with (p = 0.14).

5.3.1 Univariate analysis factors affect the length of hospital stay:

We also considered the effect of the type and extent of injury to overalllength of hospitalization by univariate analysis as a first step to validate factor entered into model of multiple regression. Blood transfusion more than 750 ml was seen

as a prognostic factor, in this study which made the hospital stay 5.1±1.8 days longer. Similar, patients with vascular injury were prolonged the hospital stay 7 ± 4.7 days compared with patients without vascular injury. Both factors prolonged hospital duration with statistical significance (p=0.009) and (p<0.001) respectively (table 5.6). The length of hospitalization was also depended on group of patients had specific intra abdominal organ injury. To compare patients with colon or solid organ injury and those patients had not. The patients with colon injured had hospital duration 2.2 ± 1 days longer with (p= 0.036). And the hospital stays was also 1.6 ± 0.6 days longer for patients with solid organ injured with (p=0.009). Number of intra abdominal organ injuries also associated with longer hospital stay. The patients with more than one organ injury prolonged hospital duration 2.2 ± 0.65 days longer (p=0.001). Patients had associated injury as chest injury had prolonged hospital stay 1.4 ± 0.7 days.

The presence of any surgical site infection increased the means ± SD length of hospital stay from 8.5 ± 3.1 days to 14 ± 9.5 days (p < 0.001).

5.3.2 Multiple linear regression results

Multiple regression analysis is one of the most widely tool used for finding the independent variable , that best predict the value of the dependent variable. In this study dependent variable was length hospital stay. All methods available; enter, stepwise, forward, backward was tried. Stepwise method was found to be having maximum fitted model. Variables had statistical significance with p-value <0.05 at the first step by univariate analysis should be entered into model. The obtained regression coefficient indicates the change in the mean response per unit increase in the independent variable when other held constant. The predicted probability was significant at p

$<0.05^{(31)}$. At first six variables were entered to regress against the dependent variable the length of hospital stay. Subsequently, there were four variables, which affected the length of hospital stay with statistical significant. The patients with blood transfusion required more than 750 ml who had B standardized coefficient largest (B=0.21). It determined that the mean hospital stay had best relative with blood transfusion. The length of hospital stay increased 3.85±1.1 days with blood transfusion more than 750 ml, when other factors were constant (p=<0.001). Similarly, Patient with vascular injury in regression function indicates that the mean hospital duration increases by 5.48±1.75 days (p=0.002). Patients with colon injury had to prolongation the mean of hospital stay 3.14±1 days (p=0.002). A patient with solid organ injury seems less affecting the length of hospital stay. The hospital duration had to increase 1.65±0.61 days when patient suffered solid organ injury (p=0.007). In the model overall factors had value of t more than 2 which indicates as useful predictor. The significant p-value < 0.001 in table5.8 indicates the independent variables do a good explaining the variation in length of hospital stay. However, the R square =0.14 was rather weak, which indicate the lack of relationship.

Table 5.6   Univariate analysis factors affect hospital stay

Dependent variable: Mean of hospital stay

Variables	Mean± SD (n)	Means difference ± SD	95% C.I of the difference		p-value
			Lower	Upper	
1.Treatment **Group I** **Group II**	9.1±3.1 (161) 10.1±7.1 (159)	1±0.6	-0.2	2.2	0.1[b]
2.Shock **Sign of shock** **No shock**	10.8±5.7 (47) 9.4±5.4 (273)	1.4±0.9	-0.28	3.1	0.1 [b]
3.Blood transfusion **≥ 750 ml** **< 750 ml**	14.2±9.9(30) 9.1±4.6 (144)	5.1±1.8	1.4	8.9	0.009 [b]
4.Colon/rectal injury **Yes** **No**	11.6±5.2 (30) 9.4±5.5 (290)	2.2±1	0.1	4.3	0.036 [b]
5.Solid organs injury **Yes** **No**	10.3±6.2(193) 8.6±4.1 (127)	1.6±0.6	0.4	2.9	0.009 [b]
6.Vascular injury **Yes** **No**	16.4±14.9(10) 9.4±4.8(310)	7±4.7	3.6	17.6	<0.001 [b]
7.Chest injury **Yes** **No**	10.6±6.6(100) 9.2±4.9(220)	1.4±0.7	0.12	2.7	0.032 [b]
8.Number of organ injury >1 **Yes** **No**	11.1±6(99) 8.9±5.1(221)	2.2± 0.65	0.9	3.5	0.001 [b]
9.Abdominal index **≥ 25 PATI** **< 25 PAIT**	10.3±2(8) 9.6±5.6 (312)	0.7± 2	-3.2	4.5	0.73 [b]

b : Unpaired t -test

Table 5.7   **Result of multiple linear regression analysis**

Dependent variable: Mean of hospital stay

Variables	Unstandardized coefficients		Standardized coefficients	t	P-value	95% C.I for B	
	B	**SE**	**Beta**			**Lower bound**	**Upper bound**
Constant	7.78	0.49		15.9	<0.001	6.82	8.74
Blood transfusion ≥ 750 ml	3.85	1.1	0.21	3.64	<0.001	1.77	5.94
Vascular injury	5.48	1.75	0.17	3.13	0.002	2.0	8.92
Colon rectal injury	3.14	1.0	0.17	3.12	0.002	1.16	5.12
Solid organs injury	1.65	0.61	0.15	2.7	0.007	0.45	2.84

R = 0.37, R square = 0.14, Adjusted R square =0.13

Table 5.8   Result of multiple linear regression ANOVA

Dependent variable: Mean of hospital stay

Model		Sum of squares	Df	Mean of squares	F	P-value
1	Regression	719.95	1	719.95	25.7	<0.001[a]
	Residual	8908.64	318	28.01		
	Total	9628.59	319			
2	Regression	920.88	2	460.44	16.8	<0.001[b]
	Residual	8707.71	317	27.47		
	Total	9628.60	319			
3	Regression	1113.28	3	371.1	13.8	<0.001[c]
	Residual	8515.32	316	26.94		
	Total	9628.60	319			
4	Regression	1306.93	4	326.73	12.37	<0.001[d]
	Residual	8321.66	315	26.42		
	Total	9628.60	319			

a. **Predictors: (constant), Blood transfusion ≥ 750 ml**

b. **Predictors: (constant), Blood transfusion ≥ 750 ml, Vascular injury**

c. **Predictors: (constant), Blood transfusion ≥ 750 ml, Vascular injury, Colon- rectal injury**

d. **Predictors: (constant), Blood transfusion ≥ 750 ml, Vascular injury, Colon- rectal injury, Solid organs injury**

5.4 The tertiary outcome analysis

One of the important issues of this study was to find out the role of the type and extent of injury to the surgical site infection. Generally, there was no postoperative mortality. At first, we used bivariate (Crude) analysis to estimate the role of all factors that could affect the SSI rate by ignoring the effect of other factors. It serves as a good tool for screening potential risk factor to be candidate and entered into the initial model.

5.4.1 Hemodynamics factor:

The distribution of shock variable was shown in table (4.3). 47 patients admitted hospital with sign of shock (BP max lower than 80mm Hg) at ED and 18 developed SSI (38.3%). Among 273 patients had hemodynamics stable, 16.5% had SSI. Patient with sign of shock at ED were 3.1 times likely to develop SSI than those had not (95% C.I: 1.6–6.1) and there is a statistical significance association between patients who had shock at ED and SSI (p<0.001).

Blood transfusion required more than 750 ml seem to be very severe. At this level we estimated the difference of SSI rate between group patient transfused more and less than 750 ml. Among 30 patients needed more than 750mL blood transfusion, 14 patients (46.7%) were infected at surgical site as compared to the correspondent rate of 17.3% for 292 patients no blood transfusion or less than 750 ml. That means patient transfused more than 750 ml was 4.3 times at risk developing SSI than whom transfused less than 750 ml (95% C.I: 1.8-9.4;p-value=0.001).

5.4.2 Colon injury

30 patients with colon injury, 14 patients (46.7%) developed surgical site infection. Meanwhile, 290 patients without colon injured 16.9% had developed SSI. Among patients with colon injury, two cases with colon injury were primarily repaired by surgery then had peritonitis by colon fistula. So the patient with colon injury was 4.3 times likely to develop SSI compared with the patients without colon injury (95% C.I: 2.0-9.4; p-value=0.001) (table 5.9).

5.4.3. Solid organs injury

Total 193 patients with solid organ injury, 46 cases (23.8%) developed SSI. One case was re-operated because there were necrotizing the right lobe of liver trauma. 127 patients had not solid organ injury, 12.4% developed SSI. We could say that solid organ injury was statistical significance and independent contributor to develop SSI (OR2; 1.1–3.7; p-value=0.02).

5.4.4. Number of viscera injuries

A noteworthy significance was recorded when compared the group with multiple organ injuries (more than one) with the setting less than one organ injury. 99 patients with more than one organ injury, 44 cases (44.4%) developed SSI, among the patients with more than one organ injury was 9 times at risk SSI than patient had one or no organ injury (95%C.I: 4.8 – 16.6; p-value< 0.001).

5.4.5. Vascular injury

Vascular injury was considered as a predictor of SSI. In this study 10 patient with vascular injury, 5 patients (50%) developed SSI. Whereas, 310 patients without vascular injury, 18.7% were developed SSI. The patients with vascular injury was

4.3 time at risk to have SSI than patients without vascular injury (95%C.I: 3.12 – 15.5; p-value=0.014). This variable certainly was a candidate for entry into the logistic regression model.

5.4.6. Penetrating abdominal trauma index (P.A.T.I)

P.A.T.I, which is a method of qualifying the risk of complication following penetrating abdominal trauma. A trauma index score was calculated by assigning a risk factor (APPENDIX C). The sum of the individual organ scores comprised the final penetrating trauma index (P.A.T.I). So, it should be seen like sum of risk factor and can be used as independent variable contributed to develop SSI. Among eight patients with P.A.T.I $\geq$ 25 and 7 patients (87.5%) developed infection (SSI), 16.9% of 312 patients who had P.A.T.I < 25 got SSI. The patients with P.A.T.I $\geq$ 25 was 32 times likely to develop SSI than those patient with P.A.T.I < 25 (95% C.I: 3.8 – 265; p-value<0.001).

5.4.7. Chest injury

Chest injury was seen as a confounding factor to develop SSI. In this study, 100 patients with chest injury, 24 patients (24%) developed SSI, compared with 220 patients without chest injury, 17.7% had SSI. So the patients with chest injury was 1.5 time likely to develop ISS than those patient without chest injury (95% C.I: 0.8 – 2.6). However, it was not statistical significance (p= 0.19). So it was not the candidate for entering the initial model.

Table 5.9   **Distribution and bivariate analysis results of the type and extent of Injury to the surgical site infection**

Variable	Any SSI n (%)	No SSI n (%)	OR	95% C.I.	P-value
1. Shock **Sign of shock** **No shock**	18(38.3) 45(16.5)	29(61.7) 228(83.9)	3.1	1.6 – 6.1	<0.001[a]
2.Blood transfusion **≥ 750 ml** **< 750 ml**	14(46.7) 49(16.9)	16(53.3) 243(83.1)	4.3	1.8 – 9.4	0.001[a]
3.Colon/rectal injury **Yes** **No**	14 (46.7) 49(16.9)	16(53.3) 241(83.1)	4.3	2 – 9.4	0.002[a]
4.Solid organs injury **Yes** **No**	46(23.8) 17(12.4)	147(76.2) 110(26.6)	2	1.1 – 3.7	0.02[a]
5.Vascular injury **Yes** **No**	5(50.0) 58(18.7)	5(50.0) 252(81.3)	4.3	1.2 – 15.5	0.014[a]
6.Chest injury **Yes** **No**	24(24.0) 39(17.7)	76(76.0) 181(82.3)	1.5	0.85 – 2.6	0.19[a]
7.Number of organ injury >1 **Yes** **No**	44(44.4) 19(8.6)	55(55.6) 202(91.4)	9	4.8 – 16.7	<0.001[a]
8. Abdominal index **≥ 25 PATI** **< 25 PAIT**	7(87.5) 56(17.9)	1(12.5) 256(82.1)	32	3.8 – 265	<0.001[a]

a : Pearson chi square test

5.4.8. Multiple logistic regression results

To test the odd ratios obtained from univariate analysis, a multiple logistic regression analysis was performed. All three methods available; forward stepwise, backward stepwise and enter were tried. Method backward stepwise (likelihood ratio) was found to have maximum goodness to fit as well as significance chi square results. The goodness to fit of the model did not differ from chi-square value after improvement. The choice of which variables should be used for adjustment and in what order can not be decisively resolved by applying statistical methods. Variables from other studies reported as important should certainly be considered for conclusion. In this study, variables which had significantly OR with valid confidence interval on univariate analysis were entered into equation.

The logistic model, called logit, which predict the probability in term of log odds can be written as:

$$\text{Log [Prob (event)/ prob (No event)]} = B_0 + B_1 X_1 + \ldots\ldots\ldots + B_p X_p$$

The obtained logistic coefficient can be interpreted as the change in the log odds association with one unit change in the independent variable. The odds ratios can easily be calculated and also the corresponding confident interval. The predicted probability was significant at $p < 0.05$[32].

Table 5.10   Classification table of SSI

Observed	Predicted		
	Any ISS		Percentage
	NO SSI	SSI	Correct
Step 1			
No SSI	242	15	94.2
SSI	48	15	23.2
Overall percent			80.3
Step 2			
No SSI	244	13	94.9
SSI	49	14	22.2
Overall percent			80.6
Step 3			
No SSI	244	13	94.9
SSI	49	14	22.2
Overall percent			80.6
Step 4			
No SSI	239	18	93.0
SSI	44	19	30.2
Overall percent			80.6
Step 5			
No SSI	239	18	93.0
SSI	44	19	30.2
Overall percent			80.6

In this study about seven variables were entered to regress against the dependent variable the condition of surgical site. Among these variables which include the variable of twenty four hours cefradin as antibiotic prophylaxis compare with five days was input into model for adjusting on another variable. Initially, six variables had shown significant results. Subsequently, there were three variables, which had odds ratio more than 2.5, other variables as the solid organ injury, situation of shock were not statistical significance after adjusted with another factors. The rest three variables were highly significant. (Table 5.11) and (table 5.12) give the results of multiple logistic regression. From the (table 5.12), it was found that patients who required blood transfusion more than 750 ml had a significant effect on the rate of surgical site infection. Those patient were 3.5 time likely to develop SSI than patients without blood transfusion or transfusion less than 750 ml (95% CI: 1.45-8.48; P-value =0.005).

Particularly, patients who had more than one organs injury could be 6.57 time likely to develop SSI than those who had not organ injury or only one organ injury (95% CI: 3.45-12.5; P-value < 0.001).

Logistic regression analysis also showed that patients who had colon injury were 2.66 time at risk to develop SSI than those who did not have colon injury (95% CI: 1.1-6.4; P-value = 0.03)

Table 5.11   Results of multiple logistic regressions

Variables	B	S.E	Wald	df	Sig.	Exp(B)	95% C.I for Exp.(B)	
							Lower	Upper
Blood transfusion >750 ml	1.26	0.45	7.79	1	0.005	3.5	1.45	8.48
Number of organ injury >1	1.9	0.33	32.9	1	<0.001	6.57	3.45	12.5
Colon/rectal injury	0.98	0.45	4.7	1	0.03	2.66	1.1	6.4
Constant	-2.5	0.25	100.5	1	<0.001	0.079		

Adjusted odds ratios and corresponding 95% C.I. are shown in table 5.12

Table 5.12   Results showing adjusted odds ratios

Variable	SSI	No SSI	Crude OR	Adjusted OR	95% C.I.	P-value
Treatment **24 hours** **5 days**	33(20.5) 30(18.9)	128(79.5) 129(81.1)	0.9 1.0	0.88	(0.46-1.65)	0.68
1.Blood transfusion **≥ 750 ml** **< 750 ml**	14(46.7) 49(16.9)	16(53.3) 243(83.1)	4.3 1.0	3.5	(1.45-8.48)	0.005
Number of organ injury >1 **Yes** **No**	44(44.4) 19(8.6)	55(55.6) 202(91.4)	9.0 1.0	6.57	(3.45-12.5)	<0.001
Colon/rectal injury **Yes** **No**	14 46.7) 49(16.9)	16(53.3) 241(83.1)	4.3 1.0	2.66	(1.1-6.4)	0.03

5.5 Bacterial of surgical site infection

Total 63 patients had sign of surgical site infection; all of them were taken the species for bacteria culture. The majority of bacterial isolates from surgical site infection could be classified as gram-negative rods, such species were predominant in patients with hollow viscus injury. Among the 33 patients were in group I: 20 species isolated (54.1%) had result to be E. coli. 6 species (16.2%) had proteus mirabilis and 5 (13.5%) with Anterococcus, 2 (5.4%) species had Kiebsiella pneumoniae.

30 species isolated from patients group II (5days antibiotic prophylaxis), 21 patients (58.4%) had species isolated were E.Coli. 3 species (8.3%) had Protesus mirabilis and 5 (13.9%) with Anterococcus. Overall, 30/41 (73.2%) species isolated had E.coli were sensitive with testing 30 mcg Antibiotic disc (cefradin). 6 species isolated had Staphylococcus aureus were sensitive with testing cefradin. Another bacteria culture resisted with testing cefradin.

Table 5.13   Bacteriology of surgical site infection

Group treatment	Organism(s)	Wound infection (n;%)	Intra-abdominal infection (n;%)	Total (n;%)
Group I	E.coli	17 (54.8)	3 (50.0)	20(4.1)
	Klebsiella pneumoniae	2 (6.5)		2 (5.4)
	Proteus mirabilis	4 (13)	2 (40.0)	6 (16.2)
	Anterococcus	4 (13)	1 (10.0)	5 (13.5)
	Staphylococcus aureus	3 (9.7)		3 (8.1)
	No growth	1 (3)		1(2.7)
Total		31 (100.0)	6 (100.0)	37(100.0)
Group II	E.coli	18 (66.7)	3 (33.3)	21(58.4)
	Klebsiella pneumoniae	2 (7.4)	2 (22.2)	4 (11.1)
	Proteus mirabilis	2 (7.4)	1(11.2)	3 (8.3)
	Anterococcus	2 (7.4)	3 (33.3)	5(13.9)
	Staphylococcus aureus	3 (11.1)		3(8.3)
Total		27(100.0)	9 (100.0)	36(100.0)

CHAPTER VI

DISCUSSION, CONCLUSION AND RECOMMENDATION

6.1 Discussion

The optimal timing of antibiotic administration in penetrating abdominal trauma has been inferred from both animal and clinical studies. Three major steps in the evolution of this understanding are noteworthy. Classic animal studies by Miles et al[26] in 1957 and Burk[25] in 1961 demonstrated that antibiotics must be given within three hours of injury if they are to be effective. In 1969 Polk and lopez-Mayor [33] were the first to validate the experimental observation in a clinical setting, using the model of the double blind, and randomized clinical trial of elective colorectal surgery. In 1972, Fullen et al[8] established that antibiotics must be given as close to the time of injury as possible in order to be effective. Subsequent studies in 1973 by Chetlin and Elliot[21] expanded these observations to biliary surgery, and Stone et al[7] in 1976 confirm the efficacy of 1st generation of cephalosporin antibiotic prophylaxis in colon and biliary surgery, and expanded the documentation to include gastric surgery. By extension antibiotics have been administered presumptively to penetrating abdominal trauma patients as soon as decision to operate is made, because the likelihood of gastrointestinal hollow viscus injury is high but cannot be determined precisely by clinical examination. In this study the mean time from injury to surgical treatment was 2.5 hours so it is the time appropriate for antibiotic prophylaxis.

Presumptive antibiotic therapy is administered in penetrating abdominal injury to reduce the incidence of postoperative infection. Appropriate antibiotic mono-therapy for use the cases of penetrating abdominal trauma had been established[11, 13-15, 27, 34-37]. Single agent, broad-spectrum coverage likes first and second - generation cephalosporin is commonly utilized, although data indicate that presumptive therapy with broad-spectrum penicillin such as ampicilline sulbactam[38], piperacine[39] or mezocilline [40] is also appropriate in trauma. There is no longer any indication for the use of combination antibiotic therapy for penetrating abdominal trauma unless the patient is known to have anaphylactoide hypersensitivity to penicillin or cephalosporin.

We conducted this study with cefradin as the 1st generation of cephalosporin, the 1st generation, which is comparable in protection of SSI with the 3th generation[41]. This study had overall infection rate was 19.7% not different from 18% to 24 % rates reported previously for similar studies of 2nd generation of cephalosporin in penetrating abdominal trauma. However, historical rates may underestimate the true incidence of infection because strict diagnosis criteria for infection were not used, or certain types of infection unrelated directly to trauma may not have been considered. The main result of this study addressed the most debating and indefinite issues of other studies, which are the optimal duration of antibiotic, used in penetrating abdominal trauma. As the methodology of this study was conducted as randomized equivalence trial, which seemed to be robust design and had certain advantages. It showed that the different rate of SSI between two groups was 0.016 (95% C.I: from -0.006 to 0.009), which lied entirely within the range of

equivalent $\Delta = \pm 0.15$, so it could demonstrate the equivalence of efficacy of SSI protection of cefradin in twenty four hours versus five days. When to analysis more detail the role timing of antibiotic on the rate of infection intra-abdominal, the result also showed no difference between to treated groups. The question of optimal duration of the use of presumptive antibiotics for abdominal trauma has only sometimes been addressed in prospective randomized studies[13 , 23, 34-36, 42]. Most such studies enrolled small numbers of patients and lack sophisticate multivariate analyses of outcome[13, 34-36]. Almost studies were published more than 10 to 15 years ago[42]. Bozorgzadeh et al conducted a randomized control trial compared twenty four hours of cephoxitin comparable with five days on 314 patients with penetrating abdominal trauma. It is sound evidence supported to use antibiotic prophylaxis twenty four hours. However the patient's population might not reflect the epidemiology of penetrating abdominal trauma in developing countries where the main cause of injury was stab wound, 41.7% compare with 91.3% in this study. The impact of this change is still being determined. We also consider the role timing of cefradin used with more detail kind of surgical site infection as superficial, deep SSI and intra-abdominal infection, which was consistent with the result previously; the infection rates were similar with Bozorgzadeh, no different between two treated groups.

Superficial, deep surgical site infections and intra-abdominal infection in this study also compared favorably with the published literature despite the use initially of 1 gram-dose prophylaxis. In the published study, most similar in design and analysis to the present study, Fabrian et al[42] randomized a cohort of 515 patients to receive either 2-grams

cefoxitine or cefotant for twenty four hours or five days. In his study forty-six percentages of their patients sustained a hollow viscus injury, which is certainly higher than 32.2% incidence in the present study (p<0.001). However, Fabrial et al administered only a single dose of antibiotics to their 280 patients without a hollow viscus injury, and excluded them from their multivariate analysis of abdominal infection risk despite a high incidence of infection. Bozorgzadeh randomized cohort of 314 patients received 1gram cefoxitin each 6 hours during twenty four hours and 5 days give the same result in protection of SSI but the incidence of hollow viscus injury was also higher 49%[23]. However, Bozorgzadeh had proportion of intra-abdominal infection (6%) higher than ours (2.2%), it seem to be related to the incidence of proximal to ileocecal valve and combined with colon was higher (23.3% versus with 8.1% in this study) and this higher rates impacted upon the intra-abdominal infection rate.

The use of a 1gram-dose of the 1st generation of cephalosporin as cefazolin was implemented in the study of Stone[7] with average concentration of 13.7 mcg/ ml and it is FDA approved the dose for prophylaxis. Some author addressed the role of lower dose monotherapy and suggested that lower dose appears to be appropriate as well[43] . Most previous studies of 2nd generation cephalosporin in penetrating abdominal trauma have evaluated a 2-g-dose[14, 37, 42]. The present study has documented comparably low infection rates with 1-gram dose, with favorable implications for cost containment [11]. Some who recommended a dose of 2 gram were concerned that the lower dose may be insufficient because fluid resuscitation and blood loss will change the volume of

distribution of the drug and decrease serum and tissue levels[44]. Livingstone et al[45] showed higher infection rates with a lower dose of cefazolin in a rate model of hemorrhaged shock and Ericsson et al[46] suggested that the lower dose of Amikacin (7.5mg / Kg versus 11 mg/kg) led to more infections in trauma patients. However, this maybe-antibiotic specific[47] in the Ericsson study[46] because a 600-mg versus a 1200-mg dose of clindamycin had no impact on infection rates. Aminoglycosides dosing is particularly susceptible to changes in volume of distribution and bacterial killing by change in volume of distribution over time also misplaced, because what is the most important is the tissue antibiotic concentration at the time the incision is made. If twenty four hours of therapy is sufficient, changes in volume of distribution due to fluid resuscitation or mobilization after that time, which is when most of these shifts occur, become irrelevant. The haft-life of elimination may be more important. Studies of additional newer agents with long haft-lives may be beneficial. A low dose (200-mg) of ciprofloxacin, given every 12 hours, achieved adequate serum concentrations to treat most bacterial pathogens found in trauma patients[48] . The issue of injury related or surgical blood loss in trauma patients, and the effect on antibiotic concentrations remains an open issue, as few studies have been performed. Ongoing blood loss would be expected to deplete antibiotics but perhaps initially the effect may be small. Some of measured operative blood loss in trauma is invariable due to losses prior to resuscitation. Antibiotic levels would be minimal in blood shed antibiotic administration; moreover, redistribution of antibiotic from the blood to the tissue during surgery will minimize operative antibiotic

loss as well. By analogy, cefazolin pharmacokinetics has been analyzed in cardiac surgical patients[49], where blood volume changes dramatically over a short time. Despite average blood loss of 110 ml /hour, total blood loss of 1.1± 0.6L, and average crystalloid replacement of 3.2±0.5 L, only 14% of the administered cefazolin dose was lost via operative blood loss. These data support the use of a 1gram cefradin for only twenty four hours on patients with penetrating abdominal injuries regardless of injuries pattern. However, Croce et al[50] noted that gunshot wounds caused more abdominal sepsis (19%) than stab wounds (4%) because of increased incidence of colon and gastric injuries, increased transfusion requirement, and number of organs injured. So the more serious injuries are, patients should received longer antibiotic administration, in the part 5.1 of chapter IV, which addressed in overall no advantage could be detected for five days treatment in reducing surgical site infection. However, still have room for doubt about the role of twenty four hour antibiotic therapy on high risk patients such as colon, vascular or several organ injuries.

The results obtained from bacterial culture were available evidence supports the use of antibiotic with activity against both aerobic and anaerobic enteric pathogens for patients with penetrating abdominal injuries and bowel penetration. Cefradin was seen less specified on bacterial anaerobic enteric, such bacteria were even more predominant in patient with colon injury. In addition anaerobe and Enterococcus were also plentiful in the colonic flora. Some authors also agreed that future studies is necessary to evaluate the efficacy of antibiotic treatment of Enterococcal infection [51]

The hospital stay did not depend on the duration administration antibiotic prophylaxis. The average hospital stay in group I and II were 9.1±3.1 days and 10.1±7.2 days respectively and the length of hospital stay was not different between two groups of cefradin treatment (p=0.1). It reflected the infection rate of no difference between two treatment groups, Bozorgzadeh et al[23] had the same conclusion when he compared the over all hospital duration between two treated groups. Beside that, we also considered the risk factors that could affect the hospital stay. The results from table 5.7 showed that the patients required blood transfusion more than 750 ml would be prolonged hospital stay from 9.4±4.6 days to 14.2±9.9 days. The patients with organs injuries as solid organ and colon injuries, who had the mean hospital stay increased from 8.6±4.1days to 10.3±6.2 days and from 9.4±5.5 days to 11.6±5.2 days with statistical significantly. Particularly, patients with vascular injury increased the mean hospital stay from 9.4±4.8 days to 16.4±14.9 days. Other factors as patients with more than one organ injury as well as chest injury could make prolongation of hospital duration. However this study unable to show statistical significance after adjusted with other factors by multiple regression. So it could be explained as the longer hospital stay corresponded with increasing infection rates in group had organ injury[23, 52-56]. When patients suffered septic complication, the hospital duration should be prolonged. In this study the present of any SSI increased the mean of length hospital stay from 8.5±3.1 days to 14±9.5 days (p<0.001). This clinical point was addressed in many published paper[23, 52, 53, 55, 56, 58], as Tybursky[57] reported the patients with any infection increased the mean ± SD length of hospital stay from

8.5±3.5 days to 23.3±10.9 days and increased the mean±SD hospital charges from $ 507±$ 9860 to $ 104902±$.

Beside the role of antibiotic prophylaxis on the development of surgical site infection had been addressed previously. Other important risk factors to affect on SSI were considered. The development of any infection at any SSI was the most strongly predicted by the number of organs injured and colon injury is well documented in published reports[23, 52, 53, 55, 56, 58]. This study showed that patients with more than one organ injuries were 6.57 times at risk surgical site infection (95% C.I: 3.45-12.5). If colon was injured, the patients were 2.66 times more likely to develop SSI than those with no colon injury (95% C.I: 1.1-6.4). The rate of surgical site infection also depended on the extent of injury to solid organ, however in this study was unable to show any statistical significance after adjusted with other factors by logistic regression. The blood transfusions required were also strong predictors to develop SSI. Blood transfusion required more than 750ml was statistical significance associated with SSI (OR: 3.5; 95% C.I:1.45-8.48; p-value=0.005). Bozorgzadeh et al also showed that infection was associated with shock on admission to emergency department, the number of intra-abdominal organ injured, colon injury specially and injury to central nervous system (CNS).

How serious degree of injury impacted the SSI? Several previous studies have examined the risk infection following penetrating abdominal trauma by P.A.T.I index. Almost authors agreed that 25 scores to be seen as level of prognostic significance[24, 59,

[60]. In this study, patients with P.A.T.I $\geq$ 25 were 32 times likely to develop SSI than patient had P.A.T.I < 25 (95% C.I; 3.8 – 265; p-value=0.001).

6.2 Conclusion

In summary, this prospective, randomized study of 320 patients with penetrating abdominal trauma, twenty four hours of IV cefradin versus five days of therapy showed no difference in prevention of surgical site infection or length of hospitalization. However, need further study to validate short course treatment on high risk patients such as colon, vascular or several organs injury.

The patient with colon, solid and vascular injuries or required blood transfusion more than 750 ml was independent factors affected prolongation hospital stay in each group treatment. When patients suffered septic complication the duration hospital stay was prolonged.

Surgical site infection was associated with blood transfusion more than 750 ml, colon injured and number of intra-abdominal organs injured specifically. Solid organ injury has important role contributed to postoperative infection, however it was not statistical significance. P.A.T.I $\geq$ 25 was good index to predict surgical site infection.

6.3 Recommendation

The patient with penetrating abdominal trauma presenting with wound contamination do not require beyond twenty four hour course postoperative administration, since the infection source is dealt with a during operation. Infections depend upon the extent of organ injury and blood loss, particularly colon injury, so need

further study to validate short course treatment on those high risk patients. Prolonged hospitalization was associated with vascular, solid organ, colon injury and blood transfusion more than 750 ml. To overcome this problem requires expeditious resuscitation and operation after wounding. Rapid control and repair of vascular injuries, optimal management of hollow viscus injuries is of key importance in operative management.

The choice of antibiotic used in this study was merited from Vietnam FDA for a long time. The results obtained from bacterial culture were available evidence supporting the use of antibiotic with activity against both aerobic and anaerobic enteric pathogens for patients with penetrating abdominal injuries, particularly with bowel penetration. Cefradin was seen less specific for bacterial anaerobic enteric. In addition anaerobe and Enterococcus were also plentiful in the colonic flora. Thus there is a need for further study to validate the role cefradin and antibiotic agents that have a spectrum of activity effective against anaerobe and Enteroccocus, Bacteroides fragilis

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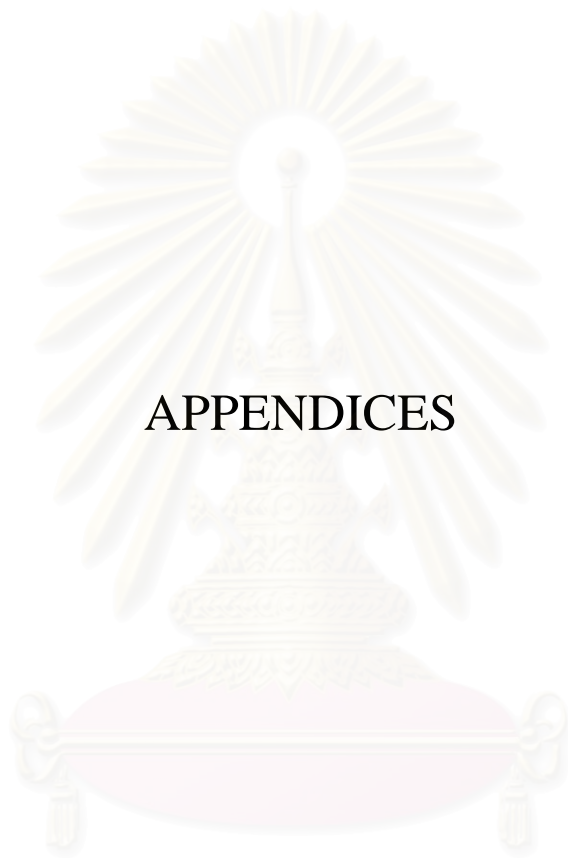
APPENDICES

APPENDIX A

DATA COLLECTION FORM

HOSPITAL ……………………….. **INVESTIGATOR NAME**…………………

Medication treated: (0= 24 hour course, 1= 5 day course) ☐

BASELINE DATA

Date of hospital admission ☐☐ /☐☐ /☐☐☐☐
Day Month Year

Date of hospital discharge ☐☐ /☐☐ /☐☐☐☐
Day Month Year

Patient's trial number ☐☐☐

Hospital number ☐☐☐☐☐☐☐

Date of birth ☐☐ /☐☐ /☐☐☐☐
Day Month Year

Sex (0= female, 1= male) ☐

Type of injury (0= gunshot wound, 1= stab wound, 2= another cause) ☐

Time from injury to surgical (hour) ☐☐

Blood pressure (mmHg) ☐☐☐/☐☐☐

Situation of Shock (0= no, 1=yes) ☐

Blood transfusion (ml) ☐☐☐☐

Number of intra-abdominal injured ☐☐

Gastrointestinal injury (0= no, 1=yes) ☐

Proximal to ileo- cecal injury (0= no, 1=yes) ☐

Colon or rectal injury (0= no, 1=yes) ☐

Liver injury   (0= no, 1=yes) ☐

Spleen injury (0= no, 1=yes) ☐

Pancreas injury (0= no, 1=yes) ☐

Kidney injury (0= no, 1=yes) ☐

Vascular injury (0= no, 1=yes) ☐

Chest injury (0= no, 1=yes) ☐

Penetrating abdominal trauma index (P.A.T.I) ☐☐

OUTCOME EXAMINATION

Superficial incision SSI   (0= no, 1=yes) ☐

Deep incision SSI   (0= no, 1=yes) ☐
Organ/ space SSI   (0= no, 1=yes) ☐

Mortality   (0= no, 1= death) ☐

Side effect of cefradin   (0= no, 1=yes) ☐

Physician's comments:
………
………
……………………………………………………………………………………………………

APPENDIX B

INFORMED PATIENT CONSENT

Name of investigator: Dr. Duong Trong Hien

The aim of the trial: The purpose of this study was to test the hypothesis that 24 hours of antibiotic therapy remains sufficient to reduce the incidence of surgical site infection in penetrating abdominal trauma.

Why is this trial being done? Although, there are many paper had sound evidence supported that antibiotic for only 24 hours course is sufficient to reduce the incidence of infection in penetrating abdominal trauma. However, in Vietnam setting, the inappropriate used antibiotic is the prevailing trend to continuous antibiotic therapy when, in fact, it could have been stopped, particularly concerning patient with penetrating abdominal trauma.

Who can be in the trial? The Patients with penetrating abdominal trauma, who is diagnosed at VietDuc and Saintpaul emergency room. After you are diagnosed and your doctors make sure that you are suitable to participate in the trial.

What happens to the patients in the trial? If you agree to take part in the trial, you will be randomized in one of two groups, in which you should be injected cefradin 1g q6h within 24hours or 5 days. You do not have to pay for drug. The doctors will take care of you until discharge from hospital.

Do you have to go in this trial? No, your participation in this trial is up to you. You can withdraw from this trial at any time without any trouble.

Are there any side effects? Cefradin were the chosen antibiotic . It has been approved by the Vietnam drug council for treatment of intra-abdominal infection before of this study. The dose 1g of cefradin is conventional dose in surgical antibiotic prophylaxis. However, it might have side effects as dizziness, nausea, vomiting. If the symptoms are severe, we will treatment all complications and change drug.

Peoples to be contacted: During the trial carry out, if you have any question or problems about this trial, you can talk to Doctor Trinh Hong Son (tel : 8626590) . He will take care you during hospital staying.

Patient's name: ……………………….. Signature……………………………
Subject's guardian's signature…………… Relation: ……………………………
Physician's name ………………………… Date of participation …………………

APPENDIX C

PENETRATING ABDOMINAL TRAUMA INDEX

Organ injured	Risk factor	Score
Duodenum	5	1. Single wall 2. ≤ 25% wall 3. >25% wall 4. Duodenal wall and blood supply 5. Pancreaticoduodenectomy
Pancreas	5	1. Tangential 2. Through –and though (duct intact) 3. Major debridement or distal duct injury 4. Proximal duct injury 5. Pancreaticoduodenectomy
Liver	4	1. Nonbleeding peripheral 2. Bleeding, central, or minor debridement 3. Major debridement or hepatic artery ligation 4. Lobectomy 5. Lobectomy with caval repair or extensive bilobar debridement
Large intestine	4	1. Serosal 2. Single wall 3. ≤25% wall 4. >25% wall 5. colon wall and blood supply
Major vascular	4	1. ≤25% wall 2. >25% wall 3. Complete transection 4. Interposition grafting or bypass 5. Ligation
Spleen	3	1. Nonbleeding 2. Cautery or hemostatic agent 3. Minor debridement or suturing 4. Partial resection 5. Splenectomy
Kidney		1. Nonbleedimg 2. Minor debridement or suturing

	3	3. Major debridement 4. Pedicle or major calyceal 5. Nephrectomy
Extrahepatic biliary	3	1. Contusion 2. Cholecystectomy 3. ≤25% common duct wall 4. > 25% common duct wall 5. Biliary enteric reconstruction
Small bowel	2	1. Single wall 2. Through -and -through 3. ≤25% wall or 2-3 injuries 4. >25% wall or 4-5 injuries 5. Wall and blood supply or >5 injuries
Stomach	2	1. Single wall 2. Through -and -through 3. Minor debridement 4. Wedge resection 5. >35% resection
Ureter	2	1. Contusion 2. Laceration 3. Minor debridement 4. Segmental resection 5. Reconstruction
Bladder	1	1. Single wall 2. Through -and -through 3. Debridement 4. Wedge resection 5. Reconstruction
Bone	1	1. Periosteum 2. Cortex 3. Through -and –through 4. Intra- articular 5. Major bone loss
Minor vascular	1	1. Nonbleeding small hematoma 2. Nonbleeding large hematoma 3. Suturing 4. Ligation of isolated vessels 5. Ligation of named vessels

Based on assigning a complication risk factor (x) to each organ system involved and grading each organ injury (1=minimal, 2=minor, 3= moderate, 4= major, 5= maximum)

VITAE

Dr Duong Trong Hien was born on September 9, 1971 in Hanoi, Vietnam. He graduated from Hanoi medical university in 1994 and earned the degree of Doctor of medicine. He finished his residency-training program in VietDuc hospital, passed the Vietnam Surgical Board examination and obtained the Certificate Board of gastro-intestinal surgery in 1998. Since November 1998 he worked in Department of gastro-intestinal surgery and as a member of clinical epidemiology unit of Hanoi medical university.

He has been admitted in Master Degree Program of Health Development in Faculty of Medicine, Chulalongkorn University since June 1999, funded by INCLEN. Currently he is surgeon in Department of Gastro-intestinal surgery, VietDuc hospital