International Research Journal of Pharmacy and Pharmacology (ISSN 2251-0176) Vol. 3(7) pp. 97-104, September 2013
DOI: http:/dx.doi.org/10.14303/irjpp.2013.034
Available online http://www.interesjournals.org/IRJPP

Full Length Research Paper

Prophylactic Antibiotics in Delayed Appendicectomy

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Abstract

Surgical site infections account for approximately 15% of nosocomial infections and are associated with increased morbidity, mortality and drain on resources. The objective of the study was to investigate the antibiotic flora of appendix wounds and the comparative status of ciprofloxacin, gentamycin, trimethoprim - sulphamethoxazole in combination with metronidazole as antibiotic prophylactics. It was designed to be a single - centre, prospective, randomized, double -blind study in which the patient and the surgeon/investigator did not know the antibiotic(s) administered till the end - point which was 30 days post - surgery. Patients were randomly assigned to receive gentamycin, trimethoprim - sulphamethoxazole, ciprofloxacin respectively in combination with metronidazole so that each combination had 100 patients. All the drugs were given intravenously except the trimethoprim - sulfamethoxazole. Analysis showed the ciprofloxacin + metronidazole, trimethoprim - sulphamethoxazole + metronidazole and gentamycin + metronidazole combinations to give 0.00%, 2.00% and 12.00% wound infection rates respectively. Results were statistically significant ($P < 0.05$) with the DMR post-hoc test showing the ciprofloxacin + metronidazole combination as the source of the significant difference. In conclusion, the results show that the administration of prophylactic antibiotics within a specific interval perioperatively reduces the burden of surgical site infection.

Keywords: Gentamycin, Ciprofloxacin, Trimethoprim - Sulfamethoxazole, Metronidazole, Prophylaxis.

INTRODUCTION

Surgical antibiotic prophylaxis is defined as the use of antibiotics to prevent infection at surgical sites (Munckhof, 2005), an area where the consumption of antimicrobials remains very high (Avorn et al., 2001). Wound infections are the commonest hospital - acquired infections in surgical patients. They result in increased antibiotic usage, increased costs and prolonged hospitalization. Appropriate antibiotic prophylaxis can reduce the risk of post-operative wound infection but additional antibiotic - use also increases the selective pressure favouring the emergence of antimicrobial resistance. Judicious and prudent use of antibiotics in the hospital environment is therefore essential and it remains an important component of optimal management of the surgical patient, an area that cannot be over - emphasized.

Studies by Burke (1961) revealed the critical dependence of prophylactic efficacy on timing of administration and also shown to depend on the presence of peak antibiotic levels in tissues corresponding to the time when local concentration of organisms would be high. It is now being recognized that, except in special circumstances, antibiotics must be given preoperatively within 30 to 60 minutes of the incision, in full dosage, parenterally, and for a duration not exceeding 48 hours (Bratzler et al., 2013; Johnson, 2012; www.acssurgery.com/acssurgery). These special instances may include when drugs such as ciprofloxacin have to be given by infusion or when ciprofloxacin and trimethoprim - sulfamethoxazole have to be given orally beforehand (McArdle et al., 1995; ClinicalTrials.gov; identifier no: NCT00613769)

Principles of surgical antibiotic prophylaxis

The expert WHO report (Avorn et al., 2001) noted that the error in prescribing practice by surgeons was the late

initiation, irrational selection and long lasting antimicrobial prophylaxis in surgery.

It is prudent for the physician to decide beforehand if prophylaxis is appropriate and determine the bacterial flora most likely to cause post-operative infection. An antibiotic with the narrowest antibacterial spectrum and the less expensive drug if two drugs are otherwise of equal antibacterial spectrum, efficacy, toxicity, and ease of administration is advised to be chosen. The stipulated dose should be administered at the right time and the physician should administer drugs for a short period of time.

Antibiotics likely to be of use in treatment of serious sepsis should be avoided. The physician should not use antibiotic prophylaxis to overcome poor surgical technique and should review antibiotic prophylaxis protocols regularly (Munckhof, 2005).

Commonly used surgical prophylactic antibiotics are intravenous first generation cephalosporins, for example, cefazolin, intravenous aminoglycoside with metronidazole, clindamycin - erythromycin, intravenous or rectal metronidazole, oral tinidazole, intravenous flucloxacillin, intravenous second generation cephalosporin that also has action against anaerobes, intravenous vancomycin and oral or intravenous trimethoprim - sulphamethoxazole (Waddell and Rotsttein, 1994).

Definition of post-operative wound infection

Post-operative wound infection (POWI) or surgical site infection is defined by the National Research Council of United States of America as the presence of pus in a wound which has either discharged spontaneously or has to be released by the removal of sutures or reopening the incision (Cruse and Foord, 1980; Pollock, 1979).

The infection is primary if it takes place in the operating room. Ward contamination is considered as secondary infection. Whether a surgical wound heals by first intention or whether it discharges pus is determined by the balance between bacterial contamination and host resistance.

The United States National Academy of Science - National Research Council (1964) classifies wound into clean, clean-contaminated, contaminated and dirty. Surgical wounds are clean if there is no chance of endogenous infection and the infection rate is reported to be 2%. A single preoperative dose of prophylactic antibiotic is usually enough (Johnson, 2012). A clean - contaminated wound arises if a sterile viscus like the gall-bladder is incised and the infection rate is 10%. A contaminated wound is diagnosed if a viscus like the appendix or colon which usually contains bacteria is incised and the infection rate is 20% (NAS – NRC). Clean - contaminated and contaminated wounds require longer duration of antibiotic prophylaxis but not exceeding 48 hours. Surgical wounds exposed to pus are classified as dirty and the infection rate is as high as 40%. Endogenous bacterial contamination of surgical wounds is far more common than exogenous in the temperate countries (de Sa et al., 1984). In a tropical setting, the exogenous source may be more significant as found by Rao and Harsha (1975). The role of the surgeon is to minimize contamination, support host defenses and reduce the bacterial burden (Woods and Dellinger, 1998) in the wound by the use of prophylactic antibiotics.

Obstacles to proper timing of prophylactic antibiotics for surgical site infections

Although the use of prophylactic antibiotics apparently has been taken cognizance of by a lot of physicians, adherence to proper timing has been found to remain problematic (Tao et al., 2006). Errors in the timing and duration of antibiotic prophylaxis in the time of surgery remain the evidence that points to widespread problems in knowledge, attitudes and behavious relating to antibiotic use among both patients and prescribers in the industrialized and the developing world's (Avorn et al., 2001). The obstacles have been found to include low priority given to the issue by physicians, inconvenience, disturbance of workflow, problems with organizational communication, role perception and conflict.

Antibiotic prophylaxis and appendicectomy

Discriminative use of antibiotic prophylactics in appendicectomy has been found essential since appendicectomy is a source of endogenous infection (Molkhou et al, 1983). Use of antibiotic prophylaxis in the National Academy of Science - National Research Council clean - contaminated operation classification which appendicectomy is, has been found appropriate (Page et al., 1993) in order to reduce the overall costs attributable to infection. Bacteriology suggests that the same flora were present in the appendiceal wall of "normal" and acute non-perforated appendices and that same risks exist (O'Rourke et al., 1984).

In appendix surgery, the main organisms causing infection are coliforms or gram- negative bacilli (GNB) and bacteriodes (Lari et al., 1976; Okoro, 1990; Ameh et al., 2007; Bratzler et al., 2013).

Trimethoprim - sulphamethoxazole in antibiotic prophylaxis

Trimethoprim - sulphamethoxazole is a sulphonamide - trimethoprim combination antibiotic which is effective against gram - negative bacilli and other gram - positive bacteria. Schmitz et al. (2010) have found it useful for

methicillin - resistant *Staphylococcus aureus* and its combination with metronidazole may be an alternative to intravenous cefuroxime + metronidazole currently used for prophylaxis of abdominal wound infections (ClinicalTrials.gov; identifier no: NCT00613769). Although the literature on the use of trimethoprim - sulphamethoxazole is at present meager, Whitby et al. (2000) reported that it has the same efficacy as cefotaxime in prophylaxis in neurosurgery and Apuzzio et al (1987) have found trimethoprim - sulphamethoxazole prophylaxis useful for wound infection prevention during caesarean - sections. Trimethoprim - sulphamethoxazole is cheap and easily available and promises to be the most cost - effective antibiotic prophylactic. It has low association with *Clostridium difficile* - associated disease which even single injections of antibiotics can cause (www.acssurgery.com/acssurgery) and may inhibit the growth of *Esherichia coli* (Matthews et al., 1977).

Gentamycin in antibiotic prophylaxis

Gentamycin is an agent for the treatment of many serious gram - negative bacillary infections. It is the aminoglycoside of first choice because of its low cost and its reliable activity although resistant organisms seem to be emerging against it. Gentamycin also has some activity against some gram - positive organisms. Gentamycin has been in use in the prevention of infection after appendicectomy (Al-Dhohayan et al., 1993; Bratzler et al., 2013).

Ciprofloxacin in antibiotic prophylaxis

Ciprofloxacin is a fluoroquinolone with good oral bioavailability and has more activity than trimethoprim - sulphamethoxazole against gram - negative bacilli while gram - positive bacteria are moderately susceptible (Davis et al., 1996). It is as effective as intravenous cefuroxime whether given orally or intravenously in antibiotic prophylaxis in appendicectomy (McArdle et al., 1995).

Metronidazole in antibiotic prophylaxis

Metronidazole is an anti-anaerobic agent (Okoro, 1990; Ameh et al., 2007) and bacteroides are some of the main bacterial culprits in appendicectomy wound infections. Intravenous and rectal metronidazole have been used for prophylaxis in appendicectomy (Gottrup, 1980) where it can completely prevent anaerobic infection (Willis et al, 1976). It has been combined with oral ciprofloxacin (Rohwedder et al., 1993) and with gentamycin (Al-Dhohayan et al., 1993) for enhanced antimicrobial prophylaxis.

The aim of the work was to study the distribution of organisms in appendix wounds and compare the combinations of:

a. Gentamycin (NAFDAC NO. 04-7703) manufactured by Ningbo Pharmaceuticals, Ningbo, China), and metronidazole (NAFDAC NO. 04-2026) manufactured by Eurolife Healthcare PVT Ltd, Uttarakhand, India) (GM),

b. Trimethoprim - sulphamethoxazole (NAFDAC NO. 04-0492) manufactured by Bond Chemical Ind. Ltd Awe, Oyo State Nigeria) and metronidazole (T-S + M) and

c. Ciprofloxacin (NAFDAC NO. 04-6280) manufactured by Micro Lab Limited Rajasthan, India) and metronidazole (CM) as antibiotic prophylactics in acute uncomplicated appendicitis to know which is more efficacious. Appendix surgery is classified as contaminated wound and infection rate is known to be 20% without prophylactic antibiotics (Ameh et al., 2007). All patients were normal and healthy with no systemic illness (American Society of Anesthesiologist (ASA) physical status Class 1) and no case with perforation of the appendix was included.

METHODS

This double-blind, randomized, prospective study was done at Department of Pharmacology, Ambrose Alli University and Oseghale Oriafo Medical Centre, Ekpoma between 2005 and 2013. Patients' informed consent was obtained in writing. One hundred consecutive adult patients between 20 and 45 years with non-perforated appendicitis were randomly assigned to receive gentamycin (4.0 mg/kg/dose intravenously) + metronidazole (1500 mg as intravenous infusion) 60 minutes before surgery. Another one hundred consecutive patients of similar age bracket also by random assignment received trimethoprim - sulphamethoxazole (800 mg sulfamethoxazole and 160 mg trimethoprim) per oral 4 hours before surgery (ClinicalTrials.gov; identifier no: NCT00613769) + metronidazole (1500 mg as intravenous infusion) 60 minutes before surgery and a third group of one hundred consecutive patients were, in similar manner, given ciprofloxacin (4.0 mg/kg/dose as intravenous infusion) + metronidazole as above 60 minutes before surgery. Wounds were inspected on 3rd and 7th post-operative days for discharge of pus (Burke, 1961; Ameh et al., 2007; Rowland et al., 1982) and any exudate was subjected to bacteriology. The classic experiments of Burke in 1961 had proved that antibiotics must be present in tissues within two or three hours of bacterial contamination, and there seems to be agreement now that the first or only dose should be given before or during surgery (Rowland et al., 1982). After oral administration, peak plasma levels of trimethoprim - sulfamethoxazole are attained after 4 hours.

All operations were done within 12 hours of presentation. Delaying appendicectomy for 12 to 18 hours has been found not to have adverse effects on 30-day outcome (Ingraham et al., 2010; Eko et al, 2013). In these delayed or planned, urgent surgeries, ketamine was used for anaesthsia supplemented with diazepam. The grid-iron incision was used in most cases. In about 10% of cases, the incision was extended. The appendix stump was dealt with by 2/0 catgut. Peritoneum was closed with 2/0 catgut after a swab was taken for bacteriology. Operations were all performed by the authors. Gentamycin (4.0mg/kg/dose) is given intravenously once a day since it has better efficacy and less side effects when administered as a single large dose than when administered as multiple smaller doses (Katzung, 2001) due to its concentration - dependent killing.

Though intravenous administration of antibiotics achieves better results than oral administration as demonstrated by Greenall (1981), oral ciprofloxacin has been found efficacious (McArdle et al., 1995) and oral trimethoprim - sulphamethoxazole is being used (Clinical Trials.gov; identifier no: NCT00613769), especially in our situation where parenteral trimethoprim – sulphamethoxazole is not readily available. Waddell et al (1994) noted that the length of time of antibiotic administration should be short and that this also depended on local circumstances. Swabs were taken from the wound during surgery for bacteriology. Opri laboratories at Auchi and Idumebo - Ekpoma helped with most of the bacteriological analysis.

The disc diffusion method of Stokes (1975) was adopted for the antibiotic susceptibility tests as previously described by Isibor et al. (2003).

Patients had their sutures removed on 7th post-operative day and were seen weekly for one month after which they were seen again at 14 days and 30 days.

Children and pregnant women were excluded from the study, since the ciprofloxacin has arthropathogenic potential in embryos and children (Schluter, 1989). Incidental appendicectomy, interval appendicectomy and perforated appendicectomy were excluded. Also excluded were patients with diabetes mellitus, bleeding disorders, heart failure, pneumonia, stroke and those on long-term steroids.

Outcome

The primary outcomes noted were on 30-day overall morbidity, and these complications were watched out for: superficial surgical site infection, deep surgical site infection, pneumonia, peripheral neurologic deficit, urinary tract infection and deep vein thrombosis. Cardiac arrest, wound dehiscence, organ space surgical site infection, pulmonary embolism, sepsis or septic shock which are serious morbidities were also watched out for.

Statistical analysis

One - way ANOVA was applied followed by Duncan - Multiple Range as *post - hoc* test. Mann - Whitney non - parametric test was used when comparing the means of two samples. The difference was considered to be significant at $P < 0.05, < 0.01$.

RESULTS

Table 1 show that coliforms or gram - negative bacteria (GNBs) were present in 80.50% of the specimens taken to laboratory for culture. Anaerobes such as bacteriodes and clostridia were present in 45.00% and 20.00% of the specimens respectively. Streptococci and staphylococci represented 5.00% and 2.50% respectively.

This is in agreement with the conclusion of most investigators (Ameh et al., 2007; Eriksen et al., 2003; Blondeau, 1999). Okoro (1990) found *E. coli* as the most frequently isolated aerobe and bacteroides as the most frequently isolated anaerobe. But Eriksen et al. (2003) working in East Africa found *Staphylococcus aureus* as the commonest organism followed by *E. coli.*

The pattern of susceptibility of *E. coli* isolates (Table 2) shows that organisms were 100.00% ± 1.02 sensitive to ciprofloxacin, 83.00% ± 1.54 sensitive to gentamycin, 60.50% ± 1.09 sensitive to trimethoprim – sulfamethoxazole and only 9.50% ± 1.51 sensitive to ampicillin.

Ciprofloxacin + metronidazole (CM) combination gave 100.00% coverage (0.00% infection rate), followed by trimethoprim – sulfamethoxazole + metronidazole (T – S + M) combination with 98.00% coverage (2.00% infection rate) and by the gentamycin + metronidazole (GM) combination with 88.00% coverage (12.00% infection rate); as shown in Table 3.

Outcome

There was no serious morbidity or mortality in the series and all the patients had full recovery at the 30th post-operative day. 2.00% of the patients on T – S + M combination and 12.00% of the patients on G + M combination had superficial surgical site infections which made their average length of hospital stay (LOS) to be 3.50 and 5.00 days respectively. The length of hospital stay for the C + M was 3.00 days. In the series, there was no re-admission or need for re-intervention.

DISCUSSION

The time-honoured practice of emergency (prompt) appendicectomy (Ditillo et al, 2006; Udgiri et al, 2011) is being challenged by accumulating evidence (Yardeni et al, 2004; Ingraham et al, 2010; Eko et al, 2013;

Table 1. Bacterial flora of appendix wounds

n	300
Sterile	10.00% ± 3.34
Coliforms (GNB)	80.50% ± 2.05**
Bacteriodes	45.00% ± 3.12*
Clostridia	20.00% ± 1.44*
Streptococcus	5.00% ± 1.56
Staphylococcus	2.50% ± 2.69
Strep. Faecalis	1.50% ± 2.98

*Table 1: Results are expressed in percentage ± SEM. There is polymicrobial bacterial flora in appendicitis with E. coli present in 80.50% of the specimens and bacteroides in 45.00% (*P < 0.05; **< 0.01)*

Table 2. Pattern of susceptibility of *E. coli* isolates

Gentamycin	**83.00% ± 1.54***
Ampicillin	9.50% ± 1.51
Sulfamethoxazole – trimethoprim	60.50% ± 1.09*
Ciprofloxacillin	100.00% ± 1.02**

Table 2. Results are expressed in percentage sensitivity ± SEM. The GNBs (E. Coli) were 100.00% ± 1.02 sensitive to ciprofloxacin and least sensitive to ampicillin (9.50% ± 1.51)(P < 0.05, **< 0.01)*

Table 3. Post-operative wound infection rates

Patients Group	Percentage wound Infected	Organisms responsible
GM	12.00%	GNBs
T-S+M	2.00%*	GNBs
CM	0.00% **	

*Table 3: Ciprofloxacin + metronidazole (CM), trimethoprim – sulfamethoxazole + metronidazole (T-S + M), gentamycin + metronidazole (GM) combinations gave 0.00%, 2.00% and 12.00% post - operative infection rates respectively. Statistical differences analyzed by ANOVA was significant (* P < 0.05; **< 0.01) and DMR showed the CM group was the source of the significant difference.*

www.georgiahealth.edu) who have found that the delayed (urgent) appendicectomy for acute appendicitis in adults does not adversely affect 30-day outcomes. The workers also noted this information is needed to prevent the extra-drain on operative and professional resources caused by emergency care of acute appendicitis (Ingraham et al., 2010) though Badruddoja (2011) observed that the delayed operation may not be as cost-effective as thought. Nevertheless, he pointed out that the results of delayed and emergency appendicectomies are the same. Present study is in agreement with these recent observations. In a retrospective study, Peiser and Greenberg (2002) have observed that the open appendicectomy reported may be comparable to laparoscopic appendicectomy with regards to complications, length of operation and hospital stay but that laparoscopic appendicectony is more expensive and may not offer significant benefit over the open approach.

Present study shows that the ciprofloxacin + metronidazole combination is the most efficacious as antibiotic prophylactic for acute uncomplicated appendicitis. In the series reported, the gram-negative bacteria (GNBs) were 100.00% sensitive to ciprofloxacin, 83.00% sensitive to gentamycin and 60.50% sensitive to trimethoprim - sulphamethoxazole (Table 2). The poor sensitivity of the culprit organisms to ampicillin (9.50%) may preclude its use for surgical prophylaxis in our locality unlike the reports of investigators from developed countries (www.johealth.com; Bratzler et al, 2013). This superior efficacy of the trimethoprim - sulphamethoxazole + metronidazole combination over the gentamycin + metronidazole combination may be due to some

unexplained synergy between trimethoprim - sulphamethoxazole and metronidazole against GNBs. The literature shows that metronidazole has activity against *Esherichia coli in vivo*, despite *in vitrio* resistance, and only in the presence of *Bacillus fragilis* (Onderdonk et al., 1979; Soriano et al., 1982). Moreover, trimethoprim - sulphamethoxazole has been shown to possess activity in vitro against anaerobes (Wust, 1980) unlike ciprofloxacin and gentamycin which have no anti-anaerobic activity in vitro (Watt and Brown, 1986; Finegold and Sutter, 1971). Special enterally - applied co - trimoxazole has proved to be as effective as intravenoue cefuroxime for prophylaxis (Blomberg et al., 2010).

The combinations of drugs used in this study are cheap alternatives to the cephalosporins and this is an advantage in the rural areas. The third - generation cephalosporins, which is reserved for treatment of established infections in surgical wards, may contribute to increased development of resistance when deployed for prophylactic antibiotherapy (Rotman et al., 1989). Trimethoprim - sulphamethoxazole, seemingly not abused in our locality, is effective against gram - negative bacilli and other gram positive bacteria and its addition to metronidazole increases coverage.

Ciprofloxacin is more effective than trimethoprim - sulphamethoxazole against gram - negative bacilli. It is active against multidrug - resistant organisms such as enterobacter (Blondeau, 1999). This may explain the superior efficacy of the CM combination.

Institution of the antibiotic combination before surgery helps to prevent endogenous infection such as blood collection during the surgery serving as good growth medium for pathogenic organisms (Burke, 1961; Rowland et al., 1982). The one - day pre - operative administration of the antibiotics is necessary to take care of both endogenous and exogenous infections and is short enough to avoid superinfection (Pollock, 1979).

The combinations, apart from preventing the emergence of drug resistant species, are necessary to treat polymicrobial infections which appendicitis constitutes. Anaerobes and aerobes are taken care of by the drug combinations.

Without antibiotic prophylaxis, surgical site infection is about 20.00% as found by Ameh et al. in 2007 who wrote that the degree of incisional contamination and long duration of surgery (> 2 hrs) are important risk factors. The results lead one to agree with Koch et al. (2000) that antibiotic prophylaxis should be given before every appendicectomy whether by laparoscopy or conventional methods.

There is antibiotic prophylaxis with the three drug combinations used in this study compared to if there is no prophylaxis at all (Katzung, 2001). Gentamycin is active against gram - positive and gram - negative organism but especially the later. It is synergistic with metronidazole though organisms now produce transferase enzymes and beta - lactamase enzymes which inactivate gentamycin and ampicillin respectively thereby decreasing their efficacy. Our results with gentamycin + metronidazole combination do not agree with the conclusion of Bratzler et al (2013) that this combination may have equivalent efficacy with ciprofloxacin + metronidazole combination. This may be explained by the fact that there may be uncontrolled access to gentamycin and also ampicillin in our locality (Erhun et al., 2001; Yah et al., 2006). Ciprofloxacin is more effective against gram - negative organism relative to gram - positive organism. Present results suggest that it may be effective even when the GNBs are resistant to ampicillin and co - trimoxazole. And it has been shown that ciprofloxacin and third-generation cephalosporins have compatible efficacy (Thadepalli, 1989). But there is evidence that point mutation in the DNA gyrase of the organism may confer resistance to ciprofloxacin which has to be watched out for. At present, anaerobes are sensitive to metronidazole and it is indicated for treatment of mixed intra - abdominal infectious.

It should be noted that antibiotics for prophylaxis cannot be taken in isolation. It must be emphasized that reduction of exogenous and endogenous contamination of wounds; with support of host defenses are also important, for example, infection rate is higher after prolonged operations (Polk and Lopez-Major, 1969) and in anaemic patients (Polk and Lopez-Major, 1969; Bennion et al., 1990; http://www.ptolemy.co/members/archives/2006).

In conclusion, results confirm previous findings that coliforms constitute most of the bacterial burden in appendiceal wounds. Present results also indicate that ciprofloxacin + metronidazole, trimethoprim-sulphamethoxazole + metronidazole and gentamycin + metronidazole antibiotic combinations reduce the bacterial burden in appendicectomy and thus can provide surgical prophylaxis. The ciprofloxacin + metronidazole combination appears to be most efficacious followed by the trimethoprim - sulphamethoxazole + metronidazole combination. Furthermore, results also show that the outcome of delayed, urgent operation for appendicitis may be comparable that of emergency appendicectomy.

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How to cite this article: Oriaifo S.E. and Oriaifo N.I. (2013). Prophylactic Antibiotics in Delayed Appendicectomy. Int. Res. J. Pharm. Pharmacol. 3(7):97-104