

Controlled trial of prophylactic penicillin in thoracic surgery

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Penicillin has often been given to patients undergoing surgery with the object of preventing post-operative infections, but there is little information about the efficacy of prophylactic antibiotics in surgery and few controlled studies have been made. This investigation was undertaken to determine the effect of large doses of prophylactic penicillin in thoracic surgery by means of a controlled trial.

MATERIAL AND METHODS

The patients were those admitted to the Thoracic Unit, St. Helier Hospital, Carshalton, during a period of one year.

Patients who underwent thoracic surgery were allocated at random to either (1) a penicillin group, who were given 2 million units of crystalline penicillin twice daily starting on the day before operation and continuing to include the fourteenth post-operative day, or (2) a control group, who had no prophylactic antibiotic. Random allocation was undertaken by a clerk who was unaware of the diagnosis of the patient.

All patients were observed for infection as follows: (1) wound infection. Wounds which appeared to be infected were noted and swabs were taken for culture; (2) pleural space infection. Where pleural space infections were thought to be present, fluid was obtained where possible by aspiration or from a drainage tube and was sent for culture; (3) lung infection. Where (in the opinion of the clinician in charge) respiratory symptoms or signs or a chest radiograph suggested a lung infection, this was noted and sputum was obtained for culture. Where post-operative infection occurred, the clinician was free to treat the patient with any antibiotic.

RESULTS

There were 96 patients in the control group and 80 in the penicillin group. The pre-operative

diagnoses were similarly distributed in the two groups (Table I), and any differences in the operations performed in the two groups were by chance (Table II).

TABLE I
DIAGNOSES

Diagnosis	Group	
	Control	Penicillin
Bronchial carcinoma ..	47	39
Pulmonary tuberculosis ..	23	21
Other	26	20
Total	96	80

TABLE II
DETAILS OF OPERATIONS

Operation	Group	
	Control	Penicillin
Pneumonectomy	27	12
Lobectomy	26	28
Segmental resection	7	11
Thoracotomy	14	16
Cardiac operation	9	3
Other	13	10
Total	96	80

POST-OPERATIVE INFECTIONS Post-operative infections occurred in 27 of 96 control patients and in nine of 80 patients who had received prophylactic penicillin. The numbers of wound, pleural space, and lung infections are shown in Table III. Some patients had more than one site of infection, hence the number of infected sites exceeds the number of infected patients.

The incidence of infection was greatest in the pneumonectomies, of which there were by chance

TABLE III
SITES OF INFECTION

Site	Group	
	Control	Penicillin
Wound	10	6
Pleural space	10	3
Lung	13	1

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twice as many in the control as in the penicillin group. In order to allow for this disparity, tests of statistical significance have been made considering the pneumonectomies only and excluding other operations. The numbers are too small to provide anything but rather suggestive evidence that penicillin had a real effect. The difference between the number of lung infections in pneumonectomy patients in the control and penicillin groups almost reaches statistical significance at the 5% level.

Staphylococcus aureus was the organism most often isolated from infected patients. It was grown from all but one of the 16 wound infections and from all but one of the 13 pleural space infections. The sputum of the 14 patients with lung infections grew *Staph. aureus* in eight, a pneumococcus in two, and *Haemophilus influenzae* in one. In the remaining two patients with lung infection, post-mortem lung swabs grew *Staph. aureus* in one and a pneumococcus in the other. Of the 14 patients with lung infection nine died. Staphylococci isolated from 30 infections were tested for penicillin sensitivity and 26 of them were found to be penicillin-resistant.

POST-OPERATIVE DEATHS There were 14 deaths in the controls and three in the penicillin group (Table IV).

Among the 14 deaths in the control group, there were six patients in whom there was clinical evidence of sputum retention; pathogenic bacteria were isolated from the sputum or post-mortem lung swab, and post-mortem examination showed lung infection. Another two patients had sputum

retention and post-mortem examination showed lung infection. In three patients, a clinical diagnosis of bronchopleural fistula was made and pathogens were isolated from the sputa or pleural aspirates. A necropsy was made in two cases and confirmed a bronchopleural fistula in both. One patient was diagnosed as having a pyopneumothorax from a leaking oesophagojejunostomy. In addition to these 12 deaths, in which pulmonary infection played an important part, there were two other deaths where infection could not be incriminated. One patient inhaled gastric contents and this was confirmed at necropsy; the other died of cardiac failure.

Of the three deaths in the penicillin group, one was attributed to bronchitis and respiratory failure. Two others were unrelated to infection; one died of cardiac infarction and the other of uncontrolled cardiac arrhythmia and cardiac failure. Post-mortem examination revealed no evidence of infection in either of these patients.

Deaths due to infection were therefore 12 in the control and one in the penicillin group. The difference is significant at the 5% level in the pneumonectomy group alone and therefore cannot be ascribed to the preponderance of pneumonectomies in the control group. It is reasonable to conclude that penicillin prophylaxis reduced the mortality in the penicillin group.

DISCUSSION

The use of large doses of prophylactic penicillin was associated with a statistically significant reduction of post-operative deaths attributable to infection. There was also a reduction in the number of post-operative wound, pleural space, and especially lung infections in the penicillin group, though the differences did not attain statistical significance.

Lung infections were often fatal. Of the 14 lung infections, nine were fatal. This high mortality can be attributed to the fact that of the 14 patients with lung infection 12 had undergone pneumonectomy; seven of these patients were infected by *Staph. aureus* resistant to several drugs. Drug-resistant staphylococcal infection in the post-operative stage after pneumonectomy is a dangerous complication especially in bronchitics with impaired pulmonary function. The statistically significant reduction in mortality in the penicillin-treated group is due mainly to the reduction of pulmonary infections, only one occurring in the penicillin group but 12 occurring in the control group.

Most of the post-operative infections and fatal pulmonary infections were due to penicillin-

TABLE IV
CAUSES OF POST-OPERATIVE DEATHS

No. of Patients	Evidence of Cause of Death		
	Clinical	Bacteriological	Necropsy
Control group			
6	Sputum retention	Pathogens isolated	Lung infection
2	Sputum retention	No pathogens	Lung infection
3	Bronchopleural fistula	Pathogens isolated	Bronchopleural fistula in two patients
1	Pyo-pneumothorax	No pathogens	No necropsy
1	Inhaled gastric contents	No pathogens	Inhaled gastric contents
1	Cardiac failure	No pathogens	Cardiac failure
Penicillin group			
1	Bronchitis and respiratory failure	No pathogens	No necropsy
1	Cardiac infarction	No pathogens	Cardiac infarction
1	Arrhythmia and cardiac failure	No pathogens	Cardiac failure

resistant *Staph. aureus*. How could penicillin prevent infection by such resistant organisms? Eriksen and Therkelsen (1954) pointed out that penicillin resistance in staphylococci isolated from clinical sources is of a special kind and due at least mainly to the production of penicillinase which destroys penicillin, the individual bacterial cells remaining highly sensitive to the drug. They suggested that, provided *large enough* doses of penicillin are given, a high concentration may be obtained which might overcome the penicillin-destroying effect of small numbers of staphylococci. This might be effectively used prophylactically in order to avoid the penetration of small numbers of staphylococci into the operative field and would remain effective whether the staphylococci were penicillin-resistant or not. The use of most other antibiotics in prophylaxis is likely to lead rapidly to the emergence of resistant organisms and the drug would become ineffective. Eriksen, Hansen, and Lund (1954) used oxytetracycline prophylactically in a thoracic surgical unit and observed a temporary decrease in post-operative infections followed by an increase and at the same time the emergence of staphylococci resistant to oxytetracycline. In a subsequent trial (Hansen, 1960) patients were given between 1 and 4 million units of penicillin daily starting on the day before operation and continuing for about a week after it. A very considerable fall in the incidence of post-operative pleural space and lung infections followed the introduction of this measure, and the beneficial effects have been found to continue since its introduction several years ago. Since other measures to control infection were taken at the same time, the decrease in the infection rate could not for certain be attributed to the use of penicillin.

Thulbourne and Young (1962) gave 2 million units of penicillin prophylactically to patients undergoing abdominal surgery, most of whom had no evidence of chest disease, and found no difference in the incidence of post-operative chest infection between them and a control group. However, only a small number of their patients had pre-existing chest disease in contrast to patients in the present trial, the majority of whom had respiratory disease. Moreover the risk of pulmonary infections is greater in thoracic surgery than in abdominal surgery. I know of no published

controlled trial of prophylactic antibiotics in thoracic surgery.

No important disadvantage to the use of prophylactic penicillin was found in the present study. Penicillin hypersensitivity was no problem; 4% of patients developed hypersensitivity reactions, but all of them were mild and they subsided rapidly when penicillin was stopped. In addition three of the patients among the 176 in the trial claimed to be already allergic to penicillin and were, of course, not given penicillin. Since, under the circumstances of this trial, most of the staphylococci found in the hospital were already penicillin-resistant, the possibility that penicillin prophylaxis might increase the incidence of penicillin-resistant organisms did not seem a serious disadvantage. The benefits from a reduction in post-operative mortality outweighed this factor.

SUMMARY

Patients undergoing thoracic surgery were allocated at random to either (1) a penicillin group who received 2 million units of crystalline penicillin twice daily started on the day before operation and continued to the fourteenth post-operative day, or (2) a control group who had no prophylactic antibiotic.

Post-operative mortality attributed to infection was 12 times less in the penicillin group than in the control group, the difference being statistically significant.

Evidence is presented which suggests that large doses of penicillin given prophylactically diminish post-operative mortality due to infection even when the infections are due to so-called 'penicillin-resistant' staphylococci.

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