

## Randomized study of antibiotic prophylaxis for general and gynaecological surgery from a single centre in rural Africa

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In a district rural hospital in Uganda, 850 surgical patients were evaluated prospectively over a 3-year period to compare the clinical efficacy of conventional postoperative penicillin therapy with single-dose ampicillin prophylaxis for hernia repair and ectopic pregnancy, and with single-dose ampicillin–metronidazole prophylaxis for hysterectomy and caesarean section. The high rate of postoperative infection usually encountered in African hospitals after conventional treatment with penicillin for 7 days was significantly reduced with the new regimen:

from 7.5 to 0 per cent in hernia repair and from 10.7 to 2.4 per cent in ectopic pregnancy; from 20.0 to 3.4 per cent in hysterectomy and from 38.2 to 15.2 per cent in caesarean section. Length of hospital stay and postoperative mortality rates were also significantly reduced. Single-dose ampicillin prophylaxis with or without metronidazole, although rarely used in developing countries, is more cost effective than standard penicillin treatment.

The role of surgery in developing countries is well recognized, and progress has been made in identifying surgical needs, suitable operative techniques and facilities<sup>1,2</sup>.

A major concern is postoperative wound and deep infection. Poor sterility and hygiene of operating theatres and wards, lack of trained personnel and delayed patient attendance to the hospital are among factors contributing to the high rate of postoperative infection in developing countries. In subSaharan Africa a record of postoperative infection is rare and few studies are available<sup>3</sup>, but a rate of 40–70 per cent is not exceptional<sup>4–7</sup>.

This study, performed at Hoima District Hospital (western Uganda), investigated the prophylactic use of ampicillin for elective and emergency hernia repair and ectopic pregnancy, and ampicillin–metronidazole for elective and emergency hysterectomy and caesarean section, and compared this regimen with postoperative penicillin treatment.

A large number of trials have shown that antimicrobial prophylaxis is effective in reducing the incidence of postoperative wound infection but all the studies have been carried out in industrialized environments. Most studies include only elective surgery on properly assessed and selected patients, with timely diagnosis and proper preparation for surgery<sup>8–16</sup>. This study is one of the few performed in a developing country, in a high-risk environment, including many emergency surgical procedures often performed on patients who presented late in the course of the illness.

### Patients and methods

Over the 3-year period from 1991 to 1993, 850 consecutive adult patients (aged over 18 years) admitted to Hoima Hospital for both elective and emergency surgical procedures were eligible for the study.

Hoima Hospital is a 150-bed government institution supported by International Service Volunteers' Association (Italian Cooperation), where more than 800 major surgical procedures are performed yearly, mainly in general and obstetric surgery, 35

per cent as an emergency. Six Ugandan and two Italian surgeons perform the surgery. No microbiological facilities are available locally and therefore no cultures were obtained from infected wounds.

After obtaining written consent, patients were divided into two categories according to the surgical condition. The first group included 479 patients: 229 had inguinal hernia repair without intestinal resection or tissue necrosis (161 elective, 68 emergency) and 250 had surgery for ectopic pregnancy (all emergencies). The second group consisted of 371 patients: 177 had total abdominal hysterectomy (95 for cervical cancer, 82 for fibroids; all elective) and 194 had caesarean section (116 emergency, 78 elective).

Patients were allocated by means of random numbers to antibiotic prophylaxis as follows: half the patients with hernia or ectopic pregnancy received a single dose of ampicillin 2 g intravenously at induction of anaesthesia (30 min before surgery), while the remainder received the standard postoperative treatment of intramuscular fortified procaine penicillin 1.2 megaunits daily for 7 days (starting about 3 h after surgery).

Of patients undergoing hysterectomy or caesarean section, 192 were randomized to receive a single dose of ampicillin 3 g intravenously plus metronidazole 500 mg at induction of anaesthesia, while the remainder (179) received benzylpenicillin 1 megaunit intravenously every 6 h for 1 day (starting about 3 h after surgery), followed by fortified procaine penicillin 1.2 megaunits daily for 6 days.

A group receiving placebo was not included since previous experience showed an unacceptably high rate of postoperative infection.

Imperfect balance between the groups resulted from the elimination of a few patients for whom treatment procedures were not strictly observed (additional self-medication, irregular treatment and self-discharged patients): 12 patients operated on for hernia repair and eight for caesarean section, all receiving penicillin therapy.

There were no differences between patient groups with respect to general and nutritional status, preoperative preparation, administration of anaesthesia (spinal for hernia repair and caesarean section, thiopentone–suxamethonium–ether with endotracheal tube for ectopic pregnancy and hysterectomy), skin disinfection (iodine), intravenous fluid therapy (for 24 h only) and management of dressings (daily with chlorhexidine). Likewise, other minor prognostic variables were similar between the groups, including the presence of a urethral catheter for 24 h (only the hernia group was without), anaemia (haemoglobin concentration less than 10 g/dl), blood transfusion and reasons for caesarean section.

After operation each patient was carefully assessed each day by two supervisors aware of the type of prophylaxis used.

Further follow-up was performed 2 weeks after hospital discharge to detect delayed infections; compliance greater than 90 per cent was achieved in all groups, although cash incentives were necessary.

Criteria for infection were pyrexia above 38°C twice within 24 h (excluding the first 24 h), urinary tract infection diagnosed if symptoms were present, together with a positive leucocyte count (more than 15 per field on urine microscopy); urine culture was not available.

Wound infections were graded according to the classification of Karl *et al.*<sup>17</sup>: grade 1, superficial infection (cellulitis with minimal purulent exudate); grade 2, deep infection (cellulitis with moderate purulent infection); grade 3, infection throughout the wound with or without dehiscence.

Peritonitis was deemed to be present when clinical signs and symptoms (fever, abdominal tenderness and pain with increased leucocytosis) were evident. The length of stay and postoperative outcome were recorded. Cost factors were analysed, including both the simple cost of the two different regimens and additional costs related to any increased length of hospital stay.

Results are expressed as mean(s.d.). For statistical comparison, the  $\chi^2$  test with Yates' correction and Fisher's exact test were used. For calculation of differences in postoperative stay, analysis of variance was performed.  $P < 0.05$  was considered significant.

**Results**

In patients who received ampicillin, postoperative morbidity was significantly reduced compared with those receiving penicillin. The overall rate of infective complications was reduced from 7.5 to 0 per cent after

hernia repair ( $P = 0.001$ ), from 10.7 to 2.4 per cent after surgery for ectopic pregnancy ( $P = 0.013$ ), from 20.0 to 3.4 per cent after hysterectomy ( $P = 0.001$ ) and from 38.2 to 15.2 per cent after caesarean section ( $P < 0.001$ ). There were three postoperative deaths, all in patients following caesarean section who received penicillin prophylaxis ( $P$  not significant) (Tables 1 and 2). There were no serious infective complications after surgery for hernia or ectopic pregnancy when ampicillin was used compared with deep infection, dehiscence and peritonitis in 10 patients when penicillin was employed. The incidence of fever was also reduced.

The mean postoperative hospital stay was significantly shortened by the use of preoperative ampicillin both in patients having hernia repair (from 7.9 to 6.2 days,  $P < 0.001$ ) and in those with ectopic pregnancy (from 8.9 to 7.0 days,  $P < 0.001$ ).

Similarly, in patients who had hysterectomy or caesarean section, postoperative infective complications were less severe and significantly fewer episodes of peritonitis and wound dehiscence were recorded in those who received ampicillin with metronidazole at the time of caesarean section.

The cause of the three postoperative deaths after caesarean section was purulent peritonitis complicated by septic shock (the patients presented late after prolonged labour with ruptured membranes in the village; moreover one was markedly anaemic). One patient required a secondary laparotomy and two were managed conservatively.

The duration of postoperative stay was shorter for

**Table 1** Clinical features of patients with hernia and ectopic pregnancy treated with prophylactic ampicillin or postoperative penicillin

	Ampicillin	Penicillin	<i>P</i>
Superficial wound infection*			
Hernia	0 (0)	4 (3.7)	0.04†
Ectopic pregnancy	3 (2.3)	6 (4.9)	n.s.‡
Deep wound infection*			
Hernia	0 (0)	4 (3.7)	0.05†
Ectopic pregnancy	0 (0)	5 (4.1)	0.03†
Peritonitis*			
Hernia	0 (0)	0 (0)	
Ectopic pregnancy	0 (0)	1 (0.8)	n.s.‡
Urinary tract infection*			
Hernia	0 (0)	0 (0)	
Ectopic pregnancy	0 (0)	1 (0.8)	n.s.‡
Wound dehiscence*			
Hernia	0 (0)	2 (1.8)	n.s.‡
Ectopic pregnancy	0 (0)	0 (0)	
Fever*			
Hernia	3 (2.4)	18 (17.0)	<0.001‡
Ectopic pregnancy	15 (11.6)	21 (17.3)	n.s.‡
Postoperative death*			
Hernia	0 (0)	0 (0)	
Ectopic pregnancy	0 (0)	0 (0)	
Mean(s.d.) postoperative stay (days)			
Hernia	6.2(1.2)	7.9(2.1)	<0.001§
Ectopic pregnancy	7.0(1.0)	8.9(1.1)	<0.001§

In all, 123 patients undergoing hernia repair received ampicillin and 106 had penicillin; 129 having surgery for ectopic pregnancy received ampicillin and 121 penicillin. \*Values in parentheses are percentages. †Fisher's exact test; ‡ $\chi^2$  test with Yates' correction; §analysis of variance; n.s., not significant

**Table 2** Clinical features of patients undergoing hysterectomy and caesarean section

	Ampicillin plus metronidazole	Penicillin	<i>P</i>
Superficial wound infection*			
Hysterectomy	2 (2)	6 (7)	n.s.‡
Caesarean section	9 (8.5)	10 (11)	n.s.‡
Deep wound infection*			
Hysterectomy	1 (1)	8 (9)	0.03†
Caesarean section	6 (6.7)	17 (19)	0.008‡
Peritonitis*			
Hysterectomy	0 (0)	4 (4)	n.s.‡
Caesarean section	0 (0)	5 (6)	0.02†
Urinary tract infection*			
Hysterectomy	0 (0)	0 (0)	
Caesarean section	1 (1)	2 (2)	n.s.‡
Wound dehiscence*			
Hysterectomy	0 (0)	4 (4)	n.s.‡
Caesarean section	0 (0)	6 (7)	0.008†
Fever*			
Hysterectomy	9 (10)	30 (33)	<0.001‡
Caesarean section	27 (25.7)	47 (53)	<0.001‡
Postoperative death*			
Hysterectomy	0 (0)	0 (0)	
Caesarean section	0 (0)	3 (3)	n.s.‡
Mean(s.d.) postoperative stay (days)			
Hysterectomy	7.7(1.5)	9.0(1.4)	0.007§
Caesarean section	7.8(1.6)	12.4(2.5)	<0.001§

In all, 87 patients undergoing hysterectomy received ampicillin plus metronidazole and 90 received penicillin; 105 having caesarean section received ampicillin-metronidazole and 89 penicillin. \*Values in parentheses are percentages. †Fisher's exact test; ‡ $\chi^2$  test with Yates' correction; §analysis of variance; n.s., not significant

Table 3 Cost analysis of regimens

Regimen	Treatment cost (US\$)	Admission day cost (US\$)	Mean duration of hospital stay (days)		Total cost per single patient (treatment plus admission) (US\$)	
Ampicillin (2 g)	0.5	3.0	7.0	6.2	21.5	19.1
			(ectopic pregnancy)	(hernia)	(ectopic pregnancy)	(hernia)
Procaine penicillin (1.2 megaunits for 7 days)	0.7	3.0	8.9	7.9	27.4	24.4
			(ectopic pregnancy)	(hernia)	(ectopic pregnancy)	(hernia)
Ampicillin (3 g) plus metronidazole (500 mg)	1.7	3.0	7.8	7.7	25.1	24.8
			(caesarean section)	(hysterectomy)	(caesarean section)	(hysterectomy)
Benzylpenicillin (4 megaunits) plus procaine penicillin (1.2 megaunits for 6 days)	2.1	3.0	12.4	9.0	39.3	29.1
			(caesarean section)	(hysterectomy)	(caesarean section)	(hysterectomy)

Costs taken from *The International Dispensary Association Price Indicator* May 1993 (PO Box 3098, 1003 AB Amsterdam, The Netherlands)

patients in the ampicillin–metronidazole group than for those in the penicillin group: 7.7 *versus* 9.0 days after hysterectomy ( $P=0.007$ ) and 7.8 *versus* 12.4 days after caesarean section ( $P<0.001$ ).

In 1992 in Hoima Hospital the running cost for a single admission day was US\$3.0 (Table 3); this was inclusive of allocated costs of personnel, drug, supplies and utilities divided by the number of admission days for the period. Since the duration of postoperative stay was shorter for both groups of patients receiving ampicillin prophylaxis, there was a cost saving. In addition, the ampicillin–metronidazole regimens were cheaper than the full penicillin course. Not only was there a cost advantage, but the indirect cost of suffering related to infective complications and absence of the patient and attendants from the domestic environment were minimized.

## Discussion

Postoperative infection rates in developing countries can reach astonishing levels. They are often underestimated and little documentation is available<sup>3–5</sup>. This high rate is not unavoidable, even in a poorly equipped environment, and all the factors leading to infection can systematically be influenced.

This study in rural Uganda confirms what has been already proved in Western countries: that appropriate antibiotic prophylaxis is effective in reducing the postoperative morbidity rate in clean general surgery and gynaecology operations<sup>18,19</sup>.

This short-course, single-dose antibiotic prophylaxis may not be optimal if significant contamination is present during the operation: care was taken to exclude from the protocol patients with established sepsis at the time of surgery.

Penicillin treatment, in spite of the narrow spectrum of antibacterial activity, is the most widely used method of prophylaxis in Ugandan and African district hospitals<sup>5,19</sup>. The reasons are that penicillin-resistant bacteria are less common than elsewhere, more appropriate antibiotics are not easily available, facilities for microbiological tests are rare and postoperative follow-up is difficult. In this study ampicillin was chosen for its low cost, broad spectrum, sufficient half-life and high wound concentration. Metronidazole was selected for its anaerobic activity and long half-life<sup>5,20–22</sup>. Resistance to either antibiotic is still rare in rural Africa.

Postoperative infection was reduced to acceptable rates by the use of prophylaxis. The high rate after caesarean

section reflects the poor socioeconomic status of the obstetric patients, characterized by undetected antenatal risk factors and delayed surgery until obstructed labour was obvious<sup>5</sup>.

The cost of the new regimen was lower than that of postoperative penicillin and thus reduced overall expense<sup>14,23</sup>. This cost advantage and the reduced length of hospital stay provide further proof that prophylactic use of appropriate antibiotics significantly reduces the morbidity rate in rural hospitals in developing countries after general and gynaecological surgery.

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