USE OF SINGLE DOSE PRE-OPERATIVE ANTIBIOTICS IN ABDOMINAL SURGERY AT THE UNIVERSITY TEACHING HOSPITAL LUSAKA

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UNIVERSITY OF ZAMBIA

DECLARATION

I hereby declare that this dissertation represents my own work; it has not previously been submitted for a degree, diploma or any other qualification at this or any other University.

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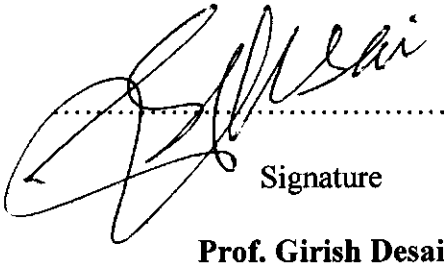
Supervisor:  .....

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This dissertation entitled COMPARISON BETWEEN THE PRE-OPERATIVE SINGLE DOSE ANTIBIOTIC PROPHYLAXIS AND POST-OPERATIVE ANTIBIOTIC USE AT UNIVERSITY TEACHING HOSPITAL LUSAKA by Dr. EGIDE SHIRIMPAKA has been approved by the board of examiners as fulfilling part of requirements for the award of the degree of Master of Medicine in Surgery by the University of Zambia.

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ABSTRACT

The objective of the study was to assess the efficacy of a single dose pre-operative antibiotic prophylaxis as compared to post-operative antibiotics in prevention of surgical site infection in elective abdominal surgery at the University Teaching Hospital Lusaka
It was a prospective randomized case control study. 80 patients undergoing clean or clean contaminated abdominal surgery were recruited using a non-probability convenience sampling method and divided into two groups: study and control.
The confidence interval was 95 percent and p Value 0.05.
The study consisted of 41 while the control consisted of 39 patients. Study patients were given a single dose of prophylactic antimicrobials (ceftriaxone and metronidazol) before their surgery, while Control patients were given postoperative antimicrobial treatment with triple antibiotics (crystalline penicillin, gentamicin and metronidazol) after surgery.

Results: Mean age was 38.48+12.48 years in study and 38.05+13.90 years in control. There was no significant difference in the proportion of male and female patients in both groups (p=0.343). Statistical analysis showed no significant difference in the proportion of early postoperative surgical site infections between the two groups: 7.3 and 10.3 percent for study and control respectively with p=0.642. The surgical site infection rate in the all studied patients was 8.7 percent. E. coli was the commonest organism cultured from the wound discharge in our study (43 percent) followed by Staphylococcus aureus and proteus mirabilis (14 percent for each). Three of our cases having postoperative wound infection showed no growth. There was no significant difference between the two groups regarding mean operating time and duration of stay in hospital.
There was no statistically significant difference in the proportion of surgical site infections between the group of patients receiving pre-operative single dose prophylactic antibiotic and the group of those who received triple antibiotic treatment post-operatively. The small sample size may explain this unexpected result that is at variance with literature in this field. However the use of a single preoperative prophylactic antibiotic was much more cost-effective than the use of combined triple antimicrobials in the postoperative period.
A larger study is recommended for more definitive conclusions to be made. We recommend the UTH to adopt the practice of pre-operative prophylaxis in patients undergoing major abdominal surgery.

To my wife Mary Jeanne Mukeshimana, my daughter Bertille Ake Shirimpaka and my son Hirwe Uwe Shirimpaka. Without their love and support this would not have been possible.

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LIST OF ABBREVIATIONS

1. UTH: University Teaching Hospital
2. AIDS: Acquired immunodeficiency syndrome
3. WHO: World Health Organisation
4. SSIs: Surgical Site Infections
5. mg: Milligrams
6. SPSS: Statistical Package for the Social Sciences
7. MIC: Minimal inhibitory concentration

TERMINOLOGIES

1. **Class I/Clean wound**: An uninfected operative wound in which no inflammation is encountered and the respiratory, alimentary, genital, or uninfected urinary tract is not entered. In addition, clean wounds are primarily closed and, if necessary, drained with closed drainage. Operative incisional wounds that follow non-penetrating (blunt) trauma should be included in this category if they meet the criteria.

2. **Class II/Clean-Contaminated wound**: An operative wound in which the respiratory, alimentary, genital, or urinary tracts are entered under controlled conditions and without unusual contamination. Specifically, operations involving the biliary tract, appendix, vagina, and oropharynx are included in this category, provided no evidence of infection or major break in technique is encountered.

3. **Class III/Contaminated wound**: Open, fresh, accidental wounds. In addition, operations with major breaks in sterile technique or gross spillage from the gastrointestinal tract, and incisions in which acute, non-purulent inflammation is encountered are included in this category.

4. **Class IV/Dirty-Infected wound**: Old traumatic wounds with retained devitalized tissue and those that involve existing clinical infection or perforated

viscera. This definition suggests that the organisms causing postoperative infection were present in the operative field before the operation.

INTRODUCTION AND STUDY RATIONALE

Surgical site infection is a common postoperative complication and causes significant postoperative morbidity and mortality. Although the total elimination of wound infection is not possible, a reduction in the infection rate to a minimal level could have significant benefits in terms of both patient comfort and medical resources used.[1]

This control of wound infection is probably one of the surgeon's most sought after aspiration.[2,3]

In developing countries, like Zambia, the risk of developing surgical site infection might be even more due to malnutrition, high HIV prevalence, high prevalence malaria induced anaemia and overall low social economic development which add to significant morbidity and mortality. Large number of factors can contribute to the development of postoperative wound infection and the mainstay of treatment is prophylaxis, which is achieved by a variety of methods including the use of antibiotics. In developed countries, single dose antibiotic has proven to be an effective prophylaxis in abdominal surgery.[4]

In the interest of promoting cost-effective surgical practice as well as reducing the development of bacterial resistance to antimicrobial agents, several surgical centres in many countries have adopted this practice of using a "single dose pre-

operative prophylactic antibiotic(s)" to prevent surgical site infections in suitable surgical patients.[4] However at the Lusaka University Teaching Hospital and many other health institutions in Zambia, most of patients undergoing elective major surgery are still being subjected to prolonged "post-operative prophylactic antibiotics". This probably increases not only the expenditure for purchase of antibiotics, but also the emergence of bacterial resistance strains to antimicrobials. No study has ever been carried out in Zambia to assess the efficacy and practicability of single dose pre-operative prophylactic antibiotic(s), using readily available and relatively affordable drugs. It might be expected that surgeons at the UTH (and other health institutions countrywide) could change their practice if evidence based results on the efficacy of single dose prophylaxis were available. This study is therefore prudent and essential.

The purpose of this study was to compare the rate of surgical site infection in patients receiving a single dose pre-operative prophylactic antibiotic with that in patients receiving prolonged post-operative prophylactic antibiotics as per current practice.

At UTH, nearly all the patients having major surgery in general and abdominal surgery in particular receive intravenous antibiotics for up to five days in the post-operative period, and this is what is considered to be "antibiotic prophylaxis". For major abdominal surgery, antibiotics prescribed most of the times are a combination of crystalline penicillin, gentamicin and

metronidazole. The patient receives these antibiotics within two to six hours after surgery.

The purpose of this study was to compare the rate of surgical site infection in patients receiving a single dose pre-operative prophylactic antibiotic with that in patients receiving prolonged post-operative prophylactic antibiotics, assess therefore the efficacy of a single dose pre-operative antibiotic prophylaxis in prevention of surgical site infection in elective abdominal surgery in the setting of the University teaching Hospital Lusaka.

NULL HYPOTHESIS

Surgical site infections in abdominal surgery at UTH cannot be reduced by single dose pre-operative prophylactic antibiotic use.

AIM AND OBJECTIVES OF THE STUDY

AIM: To assess the efficacy of a single dose pre-operative antibiotic prophylaxis in prevention of surgical site infection in elective abdominal surgery.

SPECIFIC OBJECTIVES:

1. To determine the pattern and incidence of surgical site infections following elective abdominal surgery at UTH
2. To compare the rate of SSI in patients receiving a single dose pre-operative prophylactic antibiotic with that in patients receiving prolonged post-operative antibiotic therapy.
3. To determine the nature and susceptibility of bacteria causing SSI in the study patients
4. To compare the cost of a single dose pre-operative prophylactic antibiotics with that of prolonged post-operative "prophylactic antibiotics".

2. LITERATURE REVIEW

2.1. Historical perspective of wound infection and its management

The ancient Egyptians were the first civilization to have trained physicians to treat physical ailments. Medical papyri, such as the Edwin Smith papyrus (1600 BC) and the Ebers papyrus (1534 BC)[5] provided detailed information of management of disease, including wound management with the application of various potions and grease to assist healing.[6] It is clear that the Egyptians knew about infection. They certainly were able to prevent putrefaction, that is testified in their skills of mummification. At some point in the early days wounds management required use of a creechle of worms, rose oil and moss from the skull of a mummy collected at full moon, and this boiling concoction was incomplete without the addition of fresh puppies[7].

Hippocrates (460-377 BC), father of medicine, used wine or vinegar to irrigate open and infected wounds and introduced wound dressing to prevent further injury. His teachings remained unchallenged for centuries. Galen (Roman gladiatorial surgeon, 130-200 AD) recognised that localisation of infection (suppuration) in wounds inflicted in the gladiatorial arena often heralded recovery, particularly after drainage of the pus[8] In the 1600s, wound infection was so common that redness, warmth and purulence were thought to be desirable features of wound healing (*pus bonum et laudabile* ["good and

commendable pus"])[7]. Unfortunately, this observation was misinterpreted, and the concept of pus preempting wound healing continued well into the eighteenth century. The link between pus formation and healing was emphasized so strongly that foreign material including faeces, was introduced into wounds to promote suppuration[8,9].

The concept of wound healing remained a mystery, as highlighted by the famous saying by Ambroise Paré (French military surgeon, 1510-1590), "I dressed the wound, God healed it."[10]. This surgeon used egg yolk, rose oil, unboiled turpentine and dressing to treat wounds.

Major surgery was almost invariably followed by infectious complications, typified by erysipelas, rapidly progressive soft tissue infections (streptococcal or mixed synergistic infections) and tetanus. This was associated with a very high mortality.[7,9,11] Compound fractures at the time almost always were associated with infection; amputation was the only option despite a 25-90 percent risk of amputation stump infection.

In his nineteenth century postulates, Koch (Professor of Hygiene and Microbiology, Berlin, 1843-1910) first recognized the cause of infective foci as secondary to microbial growth. Semmelweis (Austrian obstetrician, 1818-1865) demonstrated a five fold reduction in puerperal sepsis by hand washing between performing postmortem examinations and entering the delivery room.[7,9] Lister (Professor of Surgery, London, 1827-1912) and Pasteur

(French bacteriologist, 1822-1895) revolutionised the entire concept of wound infection. Lister recognized that antisepsis could prevent infection.[12] In 1867, he placed carbolic acid into open fractures to sterilize the wound and prevent sepsis and hence the need for amputation. In 1871, Lister began to use carbolic spray in the operating room to reduce contamination. However, the concept of wound suppuration persevered even among eminent surgeons, such as John Hunter.[13]

During World War I, new types of wounds from high-velocity bullet and shrapnel injuries coupled with contamination by the mud from the trenches were experienced. Depage (Belgian military surgeon, 1862-1925) introduced wound debridement and delayed wound closure and relied on microbiological assessment of wound brushings as guidance for the timing of secondary wound closure. Fleming (microbiologist, London, 1881-1955) performed many of his bacteriological studies during World War I and is credited with the discovery of penicillin.[14]

Aseptic surgery was not routine practice as late as the nineteenth century. Sterilization of instruments began in the 1880s as did the wearing of gowns, masks, and gloves by Halsted and his student J. Bloodgood. Howard Floery used penicillin clinically for the first time in 1940. With the use of antibiotics, a new era in the management of wound infections commenced. Despite that, even in the 1960s, before the correct use of antibiotics and the advent of modern preoperative and postoperative care, as much as one quarter of a

surgical ward might have been occupied by patients with wound complications. Unfortunately, eradication of the infective plague affecting surgical wounds has not ended because of the insurgence of antibiotic-resistant bacterial strains and the nature of more adventurous surgical intervention in immunocompromised patients and in implant surgery[9]

2.2. Classification of SSIs

Surgical sites infections are classified as being either incisional or organ/space. Incisional SSIs are further divided into those involving only skin and subcutaneous tissue (superficial incisional SSI) and those involving deeper soft tissues of the incision (deep incisional SSI). Organ/space SSIs involve any part of the anatomy (e.g., organ or space) other than incised body wall layers, that was opened or manipulated during an operation.[15]

2.3. Criteria for diagnosing SSIs

Details are seen in appendix A

2.4. Microbiology of SSIs

The distribution of pathogens isolated from SSIs has remained almost unchanged for decades.[16,17] *Staphylococcus aureus*, coagulase-negative

staphylococci, *Enterococcus* spp., and *Escherichia coli* remain the most frequently isolated pathogens. An increasing proportion of SSIs are caused by antimicrobial-resistant pathogens, such as methicillin-resistant *S. aureus* (MRSA), [18,19]. The increased proportion of SSIs caused by resistant pathogens and *Candida* spp. may reflect increasing numbers of severely ill and immunocompromised surgical patients and the impact of widespread use of broad-spectrum antimicrobial agents.

Outbreaks or clusters of SSIs can be caused by unusual pathogens, These rare outbreaks have been traced to contaminated adhesive dressings,[20] elastic bandages,[21]colonised surgical personnel,[22,23]tap water,[24]or contaminated disinfectant solutions.[25]

2.5. Pathogenesis and determinants of SSIs

Microbial contamination of the surgical site is a necessary precursor of SSI. The risk of SSI can be conceptualised according to the following relationship:[26,27]

$$\frac{\text{Dose of bacterial contamination} \times \text{virulence}}{\text{Resistance of the host patient}} = \text{Risk of surgical site infection}$$

Quantitatively, it has been shown that if a surgical site is contaminated with more than 10^5 microorganisms per gram of tissue, the risk of SSI is markedly increased.[28]

However, the dose of contaminating microorganisms required to produce infection may be much lower when foreign material is present at the site (i.e., 100 staphylococci per gram of tissue introduced on silk sutures).[29-31] Microorganisms may contain or produce toxins and other substances that increase their ability to invade a host, produce damage within the host, or survive on or in host tissue. For example, many gram-negative bacteria produce endotoxin, which stimulates cytokine production. In turn, cytokines can trigger the systemic inflammatory response syndrome that sometimes leads to multiple system organ failure.[32-34]One of the most common causes of multiple system organ failure in modern surgical care is intra-abdominal infection.[35,36] Some bacterial surface components, notably polysaccharide capsules, inhibit phagocytosis,[37] a critical and early host defense response to microbial contamination.

Certain strains of clostridia and streptococci produce potent exotoxins that disrupt cell membranes or alter cellular metabolism.[38] A variety of microorganisms, including gram-positive bacteria such as coagulase-negative staphylococci, produce glycocalyx and an associated component called "slime,"[39-43] which physically shields bacteria from phagocytes or inhibits the binding or penetration of antimicrobial agents.[44]

Virulence of the Bacterial Contaminant is an important determinant contributing to SSI. The more virulent the bacterial contaminant, the greater the probability of infection. Coagulase-positive staphylococci require a smaller inoculum than

the coagulase-negative species. Uncommon but virulent strains of *Clostridium perfringens* or Group A streptococci require only a small inoculum to cause an especially severe necrotizing infection at the surgical site. *Escherichia coli* has endotoxin in its outer cell membrane that gives it a particular virulence. *Bacteroides fragilis* and other *Bacteroides* species are ordinarily organisms of minimal virulence as solitary pathogens, but when combined with other oxygen-consuming organisms, they will result in microbial synergism and cause very significant infection following operations of the colon or female genital tract. Although these and other virulence factors are well defined, their mechanistic relationship to SSI development has not been fully determined. For most SSIs, the source of pathogens is the endogenous flora of the patient's skin, mucous membranes, or hollow viscera.[45]When mucous membranes or skin is incised, the exposed tissues are at risk for contamination with endogenous flora. [46] These organisms are usually aerobic gram-positive cocci (e.g., staphylococci), but may include fecal flora (e.g., anaerobic bacteria and gram-negative aerobes) when incisions are made near the perineum or groin. When a gastrointestinal organ is opened during an operation and is the source of pathogens, gram-negative bacilli (e.g., *E. coli*), gram-positive organisms (e.g., enterococci), and sometimes anaerobes (e.g., *Bacillus fragilis*) are the typical SSI isolates.

Seeding of the operative site from a distant focus of infection can be another source of SSI pathogens, [47-56]particularly in patients who have prosthesis or other implant placed during the operation. Such devices provide a nidus for attachment of the organism. [57,58]

Exogenous sources of SSI pathogens include surgical personnel (especially members of the surgical team), [59-63] the operating room environment (including air), and all tools, instruments, and materials brought to the sterile field during an operation. Exogenous flora is primarily aerobes, especially gram-positive organisms (e.g., staphylococci and streptococci). Fungi from endogenous and exogenous sources rarely cause SSIs, and their pathogenesis is not well understood. [64]

Other determinants of SSIs are inherent to microenvironment of the wound: Hemoglobin at the surgical site is a well-known adjuvant substance. It is generally thought that the release of ferric iron during the degradation of red blood cells stimulates microbial proliferation.[65] Necrotic tissue can act as a haven for contaminants to avoid phagocytic defenses of the host. Dead space within the surgical site also provides a local environment that fosters infection.[65]

Integrity of host defenses, innate or acquired, is important factor for SSIs. Shock and hypoxemia are positively associated with SSI, especially in trauma patients. Transfusion appears to be immunosuppressive. Similarly, chronic illnesses, hypoalbuminaemia, and malnutrition are significant factors. Hypothermia and hyperglycemia are also recognized as variables that impair the host response, while corticosteroids and other medications may also adversely affect the host and increase SSI rates.[65]

2.6. Epidemiology of Surgical Site Infection

The worldwide frequency of surgical site infections (SSI) is difficult to monitor because criteria for diagnosis might not be standardized. A survey sponsored by the World Health Organization demonstrated a prevalence of nosocomial infections varying from three to 21 percent, with surgical wound infections accounting for five to 34 percent of the total.[66] In the United States of America surgical site infections account for 14-16 percent of estimated two-million nosocomial infections affecting hospitalised patients in the United States.[67]

Surgical site infections are the second most frequent nosocomial infection in most hospitals and are an important cause of morbidity, mortality, and excess hospital costs[68]. Seventy seven percent of the deaths of surgical patients in USA were related to surgical wound infection[69]. Kirkland et al[70] calculated a relative risk of death of 2.2 attributable to surgical site infections, compared to matched surgical patients without infection. Up to two to five percent of patients undergoing clean extra-abdominal operations and up to 20 percent undergoing intra-abdominal operations will develop an SSI.[71]

In Zambia, there is no available data on the incidence of surgical site infections, and it appears probable that no major studies looking into those have been carried out. The surgical site infection rate reported in audits of the Department of Surgery at University Teaching Hospital is certainly lower than its actual prevalence.[72] Infection rate of 0.8 percent in elective abdominal surgery as reported in some audits in 2004 is certainly an underestimation.

2.6.1. Classification of SSI risk

They are many patient and operation characteristics that may influence the risk of developing a surgical site infection.[73]

2.6.1.1. Patient related factors

Patient related factors are multiple and can all individually or in combination influence SSI risk: poor nutritional status, uncontrolled diabetes, smoking or use of other tobacco products, obesity, coexistent infections at a remote body site, colonization with microorganisms, altered immune response (HIV/AIDS and chronic corticosteroid use) and length of preoperative hospital stay. [73]

2.6.1.2. Operation related factors

The risk of developing SSI can also be impacted by preoperative shaving and preoperative skin preparation, duration of operation and antimicrobial prophylaxis, operating room ventilation and instrument processing (cleaning, sterilization), foreign material in the surgical site and surgical drains, surgical technique (poor haemostasis, failure to obliterate dead space, tissue trauma)and so on. [73]

2.7. Reducing the risk of surgical site infections

A number of variables that can influence SSI rates is large. Preoperative planning and intraoperative technique become important in prevention of SSI. In addition, the appropriate use of preventive antibiotics in an appropriate fashion is very important.

2.7.1. Preoperative Planning

It is good for the patient to shower and scrub the surgical site with antiseptic soap on the evening prior to the procedure.[73] The site of the planned incision should not be shaved or clipped the evening before the operation. When hair must be removed, it is clipped scissors just before the surgery. It has been suggested that surgery should be postponed if there is presence of open skin wounds or infection of the hands or arms of the surgeon or if the patient has any pre-existing infection. [73] Other factor not to loss sight of is to avoid, if possible extensive preoperative hospitalisation (more than four days) and to give a course of antibiotics leading up to the operation for a pre-existing infection that is independent of, or associated with the disease for which the operation is being performed. [71,733]

2.7.2. Prevention of SSI in the Operating Room

To optimize the prevention of SSI, contamination of surgical wound in theatre must be limited to the minimal possible. The use of antiseptic solutions for skin

preparation, use of caps, masks, sterile gowns, surgical gloves and double gloving, drapes, sterile instruments and Reducing the traffic (personnel) to the minimum are always considered.[74]

2.7.3. Intra-operative strategies

Some operative technical principles are priceless when it comes to reducing the risk of infection. Handling soft tissue gently to avoid crushing that can result in tissues devitalisation, using electrocautery sparingly to control bleeding because it leaves behind dead tissue that is more likely to become infected,[73] achieving haemostasis at the surgical site, avoiding to overuse braided silk unnecessarily, avoiding to leave a dead space within the surgical wound, removing dead tissue and foreign bodies, keeping the operative time as short as possible, using closed suction drains that exit through a separate stab wound to help prevent accumulation of tissue fluid in the dependent portion of the wound and delaying primary closure for surgical sites that are severely contaminated or frankly dirty.[74] A surgeon who meticulously observes these technical details is rewarded by a low rate of SSI.

2.7.4. Post-operative prevention of SSI

Post-operatively, changing dressings after 24 to 48 hours for clean or clean contaminated wounds and promptly discharging patients, provided they are able to return to homecare is a good strategy of preventing SSI.

2.8. Enhancement of Host Defenses

More recent studies have provided three new strategies that appear to enhance host responsiveness:

2.8.1. Increased Oxygen Delivery

Experimental evidence has favored the concept that increased oxygen delivery has a favorable influence in the prevention of infection.[75] A prospective, randomized trial of elective colon surgery has demonstrated clinical value to the administration of supplemental oxygen.[76]

2.8.2. Optimizing Core Body Temperature

Better intraoperative and postoperative temperature control of the patient may reduce the risk of SSI.[77]

2.8.3. Blood Glucose Control

Better control of blood glucose appears to have value in the reduction of SSI[78,79] adverse effects of hyperglycaemia may be an important contributor to the increases in SSI and other infections in the diabetic and non-diabetic surgical patient.

2.9. Economic impact of SSIs

SSIs impose a heavy cost on both the patient and the health services.[80] Using a standardized method, Haley[81] estimated concurrently the prolongation of stay and extra charges attributable to nosocomial infection in three hospitals. Results showed that nosocomial infection prolonged hospitalization (3.1 to 4.5 days) and added to the infected patients' charges (U$590 to U$641 in 1976). The economic consequences were influenced more by site of infection than by differences among hospitals, and their magnitude emphasizes the need for continued preventive efforts. Kirkland[70] in his study indicated that patients with surgical site infection had longer and costlier hospitalizations, were twice as likely to die, 60 percent more likely to spend time in an intensive care unit, and more than five times as likely to be readmitted to the hospital within 30 days of discharge.

2.10. Antibiotic prophylaxis

2.10.1. Definition

Antibiotic (antimicrobial) prophylaxis refers to a brief course of an antimicrobial agent administered just before an operation begins in order to reduce intraoperative microbial contamination to a level that will not overwhelm host defenses and result in infection.[69]

2.10.2. General considerations

Appropriately administered antibiotic prophylaxis reduces the incidence of surgical site infection. Antibiotic prophylaxis is only one relatively minor effort among numerous preventive measures, but the efficacy and impact of antimicrobial prophylaxis has clearly been demonstrated to be very significant.[7]

Numerous studies have been performed investigating the use of prophylactic antibiotics in surgery. A wide variety of antibiotics, either singly or in combination, have been evaluated. With regards to surgical prophylaxis, the data from these studies support several recurring themes:[69]

A single pre-operative dose of antibiotic is as effective as a full five-day course of therapy assuming an uncomplicated procedure; prophylactic antibiotics should target the anticipated organisms; complicated, contaminated, or dirty procedures should receive additional post-operative coverage; during prolonged procedures, antibiotic prophylaxis should be re-administered every three hours and prophylactic antibiotics should be administered within two hours prior to skin incision.

Administering parenteral antibiotics prior to the surgical incision ensures that adequate tissue and serum antimicrobial levels are present at the time of the contamination. There have been numerous studies evaluating the efficacy of specific antibiotics and specific combinations of antibiotics given by the parenteral route in reducing perioperative septic complications.[82]

The first prospective, randomized, double blinded study published on parenteral antibiotic prophylaxis in elective colon and rectal resections was published in 1969 by Polk & Lopez-Major[83]. They used cephaloridine (1000 mg. prior to incision and two subsequent postoperative doses less than twelve hours from the completion of the operation) intramuscularly during the perioperative period, and noted a significant reduction of postoperative infections (30 to 70 percent) in those patients that received antibiotics compared to those who were in the control group who received a placebo[83].

Multiple clinical studies using the same or similar first-generation cephalosporins were unable to duplicate the significant reduction in postoperative infections seen in Polk & Lopez-Major 's study. With the eventual development of antibiotics that possessed aerobic and anaerobic activity, the efficacy of parenteral agents was documented. In 1981, a meta-analysis by Baum et al[84] of previously published trials conclusively demonstrated the value of prophylactic antibiotics and the authors called for an end to all future placebo controlled trials. Song and Glenny[85] authored an excellent review of nearly 150 antibiotic trials carried out over two decades. They identified more than 70 different antibiotics or antibiotic combinations studied (not to mention the different dosing regimens). They confirmed that multiple antibiotic agents were effective alone or in combination with other agents in reducing wound infections

as long as they possess an adequate spectrum, which covers aerobic and anaerobic bacteria.

2.10.3. Choice of prophylactic antibiotics

The lack of consensus in selecting an antibiotic regimen is highlighted by a retrospective report by Silver et al.[86], which demonstrated that in New York State, 44 different antibiotic regimens were used in the care of 991 patients undergoing large bowel resection.

An appropriate prophylactic antibiotic should be effective against microorganisms anticipated to cause infection, and it should achieve adequate local tissue levels, cause minimal side effects and lastly it should relatively inexpensive and not be likely to select virulent organisms. The antibiotics chosen for prophylaxis can be those used for active treatment of infection. The microbial context of the wound and the hospital environment may influence the choice of antibiotic, but coverage should primarily target those organisms known to cause postoperative infection. Species of Staphylococcus may cause infection in the majority of procedures that do not violate mucosa or a hollow viscus. In general, cephalosporins fulfill these criteria and are regarded as sufficient prophylaxis for the majority of procedures.[7,87,88,89]

The antibiotics chosen for prophylaxis can be those used for active treatment of infection. However, the chosen antibiotics must reflect local, disease-specific information about the common pathogens and their antimicrobial susceptibility.

A past history of a serious adverse event should preclude administration of a particular antibiotic.

A comprehensive risk assessment should be part of the process of choosing the appropriate antibiotic.[90] This should include economic considerations, such as the acquisition costs of the drug and costs of administration and preparation, set against consequences of failure of prophylaxis and the possible adverse events. Prescribers need to be aware that infections that occur in patients who receive prophylaxis are usually caused by bacteria that remain sensitive to the prophylactic regimen. Implementation of prophylaxis should not be accompanied by radical changes in treatment policy because such changes may wipe out the benefits of prophylaxis. For example, changing to third generation cephalosporins for routine treatment of postoperative infection because of implementation of prophylaxis with first or second generation cephalosporins may lead to major drug-resistance problems.[91]

Treatment policies should be based on local information about the epidemiology of drug-resistant bacteria. Implementation of a prophylaxis policy should not trigger an automatic change in treatment policy.

2.10.4. Time of prophylaxis

The goal of antimicrobial prophylaxis is to achieve serum and tissue drug levels that exceed, for the duration of the operation, the MICs for the organisms likely

to be encountered during the operation and furthermore, the timing of the drug administration should ensure that peak therapeutic levels are attained in the immediate perioperative period [92,93]

The literature on the timing of a preoperative dose of prophylactic antibiotics is clear and supported by excellent laboratory and clinical studies. However, there are still some minor differences in schools of thoughts:

In the 1950s, Miles et al injected bacteria intracutaneously in guinea pigs and varied the timing of administration of a single dose of streptomycin and penicillin. Antibiotic administration was effective for infection prevention only in a two-hour period around the time of bacterial injection, which they termed the "decisive" period.[94]

In 1961, Burke[95,96] demonstrated that, when antimicrobials were administered before incision, experimental incisions contaminated with *Staphylococcus aureus* could not be distinguished from incisions that had not been contaminated. He found that antimicrobials were effective in reducing lesion size if administered no later than two hours after bacterial contamination was introduced in animal model.

Classen et al[93] prospectively monitored the timing of antibiotic prophylaxis and studied the occurrence of surgical-wound infections in 2847 patients undergoing

elective clean or "clean-contaminated" surgical procedures at a large community hospital. They divided the timing into four categories: They defined as *early period* the administration of antibiotics two to 24 hours before the surgical incision; the *preoperative period* was the administration of antibiotics during two hours before the incisions; the *perioperative period* was administration of antibiotics within three hours after the incision; the *postoperative period* when the antibiotics were given more than three but less than 24 hours after the incision. Their results showed 3.8 percent rate of SSI in *early category* patients. Among those who received their prophylactic antibiotics in *preoperative period* the SSI rate was 0.6 percent. The rate was 1.4 percent in patients in whom prophylactic antibiotics were administered *perioperatively.* For patients who received antibiotics in *postoperative period,* 3.3 percent subsequently developed SSI. Stepwise logistic-regression analysis confirmed that the administration of antibiotics in the preoperative period was associated with the lowest risk of surgical-wound infection.

Almost similarly in 1976, Stone et al[97] randomly assigned 400 patients undergoing elective gastric, biliary, or colonic operations to one of four regimens: antibiotics administered either 12 hours preoperatively, One hour before an operation, one hour after an operation, or not at all. The incidence of wound infections was reduced significantly in patients given antibiotics preoperatively. Patients given antibiotics postoperatively had an almost identical infection rate to those not given antibiotics.

In assessing the impact of timing the antibiotic prophylaxis, Bratzler carried out a study in which he found that the relative risk of wound infection is 0.15 when antibiotic prophylaxis is started in less than two hours before making the incision; 0.37 when started within three hours post-operative operatively; and 0.86 when started three to 24 hours after surgery[98]

Wong-Beringer et al. studied the influence of the timing of antibiotic administration and mean tissue and serum concentration.[99]The mean tissue and serum concentration was independent of whether the administration was one to 12 minutes or 15 to 60 minutes prior to the incision. In all cases, the levels were higher than the minimum inhibitory concentrations for the most common pathogens. Antibiotics given two or more hours prior to incision were associated with a 5.3 times higher risk of surgical wound infection. The lowest rate of wound infection was seen in the group receiving antibiotics 30 to 120 minutes prior to the incision. The authors' conclusion was that prophylactic antibiotics are best administered at the induction of anesthesia. The conclusion is based largely on the recognition that the half-life of many antibiotics used is less than two hours.

For maximum antibiotic effectiveness, tissue levels of an antibiotic with an appropriate spectrum must be adequate for the duration of the expected period of contamination[100] The period of contamination will vary among patients, but should be less than 24 hours for the antibiotic usage to be considered prophylactic

According to the Russian antibiotic use policy, the best timing for the prophylactic antibiotic is the induction of anaesthesia, i.e. prior to tissue contamination, so that the highest tissue and serum concentrations are maintained throughout the operation and until, at most, a few hours after the incision is closed in the operating room. It is unnecessary and may be detrimental to start them more than one hour preoperatively[101]

Schell et al also define as goals for prophylaxis the achievement of inhibitory antimicrobial levels at the time of incision and the maintenance of adequate levels throughout the procedure. They submit that agents used for parenteral prophylaxis should be administered intravenously, not earlier than 60 minutes before incision. Administration as close as possible to the time of incision is preferable[102].

The Administration of prophylaxis more than three hours after the start of the operation significantly reduces its effectiveness.[93]

For maximum effect, it should be given just before or just after the start of the operation.

However, there may be situations where overriding factors alter the normal timing of administration:[98] 1. For a caesarean section prophylaxis should be delayed until the cord is clamped in order to prevent the drug reaching the neonate. 2. When a tourniquet is to be applied to a limb, the necessary tissue concentration of antibiotic must be achieved prior to its application rather than

the time of incision. This probably occurs within 10 minutes of administration of an I.V. antibiotic injection.

From all of these, it is clear that the ideal prophylactic antimicrobial should be administered as near to the incision time as possible to achieve low SSI rates.

2.10.5. Single dose prophylaxis and duration of antimicrobial prophylaxis

Several professional guidelines support the timely use of pre-operative antibiotics for prevention of post-operative wound infections. Single-dose prophylaxis is now preferred as opposed to earlier regimens that recommended ongoing post-operative prophylaxis for 24-48 hours or longer.[103] As long as adequate serum drug levels are maintained during the operation, a single dose is often sufficient.

With regard to duration of prophylaxis in gastrointestinal surgery vis à vis wound infection, Strachan[104] compared three groups of patients undergoing biliary surgery and received cefazolin .He established that wound infection occurred in three percent of patients who were given a single dose, six percent of those who received the drug for five days and 17 percent of those who received placebo. Similarly, Hall used moxalactam in patients who had diverse gastrointestinal tract surgery and found a wound infection rate of five percent in the group administered a single dose and six percent in that receiving the same antibiotic for two days[105]. Törnqvist[106] found that infection occurred in 10

percent and 19 percent of patients given doxycycline (prophylactic) as single dose and 3 days respectively, while Juul[107] found an equal infection rate of 6% in the group of patients who received a single dose of ampicillin/metronidazole and that receiving the same combination for 3 days.[30]

Heydemann[108] studied incidence of SSI in patients having hip and knee replacement and receiving cefazolin for prophylaxis. He found zero percent wound infection in both those who received a single dose and those who continued prophylaxis for 48 hours while the infection was present in one percent and 1.5 percent of patients who continued it for 24 hours and seven days respectively. Furthermore, Mendelson[109] used cephradine prophylactically in patients undergoing vaginal hysterectomy. The protective effect was similar whether 1 g was given preoperatively followed by 500 mg I.V. 6 hours for four doses, or a single dose of 2 g I.V. given approximately one hour before surgery.

Tanos et al found the odds of SSI were significantly less with single dose prophylaxis than multiple dose prophylaxis.[110]

In his paper, DiPiro[111] examines over 40 published studies in which single doses of parenteral antimicrobials were given for the purpose of preventing surgical infection. The studies involve the comparison of single-dose antibiotic versus multiple-dose, single-dose versus placebo, single-dose of one drug versus multiple doses of another drug, or comparisons of single-dose regimens of

various antibiotics. The surgical types examined in the review of literature include hysterectomies and cesarean sections, colorectal operations, gastric, biliary, and transurethral operations, and open-heart operations. None of the trials examined showed a multiple-dose regimen to be more effective than a single-dose of antibiotic given immediately preoperatively. Single antimicrobial doses, usually cephalosporins given immediately before operation, are effective in preventing wound infections in these operations.

The single guideline exception is the preferred regimen of antimicrobial prophylaxis for cardiothoracic surgery recommended by the American Society of Health-System Pharmacists, which recommends continuing prophylaxis for up to 72 hours after the operation[112]

The majority of published evidence demonstrates that antimicrobial prophylaxis after wound closure is unnecessary, and most studies comparing single-dose prophylaxis with multiple-dose prophylaxis have not shown benefit of additional doses [69,71,89,90,111,113-116] Actually, prolonged use of prophylactic antimicrobials is associated with emergence of resistant bacterial strains [112, 117-119]

2.10.6. Prophylactic antibiotic dosing

There are limited published data on appropriate antimicrobial dosing for prophylaxis.

The drug should be provided in an adequate dose on the basis of patient body weight, adjusted dosing weight, or body mass index and administration should

be repeated intra-operatively if the operation is still in progress for a period of time equal to two half-lives after the first dose to ensure adequate antimicrobial levels until wound closure.[65]

In a study of obese patients undergoing gastroplasty, blood and tissue levels of cefazolin were consistently below the MICs for prophylaxis against gram-positive and gram-negative organisms in patients who received a 1-g dose preoperatively.[120]

Those patients receiving 2 g of cefazolin had an incidence of SSI that was lower than that among those receiving a 1-g dose. [120] In a prospective, randomized, double-blind clinical study[121], regimens of single high doses of gentamycin (4.5 mg/kg of body weight preoperatively) and of multiple standard doses of gentamycin (1.5 mg/kg preoperatively and at 8, 16, and 24 hours postoperatively), both in combination with metronidazol, were compared for prophylaxis in connection with colorectal surgery. Several observations suggested an association between low serum gentamycin concentrations during surgery and clinical failure. First, a trend towards fewer wound infections in the high-dose group suggested improved efficacy when higher antibiotic concentrations were achieved during surgery. Second, a strong association between prolonged surgery, which is a well-documented risk factor, and infection in the standard-dose but not in the high-dose group also supported an association between intra-operative antibiotic concentrations and clinical outcome.

2.10.7. Additional doses after the end of the operation

Several studies have shown that in all operations (except heart surgery), the administration of additional doses after the end of surgery does not provide any additional prophylactic benefit. [122-123]

2.10.8. Redose for long surgeries

Patients undergoing surgery that extends beyond two half-lives of an antibiotic should be redosed intra-operatively. Scher[124] randomly assigned more than 800 patients undergoing gastrointestinal surgery to one of three regimens: cefazolin (half-life of two hours) 1 g preoperatively, cefazolin 1 g preoperatively and a second dose 3 hours later, and cefotetan (half-life, three to 4.6 hours) 1 g preoperatively. Patients who underwent surgeries that lasted longer than 3 hours and were given only one dose of cefazolin had a significantly higher infection rate than patients in the other groups.

Serum antibiotic concentrations are reduced by blood loss and fluid replacement, especially in the first hour of surgery when drug levels are high.[125-126]

The precise effects of blood loss and fluid replacement are difficult to predict, depending on the timing and rate of loss and replacement.[127]

In adults, blood loss of up to 1500 ml during surgery or haemodilution up to 15 ml/kg does not require an additional dose of prophylactic agent,[128] but beyond that amount, additional doses of prophylactic antibiotic should be given after fluid replacement.

3. PATIENTS AND METHODS

3.1 Study site and duration:

This study was conducted in the Department of Surgery of the University Teaching Hospital, Lusaka, from August 2004 to May 2006.

3.2. Study design:

This study was a prospective randomised case control study

3.3 Study sample size:

The sample size calculation was based on the estimation of the rate of SSI at UTH in patients receiving the usual "post-operative antibiotic prophylaxis" to be 30%, and on the expectation of reducing this rate to 10% with the new single dose pre-operative prophylactic antibiotics. The level of the power of the study was set at 95 percent and that of the statistic significance at five percent (p value=0.05). The following formula was used: $N = \frac{[(p1.q1) + (p2.q2)_x 7.84]}{(p1-p2)^2}$

where N=sample size, p1 is the prevalence rate of wound infection (30), q1 is the percentage of absence of wound infection(70), p2 is the new reduced wound infection rate desired after intervention (10), q2 is the percentage of no wound infection after intervention(90) and 7.84 is a constant factor.

According to the calculation the sample size was 118. But in actual fact, we were not able to recruit the exact number of study subjects only 80 were enrolled.

These 80 patients were divided into two groups: Study group comprised 41patients and control group 39 patients.

3.4. Sampling technique:

The non-probability convenience sampling technique was used. Any consenting patient who presented to the department of surgery for abdominal surgery during the stated study period and fulfilling the inclusion criteria was selected.

3.5. Randomisation:

Patients were divided into two groups, i.e. the *study group* and the *control group* To avoid bias, small cards bearing the study groups and study number (from 001 to 118) were placed into a box from which each study subject was drawing a card, determining whether he/she was in the study or control: cards marked with an odd number placed the subjects into the study group, while those with an even number entered study subjects into control group.

3.6. Inclusion criteria:

Patients of either sex, aged between 21 to 70 years undergoing any elective abdominal surgery with class I (clean) and class II (clean-contaminated) operative wounds were eligible to enter the study: that is any operation in which the peritoneum was to be opened (*laparotomy*). All patients eligible to the study were fully clerked to ascertain they fulfill criteria for inclusion into the study.

3.7. Exclusion criteria:

Age below the 21 and above 70 years, renal failure, pregnancy and know state of immunosuppression like diabetes, AIDS stage IV (World Health Organization Classification System for HIV) were excluding criteria. Patients with contaminated or dirty wounds were not included in the study, neither were clinically anaemic and malnourished patients. Apart from the fact that study group patients were to receive antibiotics post-operatively and control group patients a single dose antibiotic pre-operatively, they were no other obvious and deliberate demographic, social and physical variables differentiating them.

All selected patients for the study signed an informed consent to finalise their enrolment into the study. The usual preparations of the pre-operative patients at UTH were not modified in either group.

Data was collected on a standardised data sheet then into a data base before analysis. The date collection form is shown in Appendix B.

Within one hour of the laparotomy incision, the study group patients received a one gram single dose of ceftriaxone, a third generation cephalosporin and metronidazole, which were used for antibiotic prophylaxis.

Ceftriaxone was chosen on account of several reasons: broad spectrum of antimicrobiocidal activity including most gram negative, positive enterobacteriaceae (pseudomonas aerogenosa included) and skin gram positive cocci; low toxicity; Pharmacokinetically good distribution in all the body tissues;[129,130] relative affordability and availability(manufactured in some pharmaceutical firms in Zambia). Metronidazole was added for its anti-anaerobic activity.

The administration of the drug was done intravenously in the operating room. No more antibiotic were given to these patients in the post-operative period.

Patients in the control group were given, only in the postoperative period, three different antibiotics for four to five days: gentamicin 80mg eight hourly; crystalline penicillin 2000000 I.U. six hourly and metronidazole five hundred mg eight hourly. The administration of the antibiotics was done intravenously in the patients' ward. This is routine practice at UTH

All the operations were done under general anaesthesia. Prior to the laparotomy incision for patients of either group, the skin preparation was done using the

available antiseptic solution(s) on that day: savlon, 20 percent iodine and 70 percent methylated spirit, or savlon and 20 percent iodine, or savlon and 70 percent methylated spirit, or 20 percent iodine and 70 percent methylated spirit, or just savlon alone.

All the patients were draped and incision made and the actual procedures done. The surgeon was not controlled: the operation was done according to the surgeon's usual technical routine without altering anything.

The total blood loss and duration of the operation were recorded. All the wounds were closed primarily.

Post-operatively, patients of either group had their body temperature monitored on 6 hourly basis. Operation wounds were exposed between 24 and 48 hours post-operatively in both study and control group patients. The cleaning was done on daily basis using an antibacterial soap and clean water.

Each patient, regardless of the group s/he belonged to, was seen and examined daily by the doctors in order to elicit any symptom(s) and sign(s) of wound infection. Horan SSI definition and classification were used[15] to diagnose surgical site infection in our patients. However we adjusted this definition to suit our context and setting. Adjustments are shown in appendix A.

For those who showed signs of wound infection, pus swab was collected for microbiological analysis (microscopy, culture and sensitivity) and were be offered treatment according to the UTH care standards.

Wound stitches were removed not later than day 10 post-operative in those who developed no surgical site infection. After discharge, wounds were reexamined weekly for further three weeks. Though remained in the study, patients from either group developed SSI were no longer required to proceed with follow up visit(s). Patients from both groups were discharged from the study on 30th day post-operatively. The cost of antibiotics and other consumables used by each patient were calculated. The calculation was based (at the time the study was under way) on the cost of antibiotics administered to each patient, syringes and needles giving sets and water for injection used in administering those drugs. However the cost for working man hour for the staff administering the antibiotics was not calculated.

Results were expressed as mean+ standard deviation for continuous variables (e.g. age, duration of stay in hospital and operation time) and number (percentage) for categorical data (e.g. gender, surgical outcome etc). Results were tested by Chi-square test. A p-value of <0.05 was considered as statistically significant. Calculations were done on SPSS.

ETHICAL CONSIDERATIONS

This research project involving human beings was approved the Research Ethics Committee of the University of Zambia (ref:002-04-04). All study participants gave an informed consent to freely be included in the study. Even after freely consenting to the participation in the study, any one was free to withdraw anytime though this was not encouraged. The study subjects were treated with dignity and respect.

Study subject record confidentiality was maintained.

4. RESULTS

A. Introduction

Results of this study are presented are described in three headings: descriptive, infection factors and outcome.

Two groups were followed up as stated above. Study group was given antibiotic prophylaxis pre-operatively and the Control group was given antibiotics post-operatively. The study group had 41 patients and the control group had 39 patients.

B. Descriptive

i. Age: The age ranged from 21 to 70 years in both groups. The mean age was 38.4± 12.4 SD in the study group, while for the control group it was 38.0±13.9 SD. The median age for the study group was 36 and 35 for the control group. There was no significant difference between the two groups in terms of age distribution: p value= 0.111.

ii. Sex: They were 13 (31.7 percent) females and 28 (68.3 percent) males in the study while the control group consisted of 15 (38.5 percent) females and 24 (61.5 percent) males. Figure 1 and 2 depict demographic data of the study participants.

C. Factors predisposing to infection

i. Types of operations: In the study group, there were 12 (29.3 percent) operations for bowel surgery; nine (22.0 percent) exploratory laparotomies; four (9.8 percent) gastro-enteric surgery; one (2.4 percent) adhesiolysis; three (7.2 percent) biopsy; two (4.9 percent) splenectomies; four (9.8 percent) non hollow organ repairs; five (12.2 percent) biliary tract surgery and one (2.4 percent) salpingo-oophorectomy.

For the control group patients, 16 (41.0 percent) operations were for bowel surgery; five (12.8 percent) exploratory laparotomy; three (7.7 percent) gastroenteric surgery; four (10.2 percent) adhesiolysis; four (10.2 percent) biopsy; two (5.2 percent) splenectomy; four (10.2 percent) biliary tract surgery and one (2.6 percent) salpingo-oophorectomy. Bowel surgery represents 35 percent all the operations. Figure 3 shows the different types of operations that were performed, while figure 4 relates the surgical site infection to the type of surgery the patients had.

ii. Duration of the operations: The mean operating time was 91.2 $\pm$ 23.21 minutes in the study group and 92.7$\pm$ 29.80 minutes in the control group. The difference between the two groups was not statistically significant ($p = 0.195$).

D. Outcome

i. Surgical site infections: The surgical site infection rate in all the studied patients was 8.7 percent: 7 out of 80 patients developed SSI.

Three (7.3 percent) out of 41 patients in our study group developed surgical site infection: this represents 42.9 percent of all the infection cases and 3.8 percent of all the studied patients.

Four (10.3 percent) out 39 patients in our control group developed surgical site infection: this represents 57.1 percent of all those who developed infection and five percent of all the studied patients. Table 1 demonstrates the SSI rate and compares the study and control groups, while figure 4 relates the SSI and different types of operations. The relation between of duration of surgery and occurrence of surgical site infections is depicted in figure 5.

The duration and type of operation carried out in patients of either group has no statistically significant bearing on the development of SSIs (p value=0.321).

ii. Isolated bacteria: E.coli was isolated in 42.9 percent (three patients), staphylococcus aureus in 1 patient (14.3 percent) and proteus milabilis was isolated in one patient (14.3 percent). No organism was isolated in two patients (28.6percent) despite having obvious signs of surgical site infection as shown in figure 6.

iii. Bacterial sensitivity pattern: All the isolated bacteria were sensitive to ciprofloxacin, while 80 percent were sensitive to chloramphenicol.

iv. Post-operative hospital stay: The postoperative hospital stay was a cumulative of 241 days for all the patients in study group and a mean of 5.9 days, while for control group patients the hospital stay was 310 days cumulatively with a mean of 7.9 days. 15 (36.6 percent) patients in the study group stayed in the hospital less than five days and only four (10.3 percent) patients in control group stayed for less than five days. Table 2 illustrates the duration of post-operative hospital stay in both the study and control groups.

v. Cost of antibiotic prophylaxis: The total cost of pre-operative antibiotic prophylaxis was calculated to be K12500 per patient, while that of post-operative triple antibiotic therapy was K102000.

We did not calculate the time spent by the nursing staff administering antibiotics to patients. Figure 8 displays the comparison of costs between the pre-operative and post-operative antibiotic prophylaxis.

	Number of operations	Number of SSIs	SSI rate
Study group	41	3	**7.3 %**
Control group	39	4	**10.3 %**
Total	**80**	**7**	**8.7 %**

Study group = prophylaxis with pre-operative single dose antibiotic; Study group = prophylaxis with post-operative multiple dose antibiotics

Table 1: Surgical site infections

	Cumulative post-operative hospital stay (in days)	Post operative hospital mean stay (in days)
Study Group	241	5.9
Control Group	310	7.9

Study Group = prophylaxis with pre-operative single dose antibiotic; Control Group = prophylaxis with post-operative multiple dose antibiotics

Table 2: Post-operative hospital stay

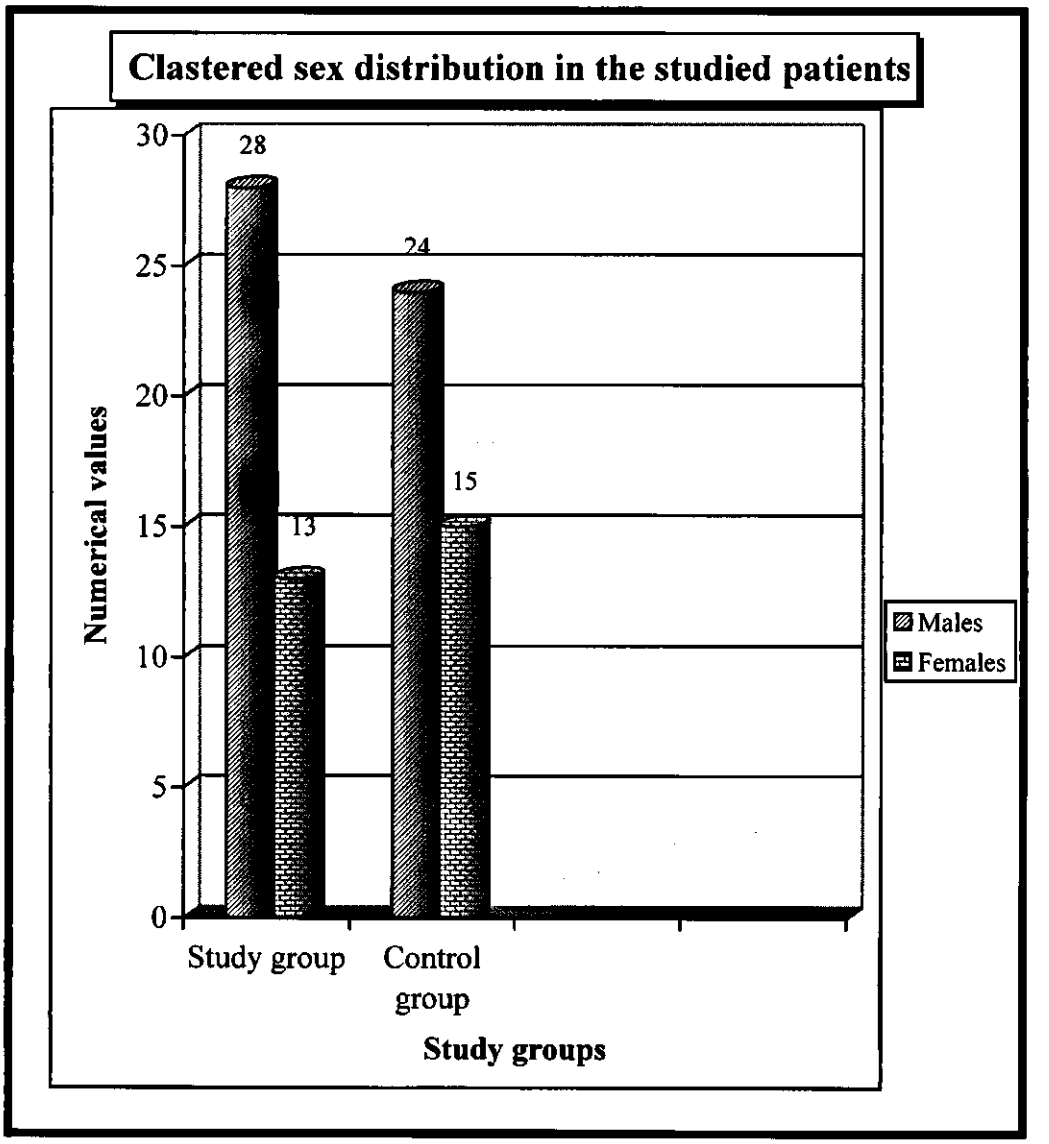

Figure 1: Sex distribution in the studied patients

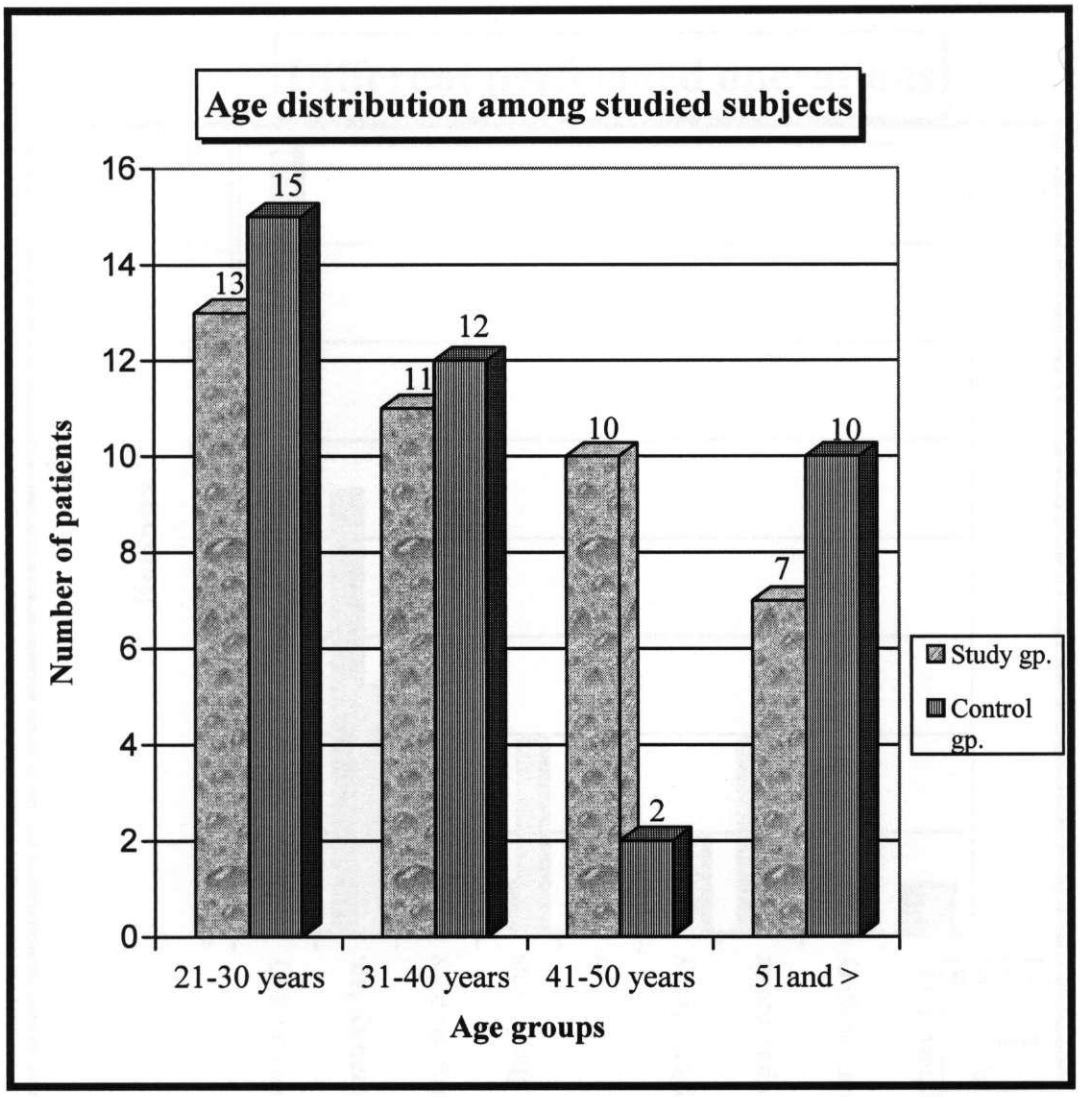

Figure 2: Age distribution among the studied subjects

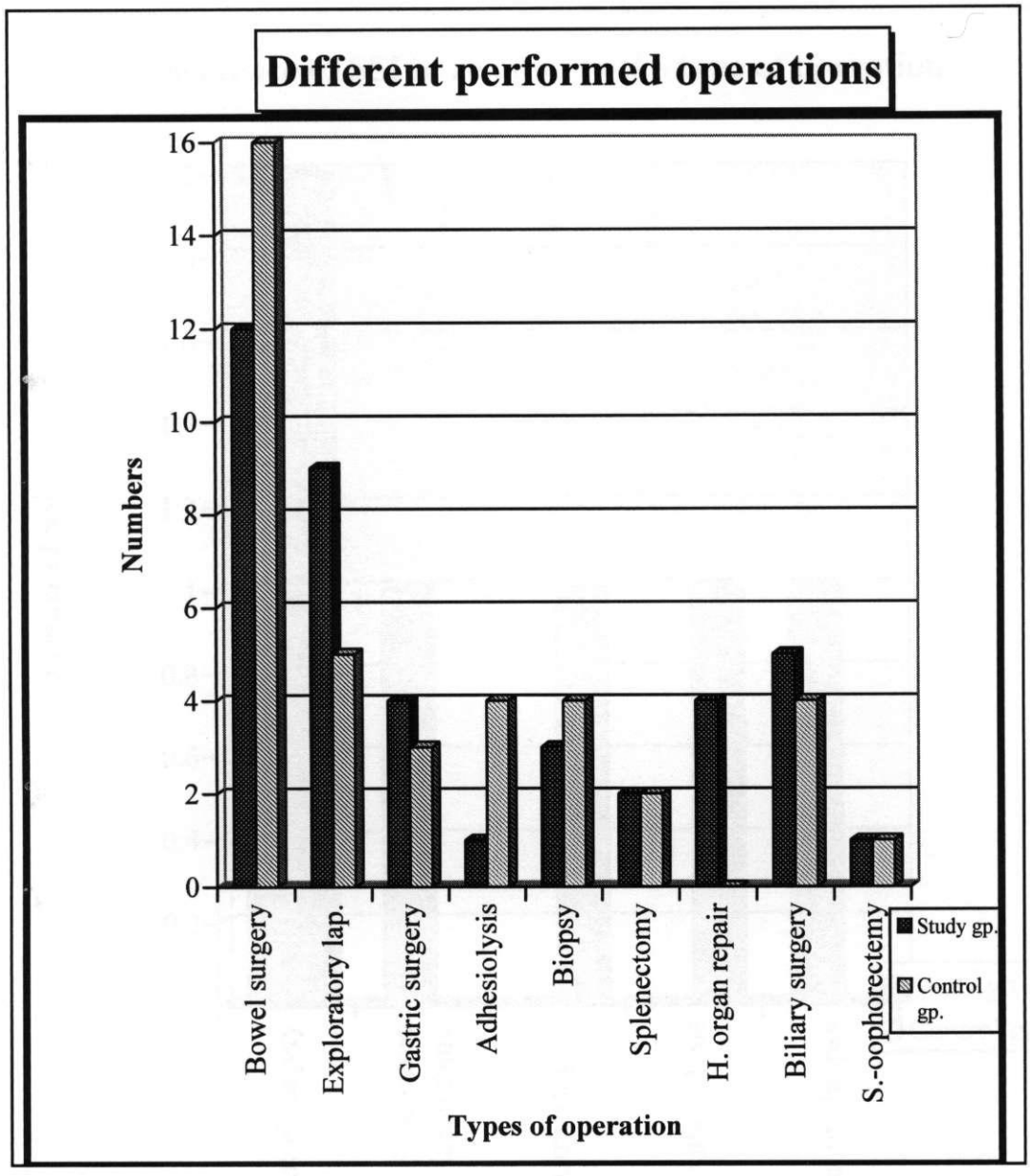

Figure 3: Different procedures performed during laparotomy

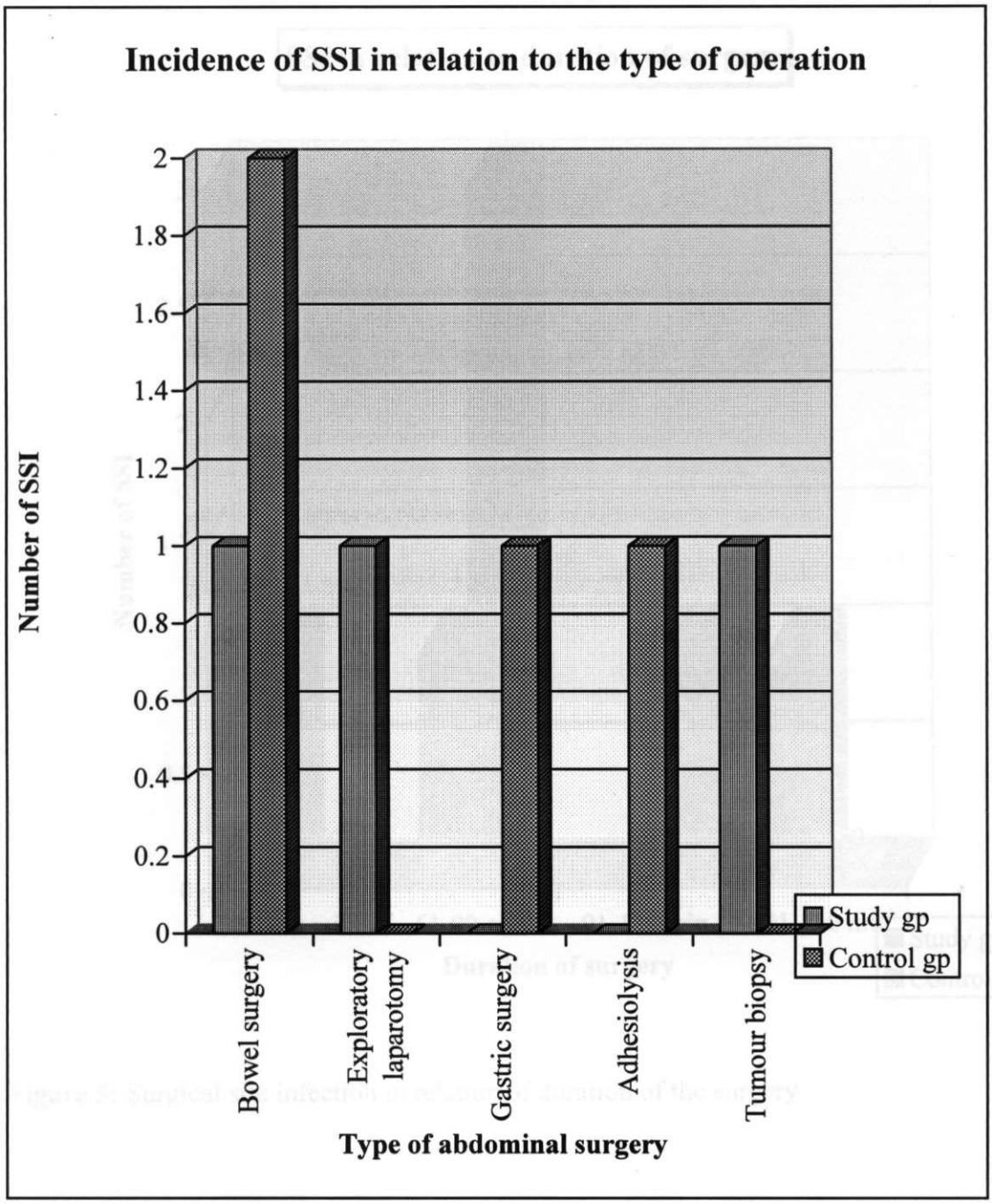

Figure 4: Surgical site infections related to different types of operations

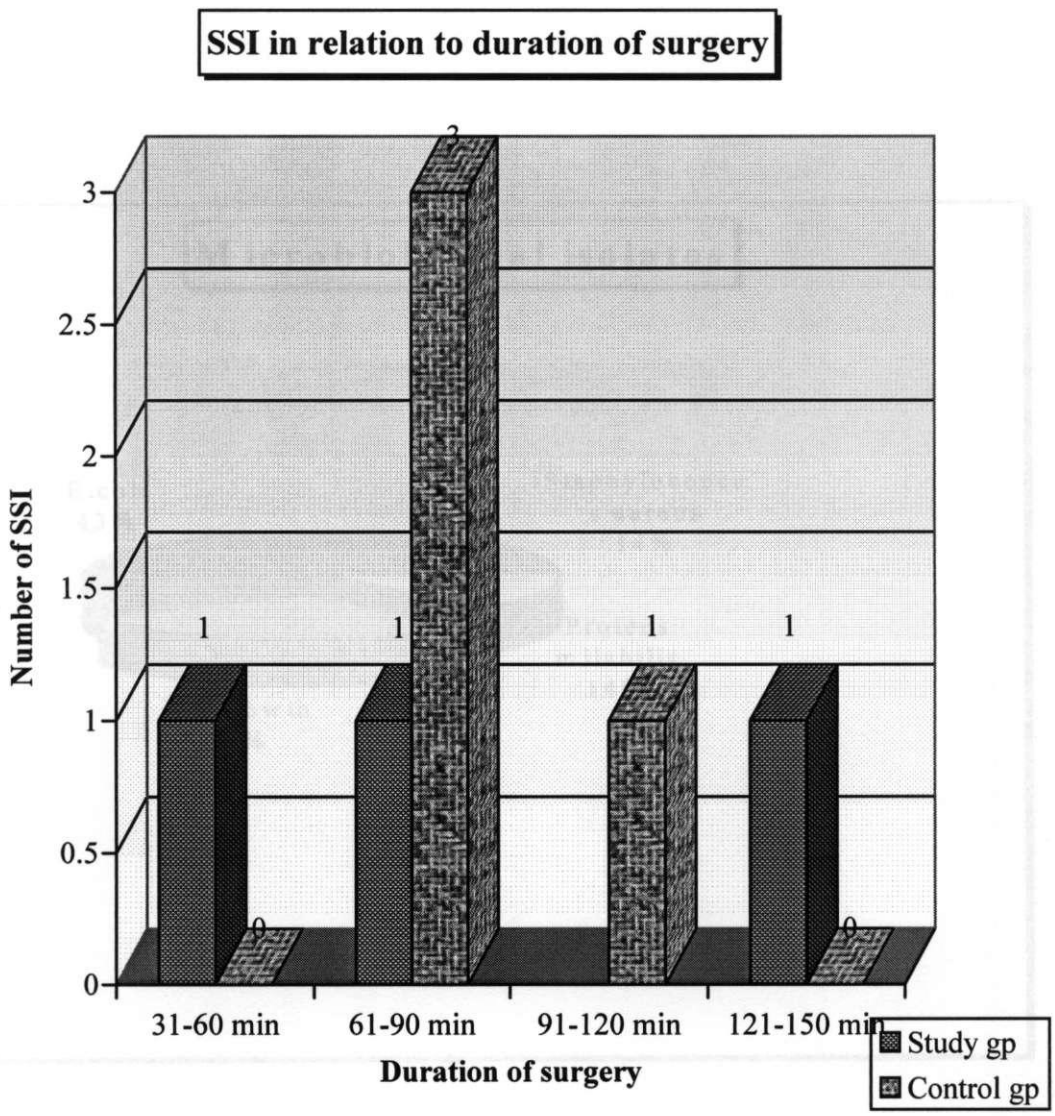

Figure 5: Surgical site infection in relation of duration of the surgery

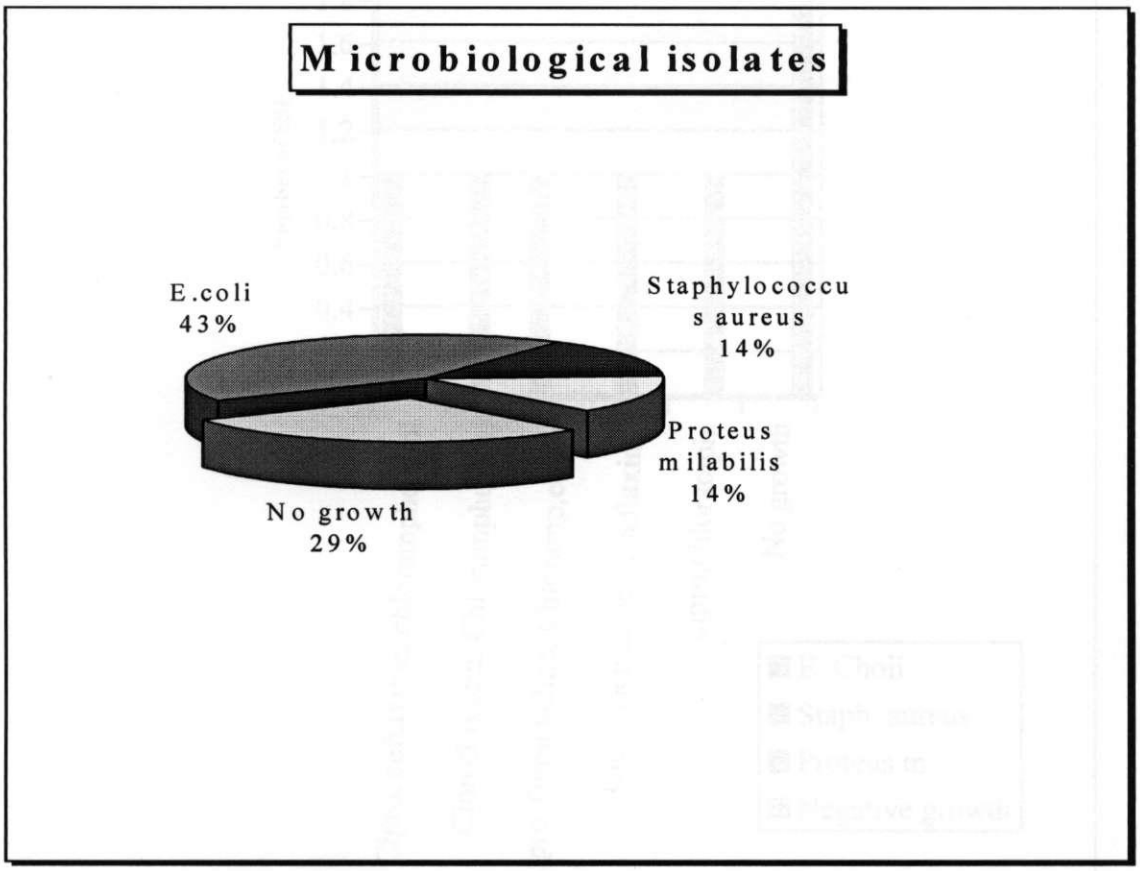

Figure 6: Bacteria isolated from SSIs

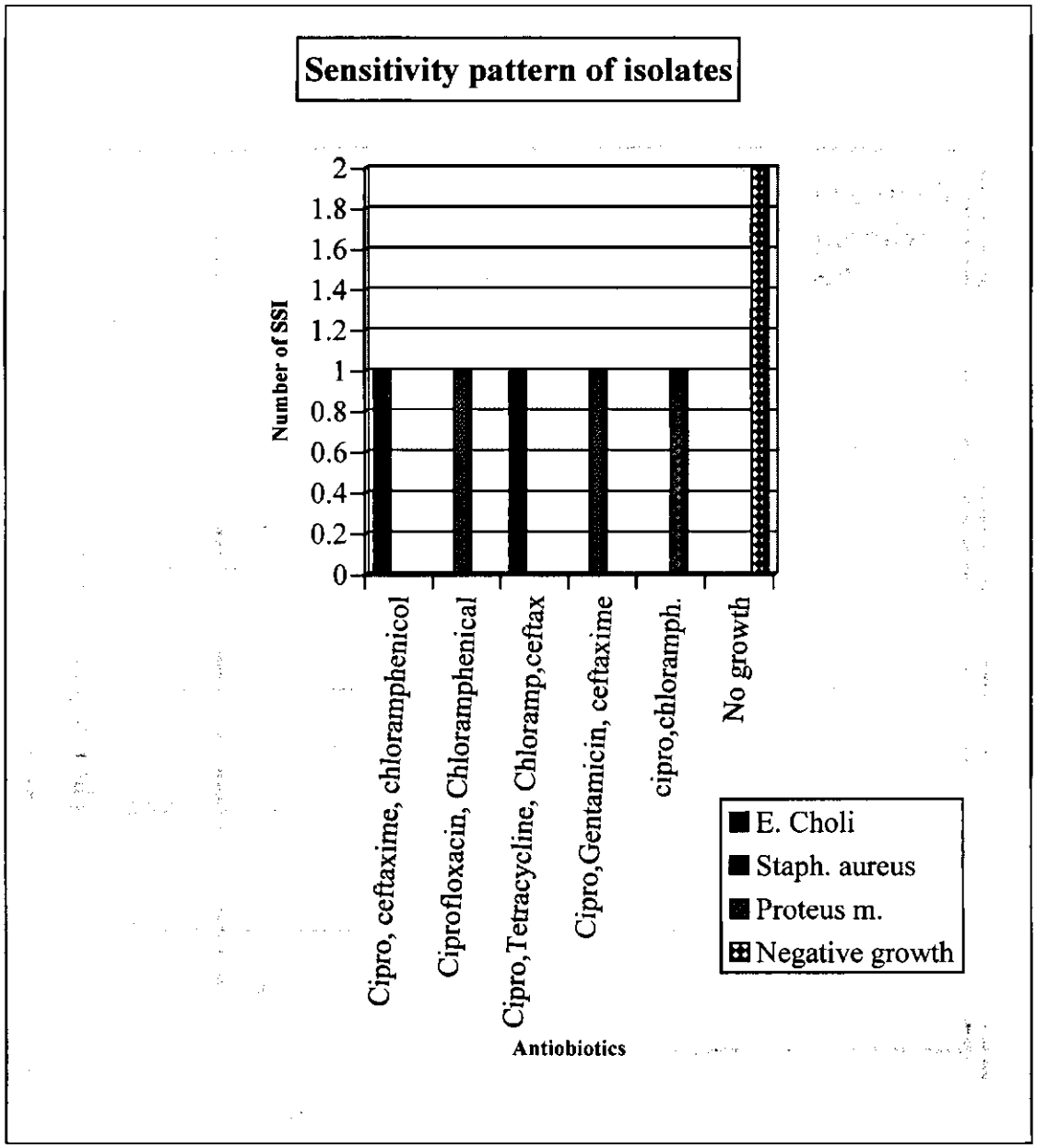

Figure 7: Sensitivity pattern of bacteria isolated from surgical site infections

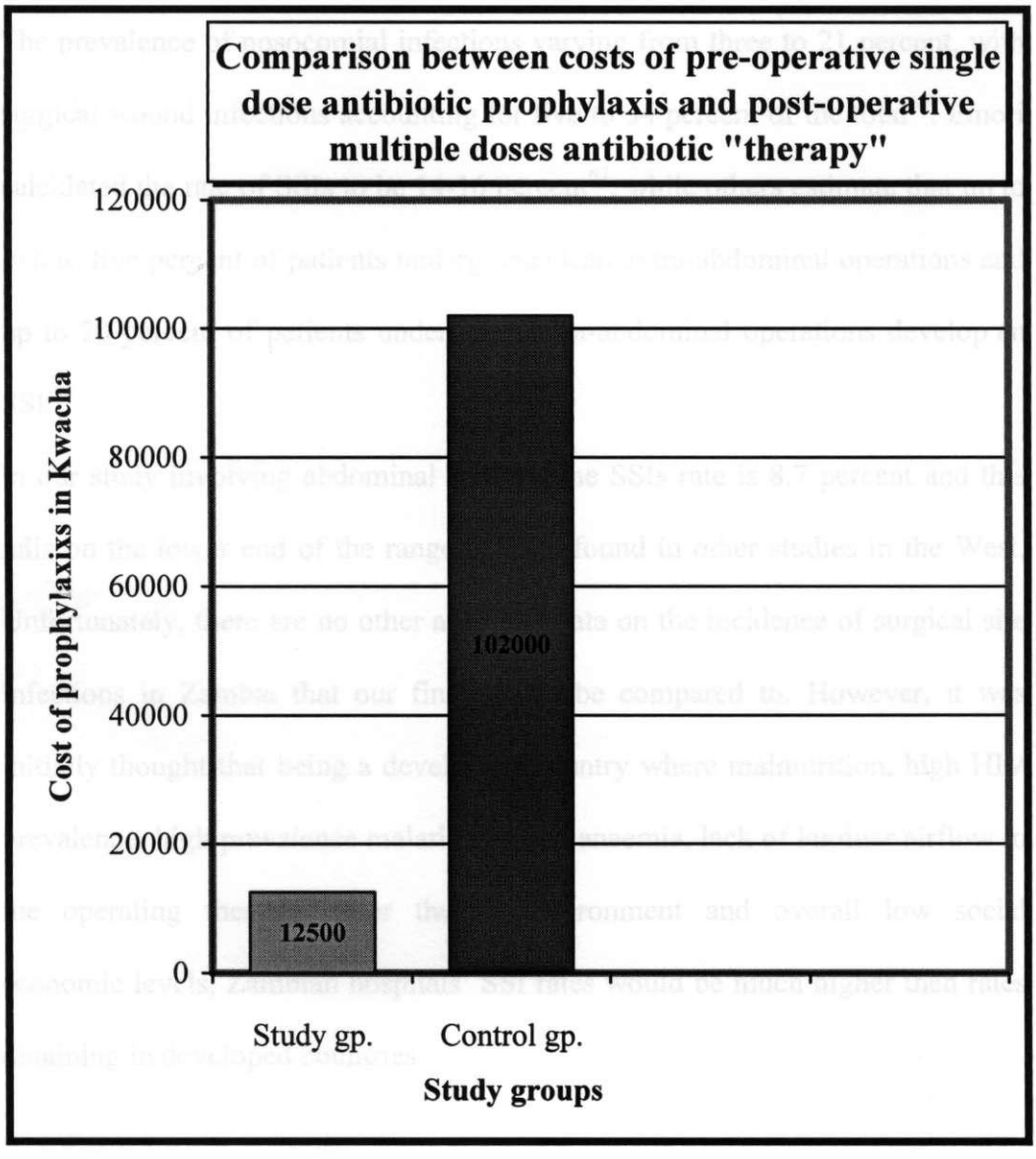

Figure 8: Cost of pre-operative single dose antibiotic prophylaxis compared with that of post-operative multiple dose antibiotic prophylaxis (in Zambian Kwacha)

5. DISCUSSIONS

The prevalence of nosocomial infections varying from three to 21 percent, with surgical wound infections accounting for five to 34 percent of the total[66]. Emori calculated the rate of SSIs to be 14-16 percent[67], while others estimate that up to two to five percent of patients undergoing clean extra-abdominal operations and up to 20 percent of patients undergoing intra-abdominal operations develop an SSI.[71]

In our study involving abdominal surgery, the SSIs rate is 8.7 percent and this falls on the lower end of the range of rates found in other studies in the West. Unfortunately, there are no other available data on the incidence of surgical site infections in Zambia that our finding can be compared to. However, it was initially thought that being a developing country where malnutrition, high HIV prevalence, high prevalence malaria induced anaemia, lack of laminar airflow in the operating theatres, poor theatre environment and overall low social economic levels, Zambian hospitals' SSI rates would be much higher than rates obtaining in developed countries.

This study nevertheless clearly demonstrates that the infection rate of 0.8 percent in elective abdominal surgery as reported in some audits of the department of surgery of the UTH Lusaka in 2004[72] was certainly an underestimation.

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Large number of factors can contribute to the development of SSIs. Appropriately administered antibiotic prophylaxis reduces the incidence of SSIs. Antibiotic prophylaxis is only one relatively minor effort among numerous preventive measures, but the efficacy and impact of antimicrobial prophylaxis has clearly been demonstrated to be very significant.[7]

In developed countries, single dose antibiotic has proven to be an effective prophylaxis in abdominal surgery [4]

Antibiotic prophylaxis as a preventive measure for SSIs is best given pre-operatively and intravenously[82-85] Administering parenteral antibiotics prior to the surgical incision ensures that adequate tissue and serum antimicrobial levels are present at the time of the contamination, that is, for the duration of the operation, serum and tissue drug levels that exceed the MICs for the organisms likely to be encountered during the operation.[92,93].

In extra-abdominal clean surgery, the rate of SSI is 0.6 percent when prophylactic antibiotics are administered in preoperative period, while the rate rise to 3.3 percent when the administration of the same antibiotics is done in the post-operative period.[93] In abdominal surgery, incidence of wound infection could be cut significantly by timely administration of prophylactic antibiotic in operations on the stomach (22 to four percent), on the biliary tract (11 to two percent) and large bowel (16 to six percent) when antibiotic prophylaxis is given pre-operatively, but the initiation of antibiotic postoperatively gave almost the

same wound infection rate as if antibiotic had not been given at all (15 and 16 percent, respectively)[97].

From all of these, it is clear that pre-operative prophylaxis is much better than the post-operative one in terms of reducing SSIs. However, as depicted in table 5, our study showed no significant statistical difference between the two regimens, as objectively measured by the SSI rate in the group of patients that received pre-operative single dose antibiotic and that of patients who received triple antibiotics post-operatively): the SSI=7.3 percent and SSI=10.3 percent respectively with P value=0.642. It is uncertain whether our study small sample size could explain this rather unexpected finding.

Isolated pathogens from SSIs are frequently found to be *Staphylococcus aureus*, coagulase-negative staphylococci, *Enterococcus* spp., and *Escherichia coli.* There is an increasing proportion of SSIs caused by antimicrobial-resistant pathogens, such as methicillin-resistant *S. aureus* (MRSA)[16,17,18,19].

When mucous membranes or skin is incised, the exposed tissues are at risk for contamination with endogenous flora. These organisms are usually aerobic gram-positive cocci (e.g., staphylococci), but may include fecal flora (e.g., anaerobic bacteria and gram-negative aerobes) when incisions are made near the perineum or groin. When a gastrointestinal organ is opened during an operation and is the source of pathogens, gram-negative bacilli (e.g., *E. coli*), gram-

positive organisms (e.g., enterococci), and sometimes anaerobes (e.g., *Bacillus fragilis*) are the typical SSI isolates[46]

Our study concurs with these bacteriological findings by other studies: enterococci (E.coli and proteus milabilis) were isolated in 57.1 percent and staphylococcus aureus in 14.3 percent. However in 28.6 percent of SSIs there was no growth as portrayed in figure 6.

Post-operative hospital stay: The postoperative hospital stay was a cumulative of 241 days for all the patients in study group and a mean of 5.9 days, while for control group patients the hospital stay was 310 days cumulatively with a mean of 7.9 days. 15 (36.6 percent) patients in study group stayed in the hospital less than five days and only four (10.3 percent) patients in the control group stayed for less than five days. Table 2 illustrates the duration of post-operative hospital stay in both the study and control groups.

If the patient has had an extensive preoperative hospitalization (more than 4 days), colonization of the patient with hospital-based microbes is likely and appears to increase the rate of SSI.[12]

Looking at the total cost of pre-operative single dose prophylactic antibiotic, K 12500 was spent on each patient. This includes the cost of ceftriaxone (K 7800), metronidazole (K 4000) and that of one syringe and one needle used to administer the medicine.

As seen in the results, the cost of post-operative "antibiotic prophylaxis" cost K 102000. This amount included the cost for drugs and syringes and needles. For four to five days, crystalline penicillin, gentamycin and metronidazol cost K 12500. It is obvious that for patients in the control group, the nursing staff spent more time administering antibiotics thrice or four times a day for four to five days than the time spent administering a pre-operative single dose. Had the cost for antibiotic administration time been converted into monetary value, the post-operative antibiotic patient group would still have less cost-effective.

Comparing the cost of the two different prophylaxis regimens, it very clear that pre-operative antibiotic prophylaxis in this study is 12 times cheaper and therefore much more cost effective than the "post-operative antibiotic prophylaxis. The use of the former type of prophylaxis can allow the hospital or patients to save K 89500 per patient than when the latter is used.

Statistical analysis using SPSS bivariate table showed raw observed frequencies as being 3 and 4 (number of SSIs observed in study and control group respectively) therefore making it lesser than the recommended 5, the expected frequencies were also too low for an appropriate and meaningful use of chi square. It has been therefore difficult to test the statistical significance and thereafter measure the degree of correlation and association between the observed infections in this study and the regimen of antimicrobial prophylaxis in question.

6. CONCLUSION

This study shows a surgical site infection incidence of 8.7 percent in eighty patients who had abdominal clean and clean-contaminated operation. All the surgical site infections were superficial and 14.2 percent clinically manifest within the first seven days of surgery.

There was no statistically significant difference (with regard to reduction of surgical site infections) between the study group of patients who had pre-operative single dose prophylactic antibiotic and the control group patients who had their "antibiotic prophylaxis" after surgery. However this unexpected finding which is at variance with literature might be attributed to the fact that the number of patients studied was only 66.6 percent of expected sample size.

Escherchia coli is the most isolated bacteria in pus swabs from patients who had surgical site infection. All the cultured pathogens are sensitive to ciprofloxacin and 80 percent of were sensitive to chloramphenicol.

The single dose pre-operative prophylactic antibiotic is (eight times) more cost effective that the current UTH post-operative triple antibiotic therapy.

7. RECOMMENDATIONS

1. Considering that this study showed no statistically significant difference in prevention of SSIs between patients who receiving pre-operative prophylaxis and those receiving it post-operatively, and taking into account that it proved that single dose pre-operative antibiotic prophylaxis is way too cost-effective than post-operative antibiotic therapy, we recommend to the UTH Management and the Department of Surgery to adopt the practice of pre-operative prophylaxis in patients undergoing major abdominal surgery.

2. We further recommend a similar but larger study to be carried out to help identify other benefits, which may be derived from the single pre-operative antibiotic prophylaxis.

3. Lastly, we recommend that normal elective operating schedules in UTH Phase V theatres be resumed for both the benefit of patients and trainee surgeons.

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APPENDIX A

Criteria for Diagnosing a Surgical Site Infection (SSI)[15]

1. Superficial Incisional 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 following:

1. Purulent drainage, with or without laboratory confirmation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat and superficial incision is deliberately opened by surgeon, unless incision is culture-negative.
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.

Do not report the following conditions as SSI:

A. Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration).
B. Infection of an episiotomy or newborn circumcision site.
C. Infected burn wound.
D. Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI).

Note: Specific criteria are used for identifying infected episiotomy and circumcision sites and burn wounds.[129]

2. Deep incisional SSI

Infection occurs within 30 days after the operation if no implant† is left in place or within 1 year if implant is in place and the infection appears to be related to the operation and infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision and at least one of the following:

1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site.
2. 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 (>38°C), localized pain, or tenderness, unless site is culture-negative.
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.

Notes:

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

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

3. Organ/space SSI

Infection occurs within 30 days after the operation if no implant† is left in place or within 1 year if implant is in place and the 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:

1. Purulent drainage from a drain that is placed through a stab wound into the organ/space.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of an organ/space SSI by a surgeon or attending physician.

Our definition for SSI

1. Superficial surgical site infection: Infection that occurred within 30 days after the laparotomy and involved only skin or subcutaneous tissue of the incision characterized by one or more of the following signs: local redness, swelling, purulent discharge, local tenderness and heat.
2. Deep surgical site infection: Infection that occurred within 30 days after the laparotomy and involving deep soft tissues like abdominal muscles or fascia, presenting with purulent discharge and or wound dehiscence.
3. Organ or space surgical site infection: Infection that occurred within 30 days after the laparotomy involving the organ or space opened during the operation presenting with pus collection or infected fluid (confirmed by bacteriology) within the organ or space.

APPENDIX B

DATA SHEET

I. DEMOGRAPHIC DATA

1. *Study number*:..... Name:.....
2. *Group after randomisation* (group I or II): .....
3. *Sex*: F=1, M=2: .....
4. *Age*: .....
5. *Marital status*: Married=1, Divorced=2, Single=3, Widowed=4: .....
6. *Residence*: Town = 1, Rural = 2: .....
7. *Education*: University/college=1, secondary=2, Primary=3 None =4: .....
8. *Occupation*: Formal employment = 1, Informal employment = 2, Self-employed= 3, Non employed = 4: .....

II. PAST MEDICAL AND SURGICAL HISTORY

9. Any *previous laparotomy? If yes, when was it done?* Within the last one month=1, Within the last three months=2, More than three months ago=3: ...
10. *Any current surgical infection*? Yes=1, No=2. If yes: (specify) .....
11. *If the answer to number 10 is yes, estimate in centimeters the distance between the infection focus and the expected operation incision line*: .....cm
12. *Current medical condition:* (specify).....

III. PRE-OPERATIVE PREPARATIONS

13. *Number of days in admission before surgery*: .....
14. *For bowel surgery*: .....

a. Three doses of metronidazol + gentamycin orally a day prior to the operation + Saline enema on the pre-operative day + Fasting on day one pre-operative + Absolute liquid diet on day two pre-operatively =1,
b. Three doses of metronidazol & gentamycin orally a day prior to their operation + Saline enema on the pre-operative day + Fasting on day one pre-operative = 2
c. Three doses of metronidazol & gentamycin orally a day prior to their operation + Saline enema on the pre-operative day = 3
d. Three doses of metronidazol & gentamycin orally a day prior to their operation = 4
e. None of the above=5

15. D*id the patient have any general bath using an antibacterial soap the evening before the operation day*? Yes = 1, No = 2 : .....
16. *If the patient required shaving, it was done*: In theatre = 1, Within 6 hours of the operation = 2, More than 6 hours before the operation = 3, Not applicable = 4 : .....

17. *Interval between the administration of antibiotics and the making of laparotomy incision*: .....min.
18. *Skin preparation with*: Savlon + iodine + methylated spirit = 1; Savlon + iodine = 2, Savlon + Methylated = 3; Iodine+ methylated spirit= 4; Just one solution = 5: .....
19. *Administered dose of ceftriaxone*: .....mg/kg
20. *Administered dose of metronidazol*: .....mg/kg

IV. INTRA-OPERATIVE EVENTS

21. Type of the operation:.....
22. *Estimation of total blood loss*: .....ml
23. *If the intra-operative blood loss is greater than 1000ml, was ceftriaxone dose repeated?* Yes = 1, No = 2: ...
24. *Any gross contamination during surgery?* Yes =1, No = 2: ...
25. *Total duration of the operation*: .....min.
26. *If the operation lasted for > than 3 hours, was the ceftriaxone dose repeated?* Yes =1, No = 2: .....

V. THE POST-OPERATIVE

27. *For group I patients, the interval between the closure of laparotomy incision and the first dose of antibiotics*: .....min.
28. *Interval between the wound closure and the first wound exposure*: .....hours
29. *Was the wound cleaning adequate*? : Yes = 1, No = 2 : .....
30. *Administered dose of gentamycin*: .....mg/kg
32. *Administered dose of metronidazol*: .....mg/kg
33.
34. *Administered dose of crystalline penicillin*: .....mg/kg
35. 33. *Did the patient have any fever*?: Yes = 1, No = 2: .....
34. If yes, how long after surgery? : .....days
35. *Post-operative hospital stay* (including the operation day): .....days

VI. FOLLOW UP

36. *Did the patient develop surgical site infection at any time in the post-operative period* (please refer to Surgical Site Infection diagnosis)? Yes = 1, No = 2: .....
37. *If yes, specify at least 2 symptoms/signs of infection observed in the patient*: .....
38. How *long after the operation did the symptoms/signs begin*? : .....days
39. *In case of wound infection, what was (were) the isolated organism(s)on culture?*.....
40. *Which drug(s) was (were) the organism(s) sensitive to*? : .....
41. *Which drug(s) was (were) the organism(s) resistant to*? : .....
42. *How many follow up visits did the patient have*? : .....

APPENDIX C

INFORMATION SHEET

1. This is a research study aiming at finding out the number of patients who will have infection of their wound after operation.
2. This research is being done to help reduce the total cost of antibiotics given to patients after their operation.
3. The hospital usually gives patients antibiotics for 5 days after the operation to prevent infection. This study will help to reduce that period to only one day.
4. A group of patients undergoing abdominal operation will be chosen. This group will be divided into two: one group will receive 5 days of antibiotics after the operation. The other group will receive antibiotics once before the operation. These patients will be observed as to whether they develop wound infection or not. This will help to decide which antibiotic regimen is better.
5. The antibiotics that will be used in this study are well known drugs that many of other surgical and non-surgical patients in UTH, as well as in other hospitals use (ceftriaxone and metronidazol on one hand and gentamycin, metronidazol and crystalline penicillin on the other hand).
6. When enrolled into the study, a participant might be in the group that will receive the antibiotics through the vein just once shortly before the operation or in the group of patients that will receive the antibiotics several times after the operation.
7. The hospital/investigator will provide the drugs required.
8. Like many other drugs those antibiotics might sometimes cause some mild side effects: Nausea, abdominal discomfort, vomiting, rash, diarrhoea, fever, joint pains, headaches...etc. These are reversible when the medication is discontinued
9. After the operation every study participant will be seen and examined by doctors to check whether he/she has any wound infection.
10. Each participant will be required to come for review on weekly basis four times after discharge from the hospital, and the duration of the study is 30 days from the operation day.
11. Participant to the study will be free to come back to the contact doctors any time he/she has any operation related problem within the period he/she will be in the study.
12. Participation in this study is voluntary and one might chose to withdraw without suffering any penalty or losing any of the patient's rights: receiving medical care.
13. The investigator might decide to terminate a person's participation into the study when circumstances dictate it, for the best result of the study.

14. Agreement to take part in this study does not place any obligation to the investigator or the hospital authorities other than that due to any other patient at the hospital
15. Should any surgery or drug related complication(s) occur(s), study participants will be offered treatment according to the UTH care standards.
16. Records will be identified by a study number not by the participant's name; the two will be unlinked in order to safeguard confidentiality. The information provided by participants will not be used for their detriment. Their names will not used in any report.
17. Benefits associated with participation in the study: Participants in the study will have the following:

    a. Close monitoring after the operation
    b. Free of charge antibiotics
    c. Prompt treatment in case of surgical site infection
    d. 4 follow up visits

18. The study final report will be accessible in the event one might be interested to know the study results.

19. Contact people are:

1. Dr. E. Shirimpaka, Department of Surgery, UTH

Tel: 095432751 or 01256143

2. Prof. Gerish Desai Department of Surgery, UTH

Tel: 097883068

3. Mr. Kasonde Bowa, Department of Surgery, UTH

Tel: 097849302 or 01226604

APPENDIX D

INFORMED CONSENT FORM

I----------, have received clear explanations of this research study on the role of use of antibiotics in patients having abdominal operation at UTH. I understand that:

1. This study is aiming at finding out the number of patients receiving antibiotics who will have infection of their wound after operation, and that it is being done to help reduce the cost the total cost of antibiotics given to patients around the period of their operation.

2. That once enrolled in this study I can be either be in the group of patients that will receive 5 days of antibiotics after the operation or in that which will receive antibiotics once before the operation.

3. That regardless of group I belong to, I will be closely observed during my hospital stay to rule out or detect any wound infection. This will help doctors running the study to decide which antibiotic regimen is better.

4. That antibiotics which will be used in this study are well known drugs that many of other surgical and non-surgical patients in UTH, as well as in other hospitals use (ceftriaxone and metronidazol on one hand and gentamycin, metronidazol, crystalline penicillin on the other hand).

5. That the hospital/investigator will provide the required antibiotics.

6. That like any other drug those antibiotics might sometimes cause some mild side effects: Nausea, abdominal discomfort, vomiting, rash, diarrhoea, fever, joint pains, headaches.... These are reversible when the medication is discontinued

7. That I will be required to come for review on weekly basis four times after discharge from the hospital, and that the duration of the study is 30 days from the operation day.

8. That I am free to come back to see the contact doctors any time I have any operation related problem within the period I will be in the study.

10. That participation in this study is voluntary and I might chose to withdraw without suffering any penalty or losing any of the patient's rights: receiving medical care.

11. That the investigator might decide to terminate my participation in the study when circumstances dictate it, for the best result of the study

12. That the agreement to take part in this study does not place any obligation to the investigator or the hospital authorities other than that due to any other patient at the hospital

13. That should any surgery or drug related complication(s) occur(s), I will be offered treatment according to the UTH care standards.

14. That records will be identified by a study number not by my name; the two will be unlinked in order to safeguard confidentiality. The information I provided will not be used for my detriment. My names will not used in any report.

15. That there are benefits associated with participation in the study:

a. Close monitoring after the operation

b. Free of charge antibiotics

c. Prompt treatment in case of surgical site infection

c. follow up visits

16. That in the event I am interested to know the study results, the study final report will be accessible.

17. The names of the contact doctors have been given to me.

I understand that the study does expose me to no added danger than any other patient undergoing similar operation. The methods of the study have been explained to me and do not violate my personal rights and conscious in any way.

In signing this document I agree that I do so voluntary and under no coercion from anyone.

Patient's signature/fingerprint----------Date----------

Witness' name:----------Signature:----------Date:----------