STUDY ON THE PRESCRIBING PRACTICE OF ANTIBIOTIC PROPHYLAXIS IN SURGERY AND ITS IMPACT DURING HOSPITALIZATION.

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Summary

It was proposed to undertake a prospective study of patterns of choice, timing, dose and duration of prophylactic antibiotic regimens used in different surgeries and the surgical site infection rate in Dhulikhel Hospital/ Kathmandu University Teaching Hospital (DH/KUTH), Dhulikhel, Nepal.
The study was conducted in DH/KUTH, Dhulikhel during January 2006 to May 2006. This hospital is a 160 bedded community hospital. Patients undergoing emergency or elective operations in the department of surgery were sampled for study (n=100). Patients were followed up until they were discharged from the hospital.
The study revealed that there was a practice variation in the prophylactic antibiotic use. No guideline for antibiotic prophylaxis of surgery was developed in the hospital. The first dose timing was not preoperative in all the recommended cases. The duration of prophylaxis was unnecessarily long (up to 11 days in some cases). However, the rate of infection (7%) was less than that of the rate of infections found in most of the previous studies done in the third world. *Staphylococcus aureus* was the organism responsible for majority of surgical site infections (28.5%). In all the cases *S. aureus* was sensitive to Chloramphenicol. Though the surgical site infection rate was found to be less than that of most of the previous studies, the hospital infrequently followed the internationally published guidelines for antibiotic prophylaxis.

Key words: Post operative complications, antibiotic prophylaxis, guidelines, nosocomial infections

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Introduction

Surgical prophylaxis is the use of antibiotics to prevent infections at the surgical site. Prophylaxis should be considered where there is a significant risk of infection. Antibiotic prophylaxis can not be

relied upon to overcome excessive soiling, damage to tissues, inadequate debridement or poor surgical technique. In general, antimicrobials should be directed against the likely causative organism(s) [1].

The practice of using antibiotic prophylaxis before surgery has evolved greatly in the last 20 years [2]. One-third to one-half of antibiotic use in hospital practice is for surgical prophylaxis [1]. Improvements in timing of initial administration, the appropriate choice of antimicrobial agents, and shorter duration of administration have defined more clearly the value of this technique in reducing postoperative wound infections [2].

Confusing and heated debate concerning the efficacy of prophylactic antibiotics in surgery followed the publications of clinical trials during the 1950s [2]. Errors in study design of these early efforts included non randomization, lack of blinding, faulty timing of initial antibiotic administration, prolonged antibiotic use, and incorrect choices of antimicrobial agents.

Experimental studies published during the early 1960s helped clarify many of these problems and resulted in a more evidence based approach to antimicrobial prophylaxis. Most important was the report by Burke, which demonstrated the crucial relationship between timing of antibiotic administration and its prophylactic efficacy [3]. His experimental studies showed that to greatly reduce experimental skin infection produced by penicillin-sensitive *Staphylococcus aureus*, the penicillin had to be in the skin shortly before or at the time of bacterial contamination. This important change in strategy helped correct the common error of first administering the prophylactic antibiotic in the recovery room.

As early as 1964, Bernard and Cole reported the successful use of prophylactic antibiotics in a randomized, prospective, placebo controlled clinical study of abdominal operations on the gastrointestinal tract [4]. The success of antibiotic prophylaxis noted in this early study was clearly due to the author's appropriate patient selection and wise choice of available agents, as well as the timing of administration.

Further advances in understanding of antibiotic prophylaxis in abdominal surgery occurred in the 1970s. During this decade, the qualitative and quantitative nature of endogenous gastrointestinal flora in health and disease was appropriately defined. Many prospective, blinded clinical studies in the

1980s and 1990s prompted definitive recommendations concerning the proper approaches to antibiotic prophylaxis in surgery.

Wound site infections, which are a major source of post operative illness, account approximately a quarter of all nosocomial infections. These infections number approximately 500,000 per year, among an estimated 27 million surgical procedures, and account for approximately one quarter of the estimated 2 million nosocomial infections in the United States each year [2]. Infections results in longer hospitalization and higher costs. One study done in the surgical ward of Bir Hospital, Nepal showed the overall incidence of wound infection to be 7.9% [5].

Prophylactic administration of antibiotics inhibits growth of contaminating bacteria and their adherence to surgical wound and prosthetic implants, thus reducing the risk of infection. However, improper administration of antibiotics increases the prevalence of antibiotic resistant bacteria, predisposes the patient to infection with organisms such as C*lostridium difficile* [6]. Studies have shown levels of inappropriate antibiotic use for surgical prophylaxis ranging from 30 to 90 percent, especially with respect to timing and duration [1].

This study primarily focuses on the practice of prophylactic antibiotic regimen used in different surgeries in Dhulikhel Hospital/ Kathmandu University Teaching Hospital (DH/KUTH), Dhulikhel and its impact on patient during hospitalization in terms of infection. It is anticipated that this study would provide an analysis of the practice trends for prophylactic antibiotic use in different surgical procedures. It would also highlight on the effectiveness of the different regimens and their cost. It will also help to develop the protocols for antibiotic prophylaxis in different surgeries.

The outcome and recommendations made from the study would be of use as a reference:

- To the participating hospital to develop the protocols for antibiotic prophylaxis in different surgeries.

- To Government of Nepal, Ministry of Health and Population for the evaluation of the effectiveness of therapy used and for the formulation of standard surgical guidelines on prophylactic antibiotic use in different surgeries.

- To the interested researchers/ clinicians as a reference work.

The aim of this study was to study the prophylactic antibiotic regimens used in different surgeries in DH/KUTH, Dhulikhel, Nepal.

The specific objectives of the study were to

- Evaluate the effectiveness of antibiotics in terms of absence/presence of postoperative complications/infection during hospitalization.
- Evaluate the timing of antibiotics used.
- Evaluate the duration of antibiotics used.
- Find the causative agent from the surgical site infection (if any) and check the antibiotic sensitivity of the organism responsible for infection.
- Evaluate the cost of prophylactic antibiotic regimen.

Methodology

Setting

The study was conducted in DH/KUTH, Dhulikhel, Nepal during January to May 2006. DH/KUTH is a 160 bedded community hospital. The study protocol was approved by the Department of Pharmacy Research Ethics committee of the University.

Study Design

This study was quantitative, prospective follow-up study. The patients included in the study were followed up until their stay in the hospital.

Selection of Patients

Patients undergoing surgery who met inclusion criteria as mentioned below were included in this study (n=100).

Inclusion Criteria

- Patients undergoing operations in DH/KUTH, Dhulikhel, Nepal.
- Absence of infection prior to operation.

Exclusion Criteria

- Patients willing to leave hospital without the consent of physicians.
- Minor operations for which the patients are discharged before three days.
- Minor operations for which patients are not admitted in hospital.
- Infection prior to hospitalization.
- Patients taking antibiotics at the time of hospital admission.

Monitoring Parameters

- Timing of antibiotic administration.
- Duration of antibiotic administration.
- Visual inspection for surgical site infection from the first and every subsequent dressing until the patient is discharged.
- Postoperative complications like: fever, urinary tract infection.
- Antibiotic sensitivity of microorganism which is responsible for surgical site infection.

Data Collection

Data about patient, surgery and antibiotic prophylaxis were collected in the specified forms. From the day of surgery, the data were collected with the help of documents listed below:

- Admission form (Name, age, diagnosis)
- Anesthesia form (beginning and ending time of anesthesia, surgery; antibiotic administration during the procedure; drug, dose and time of administration)
- Surgery form (reason and date of surgical procedure)
- Medicinal cardex (drug, dose, dose number, route of administration and interval, date and time of the beginning and end of the prophylaxis regimen, discharge date)
- Pathological reports.
- Nursing records.
- Daily postoperative report notes.

Data on the following outcome variables were collected:

- Wound infection
- Fever

- Urinary tract infection
- Organisms isolated in culture
- Bacterial sensitivity
- Postoperative length of hospital stay
- Antibiotic on discharge
- Cost of prophylactic antibiotic

After the completion of data collection, the cost for antibiotic was obtained from the pharmacy in hospital.

Data Analysis

The data were entered in MS EXCEL spreadsheet and analyzed using SPSS 11.5 software. The statistical tool used for the data analysis was χ^2 test. $P<0.05$ was considered statistically significant. Graphs were plotted using EXCEL 98.

Results

Age of the Patients

The age distribution of the patients was as shown in the Figure 1.

The types of surgeries, number of males and females, number of cases in each type of surgery, duration of hospital stay, duration of antibiotic prophylaxis and average cost of antibiotic prophylaxis in each type of surgery are given in Table 1.

Timing of Antibiotic Prophylaxis

In 38 out of 100 surgeries, no antibiotics were used for prophylactic purpose. In rest of the 62 cases, antibiotic prophylaxis was started preoperatively in 22 cases (35%), intraoperatively in 15 (24%) and postoperatively in 25 (41%) cases respectively.

Number of Antibiotics Used

In 62 cases, more than 70 % of the patients were exposed to, at least, two antibiotics as a prophylaxis. A single antibiotic was used in 18 (29 %), two antibiotics in 25 (40.3 %) cases and three antibiotics in 18 (29 %) cases respectively. More than three antibiotics were used only in one case.

Commonly Used Regimens

The three most commonly used regimens were the combination of ciprofloxacin and metronidazole (27.4%) followed by cefazolin (14.5%) and combination of ampicillin, cloxacillin and metronidazole (8%). The details are shown in Table 2.

Route

In almost all the cases, the route of administration was intravenous followed by oral.

Dose

It was found that the dose of antibiotic was the same as that of therapy of infection in all the cases.

Post Operative Complications

Post operative complications were observed in 18 cases. These varied from simple fever to complicated wound infections. Fever, urinary tract infection (UTI) and wound infections were observed in 5, 6 and 7 cases respectively.

Causative agents of Surgical Site infections (SSIs)

Out of the seven postoperative infection cases, two infections were caused by *Staphylococcus aureus*, one each by *Escherichia coli* and *Klebsiella pneumoniae.* In other two cases, no growth was observed whereas in one case culture was not done.

Antibiotic Sensitivity of Isolated Microorganisms

Out of two *S. aureus* infection, in one case *S. aureus* was sensitive to cloxacillin, gentamicin and chloramphenicol and in other case it was sensitive only to chloramphenicol. *E. coli* was sensitive to ciprofloxacin and amikacin. *K. pneumoniae* was sensitive to gentamicin, chloramphenicol and norfloxacin.

Figure 1

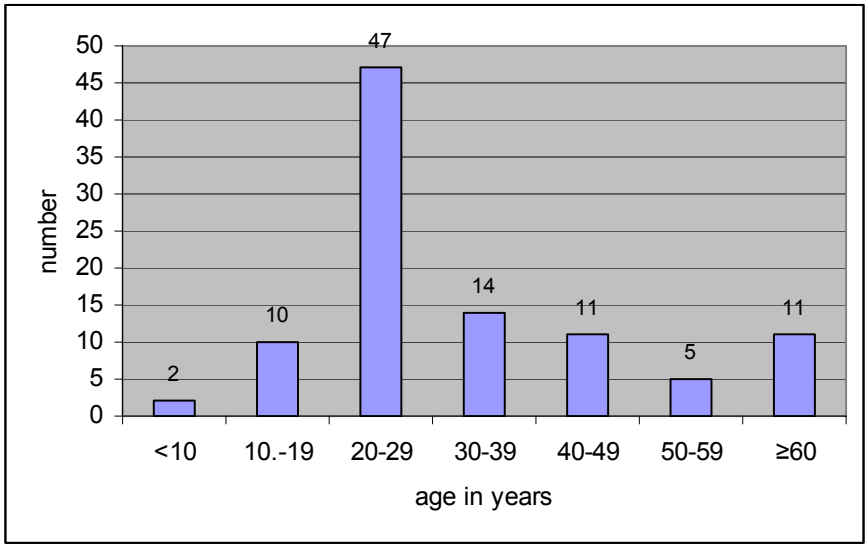

Table 1

Type of surgeries	Number (N=100)		Hospital stay (days)	Prophylaxis		Prophylaxis Duration (days)	Average Cost (NRs*)
	Male (n)	Female (n)		Used	Unused		
LSCS**	0	33	7.61±2.19	21	12	4.90±2.61	285.55±171.08
Cholecystectomy	3	15	5.72±3.01	13	5	2.92±2.75	220.46±183.61
Herniorrhaphy/ herniotommy	8	2	4.22±2.22	2	8	1±0	41.8± 27.15
TAH***/VH****	0	9	6.67±1.94	1	8	11±0	112.5± 0
Appendectomy	5	4	3.56±1.33	9	0	3±2.78	280.24±230.07
Tonsillectomy	2	3	4.8±0.84	5	0	8.6±1.67	726.57±324.35
Others	10	6	7±3.83	11	5	4.73±3.23	550.26±629.38
Total	28	72	-	62	38	-	-

NRs*= Nepali Rupees
LSCS**=Lower Segment Caesarean section
TAH***=Total Abdominal Hysterectomy
VH****=Vaginal Hysterectomy

Table 2. Commonly used regimens

S.No.	Regimen	Percentage (%)
1.	Ciprofloxacin and metronidazole	27.41 (n=17)
2.	Cefazolin	14.51 (n=9)
3.	Ampicillin, cloxacillin and metronidazole	8.06 (n=5)
4.	Ampicillin and cloxacillin	6.45 (n=4)
5.	Cefotaxime	4.83 (n=3)
6.	Ampicillin	4.83 (n=3)
7.	Ampicillin, ciprofloxacin and metronidazole	4.83 (n=3)
8.	Cefazolin, metronidazole and ciprofloxacin	3.22 (n=2)
9.	Others	25.8 (n=16)

Discussion

Length of Hospital Stay after Surgery

The length of hospital stay after operation varied according to the type of operation. It was maximum in lower segment caesarean section (LSCS) (7.6 days) and minimum in appendectomy (3.5 days). The average length of hospital stay was 5.6±1.5 days. One study done in Manipal Teaching Hospital (MTH) and Western Regional Hospital (WRH), Nepal showed that the mean length of stay in caesarean section surgery was 7.9 and 7.0 days respectively [7]. Thus the length of hospital stay was similar to that of the previous studies done in Nepal. However, the mean duration of hospital stay in an Indian hospital was 7.4 days in non infected group and 16 days in the infected group [8].

Duration of Antibiotic Prophylaxis

For most procedures the duration of antimicrobial prophylaxis should be 24 hours or less. If the operation lasts for four hours or less, one antibiotic dose is usually sufficient. Continuing antibiotic prophylaxis for longer durations than recommended is illogical and also of unproven benefits [9]. American society of health-system pharmacist (ASHP) guideline recommends continuing prophylaxis for 24 hours or less except in cardiothoracic procedures (up to 72 hours durations).

If a short acting agent is used, it should be re-administered if the operation extends beyond three hours in duration [10]. It was found that in almost all the cases the duration of total antibiotic use was higher. The long duration of prophylaxis regimen expose the patient to adverse drug reaction, increased treatment cost and certainly increases the possibility of microbial resistance, not only in these patients, but also in the hospitals [7].

A study done in an Indian hospital (Kasturwa Medical College, Manipal) showed that in 82% of the cases the prophylactic antibiotic was continued for 5 to 7 days after surgery [8]. In the present study we found that only 33.8% adhere to the recommended duration (i.e. ≤ 24 hours) [10].

Number of Antibiotics Used

More than 70 % of the patients were exposed to, at least, two antibiotics as a prophylaxis. In 29% of the cases single antibiotic was used. Two antibiotics were used in 40.3% cases, three in 29% and four in 1.6% cases. But most of the internationally published guidelines recommend one or two antibiotics for prophylactic use. However, the numbers of antibiotics used were less than in the two hospitals of Pokhara, Nepal where three antibiotics were used in 54% and more than three in 12% of the cases [7].

Commonly Used Regimens

In DH/KUTH, Dhulikhel the three most commonly used regimens were the combination of ciprofloxacin and metronidazole (27.4%) followed by cefazolin (14.5%) and combination of ampicillin, cloxacillin and metronidazole (8%). Most of the guidelines, including ASHP guideline, preferred first generation of cephalosporin (cefazolin) for the antibiotic prophylaxis but in this study ciprofloxacin and metronidazole combination was most commonly used. A study done in 10 general hospitals in Japan showed that cefazolin was most commonly used in all types of surgeries, and the proportion of surgeons who used cefazolin in first line therapy ranged from 39% (hysterectomy) to 97% (cataract surgery) [11]. It was found that the regimens used in surgical prophylaxis were widely varied even in the similar type of surgery. Variations in the choice of antibiotic, its timing and the treatment duration may have been due to the lack of protocol/guidelines in the hospital.

Commonly used surgical prophylactic antibiotics include [9]:

- intravenous first generation cephalosporins - cefazolin or cephalothin
- intravenous gentamicin

- intravenous or rectal metronidazole (if anaerobic infection is likely)
- oral tinidazole (if anerobic infection is likely)
- intravenous flucloxacillin (if methicillin susceptible staphylococcal infection is likely)
- intravenous vancomycin (if methicillin resistant staphylococcal infection is likely).

Route

In almost all cases of the present study, the route of administration was intravenous followed by oral. Almost all guidelines recommend intravenous route although some claim that oral administration prior to colorectal surgery is effective. The intravenous route followed by oral pattern also indicates that the duration of prophylactic antibiotic use is longer than that of the recommended.

Dose

It was found that the dose of antibiotic used was the same as that of therapy of infection in all the cases. This complies with most of the guidelines including the Scottish intercollegiate guidelines network (SIGN) guideline for the antibiotic prophylaxis in surgery.

Post Operative Complications

Out of 100 patients postoperative complications were observed in 18 patients that ranged from simple post operative fever to surgical site infection. In 5% patients fever was seen which was treated with NSAIDs like ibuprofen and paracetamol. In 6% of the cases, UTI was seen as post operative complication for the treatment of which antibiotics like ciprofloxacin and norfloxacin were used. In 7% of the cases postoperative wound infection was observed.

The infection rate in the Kasturwa medical college and hospital, Manipal, India was 9.5% in inpatient undergoing surgery under clean and clean contaminated categories [8]. A study done in Bir hospital, Nepal in 2002-2003 showed that the infection rate was 7.9% [5].

The rate of infection in DH/KUTH, Dhulikhel is comparable and even in lower side than in the other hospitals of Nepal (7.9% in Bir Hospital), India (9.5% in Kasturwa Medical College) and Tanzania (19.4% in Kilimanjaro Christian Medical Centre, Tanzania) [12]. However, it is greater than in the studies done in US (1.8%) [2] and UK (2.6%) [13].

Thus the rate of infection in DH/KUTH, Dhulikhel is significantly less than in Kilimanjaro Christian Medical Centre, Tanzania ($p<0.05$), $p=0.003$; not significantly different than in Bir Hospital, Nepal and Kasturwa Medical College, Manipal, India ($p>0.05$), $p=0.771$ and 0.469 respectively. However, the rate of infection is significantly higher than in the hospitals of UK ($p<0.05$), $p=0.001$.

The reason of less infection rate in DH/KUTH, Dhulikhel could be due to:

- Duration of follow up after surgery. Patients were followed up only during hospitalization. The centre for disease control (CDC) definition states that infections occurring within 30 days of surgery (or within a year in case of implants) should be classified as SSIs.
- Exclusion of dirty/infected wounds from the study. Infection rates in US national nosocomial infection surveillance (NNIS) system hospitals reported that the maximum rate of infection was in surgeries categorized as dirty (7.1%) [14].

Out of the 7 post operative infection cases (n=100), 6 were clean contaminated categories and 1 from contaminated category. In present study, 80 cases were clean contaminated. The rate of infection in clean contaminated category was 7.5%. Infection rates in US NNIS system hospital were reported to be 3.3% in clean contaminated cases. It was found that the rate of infection in contaminated category was 14.2% which was 6.4% in US NNIS system hospitals. Out of seven infections, three were in LSCS, two in open cholecystectomy and other two in laparotomy.

Causative Agents of SSIs

Staphylococcus aureus was the organism responsible for majority of surgical site infection (28.5%). Similar to present finding, a study done in Bir Hospital also showed that *Staphylococcus aureus* was the main organism responsible for infections (27.7%) [5]. It is also supported by the literature that species of staphylococcus is the cause of infection in the majority of the procedures [15]. However, in two cases no growth was seen. The absence of growth in pus culture may be due to:

- Anaerobic infection. There was no provision for the culture of anaerobic bacteria in DH/KUTH, Dhulikhel.
- Time gap between taking a swab of pus and culturing the swab in media. In such case there remains a chance of death of microorganism before its transfer to the media.

Conclusion

The results obtained from the study revealed that there was a practice variation in the prophylactic antibiotic use in the same type of surgery. No guidelines were developed in the hospital. The first dose timing was not preoperative in all the recommended cases. The duration of prophylaxis was unnecessarily longer, up to 11 days in some cases that led to the increased prophylactic cost for the patients. Though the rate of infection in DH/KUTH, Dhulikhel was significantly less than in the hospitals of third world, it was significantly higher than in the hospitals of first world.

Recommendations

Based on the result of the study, following recommendations are made:

- A standard guideline for the antibiotic prophylaxis should be formulated in the hospital. It will help for the less variation in prescription.
- Formulation and implementation of hospital formulary is recommended.
- Drug and therapeutic committee can play a pivotal role for the development of antibiotic policy in the hospital.
- All prophylactic and early treatment regimens should be reviewed on a regular basis as a part of hospital's quality assurance program.
- Further intervention studies should be carried out.

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