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Novel approach to antibiotic prophylaxis in percutaneous endoscopic gastrostomy (PEG): randomised controlled trial

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ABSTRACT

Objective To evaluate a new and simpler strategy of antibiotic prophylaxis in percutaneous endoscopic gastrostomy (PEG).

Design Single centre, two arm, randomised, controlled, double blind clinical trial.

Setting Endoscopy unit in Karolinska University Hospital, Stockholm, Sweden, between 3 June 2005 and 31 October 2009.

Participants 234 patients with an indication for PEG who gave informed consent to participate.

Intervention A single 20 ml dose of the oral solution of sulfamethoxazole and trimethoprim (also known as co-trimoxazole or Bactrim; F Hoffmann-La Roche Ltd, Basel, Switzerland) deposited in the PEG catheter immediately after insertion. The control group received standard prophylaxis consisting of a single intravenous dose of 1.5 g cefuroxime (Zinacef; GlaxoSmithKline, London) administered before insertion of the PEG tube.

Main outcome measure Primary outcome was the occurrence of clinically evident wound infection within 14 days after insertion of the PEG catheter. Secondary outcomes were positive bacterial culture and blood tests (highly sensitive C reactive protein and white blood cell count). All randomised patients were included in an intention to treat analysis.

Results Of the 234 patients included in this study, 116 were randomly assigned to co-trimoxazole and 118 to cefuroxime. At follow-up 7-14 days after insertion of the PEG catheter, wound infection was found in 10 (8.6%) patients in the co-trimoxazole group and 14 (11.9%) in the cefuroxime group, which corresponds to a percentage point difference of −3.3% (95% confidence interval −10.9% to 4.5%). The per protocol analysis, which comprised 100 patients in each group, gave similar results—10% and 13% infection in the co-trimoxazole and cefuroxime groups, respectively (percentage point difference −3.0%, 95% CI −11.8% to 5.8%). Both these analyses indicate non-inferiority of co-trimoxazole compared with cefuroxime because the upper bounds of the confidence intervals are lower than the pre-determined non-inferiority margin of 15%. Analyses of the secondary outcomes supported this finding.

Conclusion 20 ml of co-trimoxazole solution deposited in a newly inserted PEG catheter is at least as effective as cefuroxime prophylaxis given intravenously before PEG at preventing wound infections in patients undergoing PEG.

Trial registration Current Controlled Trials ISRCTN18677736.

INTRODUCTION

Percutaneous endoscopic gastrostomy (PEG), which is mainly used to maintain enteral nutrition in patients with longstanding eating difficulties, has, since its introduction in 1980,[1] steadily increased in use to become a common intervention. As a consequence of malnutrition and comorbidities, patients receiving a PEG catheter are often vulnerable to infection,[2] which is the main acute problem after insertion of the PEG catheter.[3]

Infection at the insertion site occurs in about one third of all patients who receive a PEG catheter,[4-8] and such infections are often difficult to treat. Meta-analyses of randomised trials have established that wound infection rates decrease substantially when intravenous antibiotic prophylaxis is given before the PEG procedure.[9-12] A single intravenous dose of the cephalosporin cefuroxime (Zinacef; GlaxoSmithKline, London), given one hour before the PEG procedure, is well established as the gold standard method of antibiotic prophylaxis and is recommended by the British Society of Gastroenterology (evidence grade Ia and recommendation grade A)[13] because of its good effect on the bacteria commonly found in the upper gastrointestinal tract.[14 15] Disadvantages of this strategy include the high cost, the need to give the medication intravenously, and the need to give it before insertion of the PEG catheter, even though in about 10% of patients insertion of the catheter proves to be impossible.[16]

We hypothesised that there is a less expensive, technically easier, and at least as effective way of infection prophylaxis than using cefuroxime; that is, depositing a single dose of a combination of a sulphonamide and trimethoprim (also known as co-trimoxazole or Bactrim; F Hoffmann-La Roche Ltd, Basel, Switzerland), as an oral solution, directly in the newly inserted PEG catheter. To test this hypothesis we conducted a large randomised clinical trial.

METHODS

Design and intervention

We undertook a double blind, randomised clinical trial to test whether a single dose of 20 ml co-trimoxazole

(800 mg sulfamethoxazole and 160 mg trimethoprim) deposited in the PEG catheter immediately after insertion was at least as good (non-inferiority assumption) for the prevention of acute wound infections as the standard antibiotic prophylaxis of a single intravenous dose of 1.5 g of cefuroxime administered one hour before insertion of the PEG catheter. We chose co-trimoxazole rather than an oral cephalosporin as the test drug because of the following advantages: more rapid absorption in the upper gastrointestinal tract; longer half life; doesn't need to be mixed with food intake (which is difficult immediately after PEG); lower risk of infection with *Clostridium difficile*[17 18]; and lower price.

Patients

All patients at the Karolinska University Hospital, Stockholm, Sweden, who were referred to the endoscopy unit for PEG during the period 3 June 2005 to 31 October 2009 were considered for inclusion. Those who did not meet any exclusion criteria, had no contraindications for PEG, and were able to give consent to participation in the study after receiving oral and written information were included. Reasons for exclusion were ongoing antibiotic treatment, illness too severe to allow the patient to participate, or allergy to any of the antibiotic alternatives.

Randomisation and blinding

The randomisation process was conducted by personnel at a hospital department not engaged in the care of the included patients. After a patient had agreed to participate, these personnel were contacted by telephone and on request opened a closed envelope, taken from a pre-prepared block (50 envelopes in each block) of equally distributed and mixed envelopes, containing a randomisation sheet with information on the drug to be used. The patient's personal identity number and the date were documented on the randomisation sheet. Thereafter, the sheet was sent to the study coordinator. The patient and the nurse who evaluated the patient at the follow-up visit were both blinded to which antibiotic was to be given. The blinding of the patients was accomplished by using intravenous fluid and manipulating the newly inserted PEG catheter in all patients. This sham manoeuvre was facilitated by the use of sedation. The nurses who evaluated the patients at the follow-up visit were not involved in insertion of the PEG catheter, including the administration of antibiotic prophylaxis.

The PEG procedure

All patients fasted for at least six hours before the PEG procedure. The local anaesthetic lidocaine (Xylocaine; AstraZeneca, London) was administered as a throat spray, after which midazolam (Dormicum; Roche) was given intravenously for sedation. A standard, silicon wire reinforced, 20 Charrière Bard FasTrac pull PEG catheter (Bard Norden AB, Sweden) was used in all patients. The catheter was pulled down through the mouth, into the stomach and out through the abdominal wall, and anchored with an external bolster. The tightness of the bolster position was checked by gently pulling on the catheter to see if the bolster could easily be lifted about 5 mm from the abdominal wall, thus ensuring that the fit was not too tight. The PEG catheter could then be used for infusion within two hours.

Patients were given an information folder that contained a description of what had been done during the procedure, the brand name of the PEG catheter, instructions on how to perform daily care of the catheter and the wound site, solutions to common problems associated with PEG, general nutritional advice, and a telephone number for the outpatient surgical clinic and a dietitian for contact whenever advice about the PEG device or nutrition was needed.

Data collection

The baseline data collected were name, personal identity number, age, sex, indication for PEG, comorbidities, and tobacco smoking habits. Peripheral blood samples were collected for measurement of haemoglobin, highly sensitive C reactive protein, white blood cells, and albumin. Objective measurements of weight and height were collected for assessment of body mass index (BMI).

At the follow-up appointment within 7-14 days of insertion of the PEG catheter, any visible signs of infection, leakage, diarrhoea, constipation, abdominal pain, and fever were documented and treated if necessary. A sample for bacterial culture was retrieved from the PEG stoma and blood samples were collected for measurement of the same parameters as presented above. If the patient was unable to attend the follow-up visit, the patient or caring personnel were contacted by telephone and interviewed by the study nurse, who asked whether any complications had occurred. If this interview led to any suspicion of a complication, the patient was given a new urgent appointment and was checked up at the outpatient clinic, where any infectious complications were documented.

Finally, information on any deaths was obtained by checking the complete and continuously updated Swedish Total Population Register.

Outcome assessment

The primary outcome was occurrence of a clinically identifiable wound infection, as judged by a red zone around the catheter or occurrence of pus, subcutaneous swelling, and pain on palpation in the area around the catheter. Secondary outcomes were objective signs of infection, including a positive bacterial culture, high levels of highly sensitive C reactive protein, and a high white blood cell count.

Statistical analysis

The primary objective was to assess the non-inferiority of co-trimoxazole compared with cefuroxime. The difference between the co-trimoxazole and the cefuroxime group in the proportion of patients with an infection was estimated, as was the corresponding two sided 95% confidence interval (CI). Non-inferiority of co-trimoxazole would be achieved if the upper

limit of the 95% CI was smaller than the pre-specified non-inferiority margin of 15%. The non-inferiority margin was selected on a clinical basis.

Assuming infection rates of 15% or 20% in both groups, the number of patients required to establish non-inferiority with 80% power and significance level of 5% were 89 or 112, respectively. Differences between the two treatment groups were tested with the t test or the Mann-Whitney U test for continuous variables, depending on which assumption was met. The χ^2 test was used for categorical variables as long as the expected count in every cell was at least five, otherwise Fisher's test of exact probability was used.

Intention to treat was the main analysis strategy and encompassed all randomised patients irrespective of whether they received a PEG catheter or not, or were followed up or not. A per protocol analysis was conducted as a sensitivity test, and included only those patients who underwent PEG and were followed up. The software SAS Statistical Package (Version 9.2; SAS Institute Inc, Cary, NC) was used for all statistical analyses.

RESULTS

Inclusion of patients

The figure presents a flow chart of patients considered for the study. During the four year study period, 535 patients with a need for PEG were considered for inclusion. Of these patients, 301 were unable to give informed consent or did not wish to participate in the study. The remaining 234 patients were randomly assigned to a study arm and included in the intention to treat analysis: 116 patients in the co-trimoxazole group and 118 patients in the cefuroxime group. A total of 12 (10%) patients in each group did not undergo PEG for anatomical reasons. Between the PEG procedure and the follow-up visit, five patients died, one patient pulled out the PEG catheter without ensuing complications, three patients were lost to follow-up,

Table 1 | Characteristics and indications for percutaneous endoscopic gastrostomy (PEG) for the 234 patients randomised to Bactrim or Zinacef

	Co-trimoxazole (n=116)	Cefuroxime (n=118)
Characteristic		
Female	42 (36)	31 (26)
Age (mean in years (±standard deviation))	66 (12)	65 (12)
30 day mortality	8 (7)	5 (4)
Current tobacco smoker	32 (28)	41 (35)
Diabetes	8 (7)	8 (7)
Indication for PEG		
Ear, nose, or throat cancer	58 (50)	69 (59)
Neurological disease	24 (21)	18 (15)
Oesophageal cancer	20 (17)	10 (9)
Stroke	4 (4)	7 (7)
Dementia	1 (1)	0 (0)
Gastric cancer	0 (0)	1 (1)
Other	9 (8)	13 (11)

All values are number (%) unless stated otherwise and rounded up, which in some cases gives a sum of more than 100%.

and one patient who was randomised to cefuroxime received co-trimoxazole instead. After exclusion of these 34 patients, 100 patients in each group remained for the per protocol analysis.

Patient characteristics

Basic characteristics of the 234 included patients are presented in table 1. No substantial differences existed between the two groups regarding age, mortality at 30 days, tobacco smoking status, or occurrence of diabetes, but the proportion of men in the cefuroxime group was non-significantly higher. The indications for PEG were also evenly distributed, except for a higher proportion of patients with oesophageal cancer in the co-trimoxazole group. Cancer of the ear, nose, or throat was the most common reason for PEG in both groups.
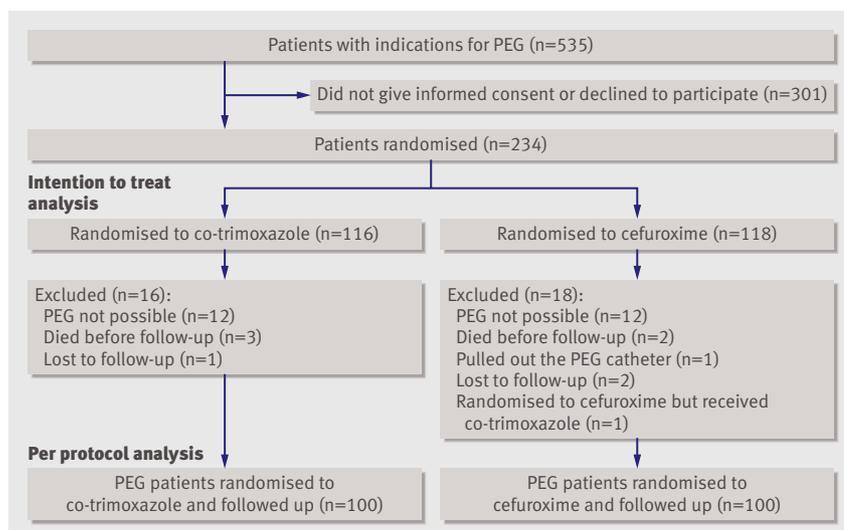
Complications

Table 2 summarises the occurrence of pre-defined complications in the two treatment groups after insertion of the PEG catheters. One or more of these complications were found in 43% (50/116) of the patients in the co-trimoxazole group and in 47% (55/118) of the patients in the cefuroxime group (P=0.590). None of the individual complications was strongly over-represented in any of the groups, but the frequencies of catheter leakage, constipation, abdominal pain, fever, and infection were non-significantly higher in the cefuroxime group (table 2).

No adverse reactions to the antibiotics used were recorded among the included patients.

Wound infection (primary outcome)

In the intention to treat analysis, the occurrence of clinically identifiable wound infection was 8.6% (10/116) in the co-trimoxazole group and 11.9% (14/118) in the cefuroxime group. The percentage point difference between the rate of infection in the co-trimoxazole

Flowchart of patients considered for the trial of antibiotic prophylaxis in patients with a need for percutaneous endoscopic gastrostomy (PEG)

Table 2 | Complications after insertion of the percutaneous endoscopic gastrostomy (PEG) catheter

	Co-trimoxazole (n=116)	Cefuroxime (n=118)
No complications	66 (57)	63 (53)
Abdominal pain	13 (11)	17 (14)
Leakage around the catheter	10 (9)	16 (14)
Infection	10 (9)	14 (12)
PEG procedure failed	12 (10)	12 (10)
Constipation	7 (6)	11 (9)
Diarrhoea	5 (4)	4 (3)
Patient died before follow-up	3 (3)	2 (2)
Fever	0 (0)	3 (3)
Patient pulled out PEG catheter before follow-up	0 (0)	1 (1)

Values are number (%). Each individual patient could have more than one complication.

group and that in the cefuroxime group was −3.3% (95% CI −10.9% to 4.5%). The per protocol analysis had similar results—10% (10/100) and 13% (13/100) infection in the co-trimoxazole and cefuroxime groups, respectively (percentage point difference −3.0%, 95% CI −11.8% to 5.8%). Both these analyses indicated non-inferiority of co-trimoxazole compared with cefuroxime because the upper bounds of the confidence intervals are lower than the pre-determined non-inferiority margin of 15%.

Positive bacterial culture or blood chemistry (secondary outcomes)

Bacterial cultures were collected in 70% (81/116) of the patients in the co-trimoxazole group and in 71% (84/118) in the cefuroxime group. A positive bacterial culture was identified in 44 out of 81 patients (54%) in the co-trimoxazole group and in 53 out of 84 patients (63%) in the cefuroxime group (P=0.252; table 3). Of the 10 patients in the co-trimoxazole group with a clinically identifiable wound infection, eight had a positive bacterial culture, whereas the corresponding proportion in the cefuroxime group was 11 out of 14 patients. The most frequent type of bacteria detected in patients with an infection was *Staphylococcus aureus.*

The comparison groups showed no differences regarding changes in blood chemistry between baseline and follow-up (table 4).

DISCUSSION

This single centre, two arm, randomised, controlled, double blind clinical trial indicates that infection prophylaxis with 20 ml co-trimoxazole, deposited in the PEG catheter immediately after its insertion, prevents wound infection at least as effectively as pre-operative intravenous cefuroxime in patients undergoing PEG.

Antibiotic prophylaxis is usually accomplished by using a second generation cephalosporin, such as cefuroxime, given as a single intravenous dose just before the PEG procedure. However, this strategy has several drawbacks. Firstly, PEG is a common procedure, and the cost of intravenous antibiotic drugs is not negligible. Secondly, giving an antibiotic intravenously is a time consuming process that requires

special equipment. Thirdly, achieving the one hour time delay between the administration of the antibiotic and the insertion of the PEG catheter requires good collaboration between the hospital ward and the endoscopy unit. Fourthly, in the roughly 10% of cases where it proves impossible to insert a PEG catheter, the prophylaxis is given in vain.[16] Fifthly, there is a risk of superimposed infection with *Clostridium difficile* after a single dose of a cephalosporin given as antibiotic prophylaxis.[17 18]

Assuming that the results of the present study are true—that is, that co-trimoxazole solution given in the PEG catheter after insertion of the catheter can replace intravenous cephalosporin—these five problems are solved. This new strategy is inexpensive, requires no intravenous administration, and is given after the PEG catheter is in place. Another advantage of using the co-trimoxazole approach is that the treatment may potentially have a local antibacterial effect with rapid peritoneal absorption.[19 20]

The efficacy of antibiotic prophylaxis in surgery has been shown to be reduced if it is administered more than one hour after incision,[21] but the PEG procedure is very rapid[22] so the time factor should not have a profound effect on the efficacy of co-trimoxazole prophylaxis. Co-trimoxazole, an inexpensive sulphonamide preparation combined with trimethoprim, in oral solution has good bioavailability and a long half life (about 10 hours for both components), and has an antibacterial spectrum suitable for the flora common in the upper gastrointestinal tract, including meticillin resistant *S aureus* (MRSA).[23 24]

Comparison with other studies

Although PEG is considered a relatively minor surgical procedure, it is associated with a general complications rate reported to be as high as 50% and a major complications rate of up to 7.4%.[16 25] Wound infection is the most common problem, with a frequency of up to 32% without antibiotic prophylaxis.[6-8 26] Such infections often require treatment with systemic antibiotics, intensive local wound care, and adjustment of the PEG catheter if fitted too tightly. These wound infections can also develop into a more devastating kind—for example, necrotising fasciitis—with high mortality.[27] Infectious complications entail patient discomfort and costs; for example, owing to a longer hospital stay.[28]

Several meta-analyses have established that antibiotic prophylaxis in PEG procedures decreases the infection rate, with an absolute risk reduction of 14-17% and a

Table 3 | Bacterial growth in culture of samples retrieved from the percutaneous endoscopic gastrostomy (PEG) stoma at 7-14 days after insertion of the PEG catheter

	Co-trimoxazole (n=116)	Cefuroxime (n=118)
Positive growth	44 (38)	53 (45)
Negative growth	37 (32)	31 (26)
No culture performed	35 (30)	34 (29)

Values are number (%).

Table 4 | Blood chemistry at baseline and at follow-up 7-14 days after insertion of the percutaneous endoscopic gastrostomy (PEG) catheter

	Co-trimoxazole (n=116)		Cefuroxime (n=118)	
	Baseline	Follow-up	Baseline	Follow-up
C reactive protein (mg/l)	7.3 (3.3, 30.7)	8.7 (4.5, 32.4)	6.9 (2.3, 21.4)	7.4 (3.9, 30.0)
White blood cell count (×10^9/l)	7.3 (5.7, 11.2)	7.2 (5.7, 9.4)	7.8 (5.9, 10.2)	7.2 (5.4, 9.3)
Haemoglobin (g/l)	125 (18)	121 (15)	124 (17)	125 (16)
Albumin (g/l)	32 (27, 36)	32 (27, 35)	33 (28, 36)	33 (29, 36)

Values are median (lower and upper quartile) for C reactive protein, white blood cell count, and albumin. Values are mean (±standard deviation) for haemoglobin.

number needed to treat to avoid one infection of between six and 10.[11 12 29 30] To reduce infections and their negative effect on patients' quality of life, antibiotic prophylaxis during PEG is recommended. Our novel approach of giving an oral antibiotic solution directly into the PEG catheter immediately after insertion has not to our knowledge been tested previously.

Strengths and limitations of the study

Advantages of this study include the prospective randomised design, the blinding of all patients and evaluators, and the complementary use of objective markers of infections—that is, bacterial cultures and blood chemistry. Among the disadvantages, the included patients had to be well enough to be able to give informed consent, and, therefore, they might have been healthier than those who were not included. On the other hand, the patients with ear, nose, or throat cancer, who made up the majority of patients in both study groups, were likely to have received chemoradiotherapy, which could have a possible negative effect on their immunological defences.

The potential for problems with the subjectivity of infection diagnosis was counteracted by the strict blinding of patients and the experienced nurses who evaluated the patients at follow-up. Moreover, the secondary outcomes were objective and the results of the analysis of these outcomes supported the main finding.

Conclusions and policy implications

In conclusion, this prospective clinical trial of patients who require PEG—which had a strict randomisation process and blinding of all patients and evaluators, and used several outcome markers—indicates that antibiotic prophylaxis with 20 ml co-trimoxazole administered through a newly inserted PEG catheter prevents infectious complications at least as well as the standard prophylaxis with intravenous 1.5 g cefuroxime given before the PEG procedure.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Wound infection is a common complication of percutaneous endoscopic gastrostomy (PEG)

Several randomised studies and meta-analyses have shown a positive effect of antibiotic prophylaxis on the risk of infection after insertion of a PEG catheter

Antibiotic prophylaxis usually comprises a single intravenous dose of a second generation cephalosporin administered just before the PEG procedure, which is rather expensive, time consuming, and can be given in vain in patients in whom the PEG procedure is impossible to accomplish

WHAT THIS STUDY ADDS

Administering the oral solution of co-trimoxazole, a combination of a sulphonamide and trimethoprim (Bactrim), in the PEG catheter immediately after insertion is as effective at preventing wound infections as the standard prophylaxis regimen of cefuroxime (Zinacef) given intravenously before the PEG procedure

This new strategy of antibiotic prophylaxis with co-trimoxazole can be administered rapidly and is inexpensive, safe, less likely to be administered needlessly, and could be used wherever in the world the PEG procedure is done

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