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A randomized trial of one versus three doses of Augmentin as wound prophylaxis in at-risk abdominal surgery

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Summary: **In a randomized prospective trial of prophylactic antibiotics in at-risk abdominal surgery, one dose of intravenous Augmentin (amoxycillin 250 mg and clavulanic acid 125 mg) on induction has been compared with three 8 hourly doses in 900 patients. Wound infection rates which included minor and delayed infections were very similar in those given one dose: 48/449 (10.7%) compared with those given three doses: 49/451 (10.9%) 95% confidence limits – 4.25% + 3.9%.**

There were more septic and sepsis-related deaths in those patients given one dose (14 deaths) than in those given three doses (7 deaths) $P > 0.1$ 95% CL – 0.4% + 3.0%. However, there were more very elderly patients in the one dose group: 64% of the deaths were aged over 80 and all but one had an emergency operation. There was no difference in the other outcome measures studied which included non-fatal deep sepsis, length of postoperative hospital stay, duration of postoperative fever or the use of antibiotics for postoperative infection.

One dose of a suitable intravenous antibiotic gives prophylaxis against wound infection in at-risk abdominal surgery which is at least as effective as multiple doses. However, there may be a risk of overwhelming systemic sepsis in very elderly patients having emergency surgery.

Introduction

The idea of a single dose of a prophylactic antibiotic in at-risk abdominal surgery was first examined over a decade ago[1-5] and there are now numerous studies in the literature. However, many trials have tested a single dose of one agent against multiple doses of one or more other agents[6] and few have achieved as many as 100 patients[7-14] in each arm of a randomized trial. Most studies have shown no significant difference between single and multiple dose regimes but there is a risk of a Type II error in concluding there is no difference when a real one exists, where small numbers are examined. We therefore set out to study a large number of patients in two hospitals within the same health district.

An agent, amoxycillin 250 mg/clavulanic acid 125 mg (Augmentin), was chosen which has been shown to be at least as effective as other single or multiple agents for prophylaxis in at-risk abdominal surgery.[15-18]

Patients and methods

Eligibility

All patients aged 16 or over admitted under two surgical firms at two adjacent district general hospitals for at-risk abdominal surgery with potential opening of a viscus were admitted to a prospective randomized trial. At-risk abdominal surgery included all appendicectomies, and all open gastric, oesophageal, colonic or biliary surgery. All patients coming to laparotomy for intestinal obstruction including that due to strangulated hernia were entered into the study as well as patients with intra-abdominal malignancy.

Exclusions (before randomization)

All patients known to be allergic to penicillin were excluded. If patients had received antibiotics within the previous 48 hours or if the surgeon considered that pre-operative antibiotics were essential they were also excluded. Patients who declined consent were not entered into the trial although all received prophylactic antibiotics.

Trial design

Eligible patients were randomly allocated to one or three doses of antibiotics by taking sequentially numbered stickers prepared from a table of random numbers. The first dose was given on induction of anaesthesia and those patients randomized to three doses received two additional injections 8 and 16 hours later.

Those patients found to have a purulent peritonitis were withdrawn from the study for

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ethical reasons and were treated in the following way. Those patients randomized to one dose were given eight doses of antibiotics while those randomized to have three doses had no change of antibiotic treatment.

The antibiotics

Augmentin is a 1:10 combination of amoxycillin and clavulanic acid. Clavulanic acid is an inhibitor of many bacterial beta lactamases and greatly increases the active spectrum of amoxycillin including *Bacteroides* sp. The trial drug was administered by slow intravenous bolus injection as 1.2 g of powder dissolved in 10 ml water.

Losses

All eligible patients who were not entered into the trial were recorded and completeness was cross-checked with the operating theatre records.

Withdrawals (after randomization)

Those patients who were ineligible on the protocol were withdrawn together with those cases in which the operation was cancelled after randomization. Patients found to have faecal peritonitis were withdrawn from the study so that treatment options were free.

Deviations

The categories of patients who were not withdrawn after randomization are as follows. Dose violations were recorded if antibiotic doses were omitted or delayed. Some patients received additional antibiotics either in continuity with the protocol doses or after an interval. Those patients in whom the operative findings did not necessitate opening a viscus and those patients with missing data were included in the study.

Table I Reasons for withdrawal from the study

	One dose	*Three doses*
No operation	5	7
Pre-operative antibiotics	4	6
Operation not in criteria	14	14
Allergy to penicillin	0	5
Faecal peritonitis	0	2
Purulent peritonitis (peritonitis protocol)	5	7
Total	28	41

Concentration of drugs in plasma and tissue

In 23 patients plasma levels of amoxycillin and clavulanic acid were measured at the time of skin incision, at the time of skin closure and at 8 hours. In eight patients drug levels in wound edge fat were also measured at the time of wound closure.

Follow-up

All patients were seen at about one month postoperatively and were specifically asked if there had been any wound discharge after they left hospital. If the outpatient record of wound status was equivocal, patients were contacted by telephone or letter.

Risk factors

The following variables were considered: age, sex, body mass index [BMI = weight in kg/(height in metres)^2], diagnostic category, degree of peritonitis, grade of surgeon and dose violation (omitted or delayed). Where sepsis found at operation was considered to require continuation of antibiotics, continuous antibiotics were sometimes given instead of the peritonitis protocol (3 versus 8 doses).

Outcome events

The outcome was assessed as follows: wound sepsis was categorized as major, minor or late (criteria of Pollock & Evans[19]) and deep sepsis was recorded separately. The causes of death within 30 days were categorized as septic, sepsis-related (for example, mesenteric infarction) or not septic (for example, terminal malignancy, even if this occurred at home). The number of postoperative days in which fever was noted to be >37.5°C was recorded. Postoperative infection requiring antibiotics (interval antibiotics) was considered an outcome event. Length of postoperative hospital stay included the day of discharge but not the day of operation. Formal outcome evaluation of each patient was completed and agreed between at least two authors who were unaware of the number of antibiotic doses given.

Consent

The trial protocol was approved by the district ethical committee and all patients signed consent to the investigation after verbal and written explanation.

Estimation of required sample size

In order to estimate the number of patients required in each arm of the study to avoid a Type II error the following assumptions were made. The proportion of events was estimated to be 20% and a clinically important reduction would be from one-third to 13%. Using Feinstein's formula[20,21] with alpha 0.05 and beta 0.20, it was calculated that 437 patients would be needed in each arm of the trial.

Statistical analysis

Statistical analysis was performed using the Solo 101 statistical program (BMDP Statistical Software, Los Angeles, California, USA) on an Apricot Qi 650t microcomputer (Apricot Computers, Birmingham, UK). Data was entered on to a relational database management system (Paradox V3, Borland International, Scotts Valley, California, USA) to ensure data integrity and transferred for statistical analysis. This allowed comparison of risk factors and outcomes. The two sample proportional test was used in most statistical comparisons testing at the 0.05% level.

Results

There were 995 eligible patients available for the study between May 1986 and June 1988. Over the same period 108 otherwise eligible patients were excluded: 60 patients had had antibiotics within 48 hours; 41 patients were said to be allergic to penicillin; and seven patients declined consent.

There were 18 losses of eligible patients due to administrative failure and there were 69 withdrawals of ineligible patients for reasons shown in Table I which included 12 patients with severe peritonitis who were re-allocated to the three versus eight dose protocol leaving 908 patients for analysis. Eight patients who died within 48 hours were not included in the wound infection analysis leaving 900 patients.

Risk factors

The two groups were well matched for risk factors (Table II) and for the numbers in each diagnostic category except that there were more patients over 80 years in the one dose group and there were more patients in this group with a normal appendix (Table II). There were more delayed or missed doses in those patients randomized to receive three doses (Table IV).

Table II Comparison of risk factors for wound infection between the two groups

	One dose	*Three doses*
Age > 80 years	57	46
Mean age (SD)	56 (21.8)	54.4 (21.6)
Males	186	195
BMI < 26	221 (50%)	240 (53%)
> 30	100	110
	(n = 446)	(n = 450)
Sepsis at operation (other than appendicectomy)	39 (11.6%)	37 (11.7%)
Appendix inflamed	71 (62%) (n = 114)	101 (76%) (n = 133)
Dose violation	3	13
Continuous antibiotics	12	18
Registrar operation	224	229

Wound infection

The overall wound infection rates were similar in both groups being 10.7% in patients receiving one dose and 10.9% in those receiving three doses (Table V). There was no difference in wound infection rates between the two hospitals when diagnostic categories were compared. There was a higher wound infection rate after appendicectomy in the three dose group and a lower rate after colorectal and biliary operations but none of these differences approached statistical significance. Major wound infection occurred in 3.9% of patients but 46% of wound infections were delayed until after the patient left hospital. There was a non-significant trend to fewer major infections in the three dose group (15 *vs* 20) and more delayed infections (26 *vs* 19) but this was not reflected in postoperative pyrexia or length of stay.

Other outcome

There were more septic and sepsis-related deaths in those patients who only received one dose of antibiotics (14 *vs* 7 N.S.; see Table V).

The median age of these patients was 81 *vs* 79 years. Of the 14 deaths in the one dose group, nine patients were over the age of 80, eight of whom had an emergency operation and five patients developed a complication after major elective surgery. There were also more non-septic deaths in this group but this difference was not significant. There was no difference in any of the other outcome measures examined.

Peritonitis protocol

Twelve patients were treated with the peritonitis protocol, of which five were in the one dose group

Table III Diagnostic category and wound infection in the two groups

	One dose		*Three doses*	
	Infected	*Total (%)*	*Infected*	*Total (%)*
Appendix	11	114 (9.6)	21	133 (15.8)*
Colorectal	23	113 (20.4)	17	111 (15.3)†
Upper gastrointestinal tract	3	62	3	52
Biliary	6	96 (6.3)	3	99 (3.0)‡
Small bowel	3	28	2	17
Hernia (strangulated)	1	26	3	31
Laparotomy (no viscus open)	1	10	0	8
Total	48	449 (10.7)	49	451 (10.9)§

*$P > 0.01$ 95% CL (− 14.3% + 2.0%); †$P > 0.2$ 95% CL (− 4.6% + 15.2%); ‡$P > 0.2$ 95% CL (− 2.7% + 9.1%); §NS 95% CL (− 4.25% + 3.9%).

Table IV Deviations from the treatment protocol

	One dose	*Three doses*
Reduced dose(s) antibiotics	2	10
No antibiotics	1	3
Continuous antibiotics	16	7
Interval antibiotics	50	47
Missing data		
Height	3	1
Follow-up	1	3
Height and follow-up	0	1

and received eight doses and seven were in the three dose group. The wound infection rates were 1/5 for those receiving eight doses and 4/7 for those receiving three doses of antibiotic. No death occurred nor was there an episode of deep infection.

Deviations

More patients in the group randomized to one dose continued to receive antibiotics in addition to the protocol (Table IV). Four patients were lost to follow-up, three having died at home before they could be reviewed.

Table V Outcome of patients related to dose group

	One dose	*Three doses*
Wound infection*		
Major	20	15
Minor	9	8
Delayed	19	26
Total	48 (10.7%)	49 (10.9%)
Deep sepsis (non-fatal)	22	21
Mortality (30 days)*		
Septic	7 (1)	2†
Sepsis-related	7 (1)	5 (1)†
Non-septic	17 (4)	10 (1)‡
Total	31 (6)	17 (2)
Post-operative days of fever		
Mean* (days)	1.0	1.05
> 10 days (patients)	4	12
Length of postoperative stay		
Mean* (days)	9.4	10.2
15–29 days (patients)	44	49
30 + days (patients)	21	16
Patients receiving interval antibiotics	50	47

*Figures in brackets denote death within 48 hours omitted for wound infection rates and means; †14 *vs* 7 septic or sepsis-related deaths – $P > 0.1$ 95% CL (− 0.4% + 3.0%); ‡$P > 0.2$ 95% CL (− 0.7% + 3.45%).

Faecal peritonitis

Two patients from the three-dose group were withdrawn at the time of laparotomy for faecal peritonitis (Table I). One patient had a major wound infection but both survived.

Drug levels

The drug levels in serum and wound edge fat are detailed in Table VI.

Details of the microbiological isolates

Of those patients having a major wound infection whilst in hospital, 34 cultures were carried out and 20 showed a mixed growth of Gram-negative organisms. The most common organisms isolated were coliforms (23), *Bacterioides* (20), *Proteus* (5), *Pseudomonas* (3) and *Enterococcus* (3). *Staphylococcus aureus* was the sole organism isolated in only three out of 12 cultures and only one of these three was coagulase positive.

Of those patients having a delayed wound infection after leaving hospital, 38/44 (86%) did not have a wound culture carried out. Three of the six cultures showed a mixed growth of Gram-negative organisms, two grew *Staphylococcus aureus* and one was sterile.

There were only four positive cultures in patients with deep sepsis in the absence of a wound infection. All grew Coliform organisms and three showed *Bacteroides* sp. in addition.

Discussion

Although no formal meta-analysis of one versus three doses of antibiotics has been carried out except in biliary tract surgery,[22], the present study adds weight to the conclusion from DiPiro's review of the literature[6] that there is no advantage to giving more than one dose in terms of wound prophylaxis or deep infection.

There were more septic and sepsis-related deaths in the one dose group but this may have been due to the greater number of very elderly patients in this group. A total of 64% of these deaths were of patients over 80 and all but one had an emergency operation. However, the possibility that sepsis-related death may be more common in those patients only receiving one dose is not excluded. This has not been noted in previous trials[8,9,12–14] but mortality has not always been reported.[7,10,11] There was no death in those patients with purulent or faecal peritonitis but all these patients received at least three doses.

Of those patients with purulent peritonitis, there were fewer wound infections in those patients receiving eight compared with three doses but the numbers were too small to draw any conclusion from this group.

The overall wound infection rate was lower than in our most recent study[23] and it is possible that more attention has been paid to surgical discipline in the present study. The difference is partly explained by the addition of all biliary cases to the present study instead of a selective policy but the levels of infection are still high compared with some reports.[8,10,11,24]

The levels of clavulanic acid in the wound fat at the time of wound closure were much lower than that found by Pollock *et al.*[25] although the methods and the assay were apparently the same. This study showed an advantage to giving a prophylactic injection of Augmentin into the site of the incision versus intravenously, although this was not shown in a previous experimental model.[26]

It seems unlikely that a reduction in wound infection rates will be achieved by variations in the dosage regimes of the current generation of antibiotics and, although improved technique probably is an important factor, it is difficult to explore this by a randomized trial. However, the reduction of wound infection rates over time underlines the risks of using historical controls.

Multiple dose regimes of prophylactic antibiotics are still widely used in clinical practice and the present study confirms that there is no justification for this practice with the sole possible exception of the very elderly having emergency abdominal surgery.

Table VI Serum levels of antibiotics in serum and fat perioperatively

	Incision serum (n = 23)	*Closure serum/fat (n = 23/8)*	*8 hours serum (n = 21)*
Amoxycillin, mean (± SD) (μg/ml)	41.2 (29)	5.2 (4)/1.5 (2)	4.2 (7)
Clavulanic acid, mean (± SD) (μg/ml)	5.2 (4)	2.5 (2)/*	0.4 (0.6)†

*All but two samples below lower limit of assay 0.23 μg/ml; †seven samples below lower limit of assay 0.08 μg/ml.

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