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Intra-operative Antibiotic Prophylaxis in Neurosurgery. A Prospective, Randomized, Controlled Study on Cefotiam

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Summary

In this prospective, randomized and controlled study the effect of cefotiam for the prevention of wound infections following trepanations was investigated. The main interest was centered on the rate of post-operative bone flap infections requiring operative revision. Administration of cefotiam was randomized for patients undergoing major craniotomies. The antibiotic was administered intravenously in a single dose of 2 g with induction of anaesthesia.

Only clean or clean contaminated cases were included. Excluded were contaminated cases, operations with a transnasal-transsphenoidal approach, shunt-operations and patients with any other preoperative infection or antibiotic therapy. Outpatients were excluded due to difficulties in obtaining sufficient clinical information.

From originally 918 consecutive patients operated on 711 fulfilled the entry criteria. With regard to age, sex, diagnosis and the site of the trepanation, control patients ($n = 355$) and cefotiam treated patients ($n = 356$) were shown to be comparable. In the various subgroups formed for different primary diagnoses, concomitant steroidal therapy and concomitant severe internal medical diseases cefotiam treated patients and controls were comparable as well.

A highly significant difference for bone flap infection could be shown with 0.3% in the cefotiam group versus 5.1% in the control group ($p < 0.001$). The overall rate of post-operative deep wound infections including meningitis and abscesses was also significantly ($p < 0.005$) different with 3.1% in the cefotiam versus 9.0% in the control group.

Thus it was concluded that a single dose of cefotiam significantly reduces post-operative deep wound infection.

Keywords: Craniotomy; peri-operative antimicrobial prophylaxis; randomized controlled study; cefotiam.

Introduction

Post-operative wound infections are a serious complication in neurosurgery, especially in major craniotomies where bone flap infections, meningitis or even brain abscesses have to be taken into consideration[5, 18]. The average deep wound infection rate in neurosurgery ranges between 2–8%[2, 3, 8, 10, 12, 14, 18], and post-operative wound infections are responsible for 14% of the post-operative deaths[11].

Various factors increasing the risk of infection have been widely discussed: Re-operations, the use of foreign materials, pre-existing shunt catheters, the free bone flap, the opening of paranasal sinuses, the length of the operation and the kind of shaving procedure[2, 3, 5, 9, 12–14, 16, 17, 21]. But besides improvement of surgical technique, material and surroundings, antibiotic prophylaxis has to be discussed in order to lower the infection rate:

In 1974 Savitz[16] retrospectively compared the administration of ampicillin for 10 post-operative days with a single dose administration of lincomycin, reducing the infection rate from 5.1 to 2.3%. Malis[14] in 1979 presented a regime of gentamycin, vancomycin and irrigation of the surgical field with streptomycin by which the infection rate was 0%. In 1981 Quartey[15] published a study on gentamycin and vancomycin with an infection rate of 0.8%. Another successful regime with cephalotin resulted in 0% infections in clean cases as published by Savitz[17]. Young and Lawner in 1987[20] tested cefazolin and gentamycin with an overall reduction from 3.6% to 1% and from 4.5% to 0% in deep wound infections after craniotomies. In 1988 Blomstedt[2] described a significant difference in post-operative wound infection rates with single doses of vancomycin alone resulting in 1.8% versus 7.3%, while Dempsey[6] in a review recommended the use of cefazolin. In 1989 Haines[12] on the other hand claimed that the decision for an antibiotic agent should depend on the individual situation of the hospital. Djindjian *et al.*[7] reported in a recent study in 1990 on the successful use of oxacillin in prolonged clean neurosurgery with 0.6%

deep infections versus 4.9% in the untreated group. Another recent study by Winkler in 1990[19] on ceftriaxone investigating all kinds of post-operative infections in neurosurgery showed a decrease not only in wound infections but in pneumonias as well.

Most of the studies published so far are retrospective and not controlled, and in the few controlled studies the number of patients is usually limited to about 400 cases. Furthermore the studies seem to be inhomogeneous as regards the neurosurgical procedures included into the studies. This applies mainly to spinal procedures and craniotomies as compared to shunt procedures. In the first case there is an interest in lowering the risk of wound infection[3, 6, 20], in the second case the implantation of a foreign body must be taken into consideration[9]. Therefore we were still interested in a study that was large, controlled, prospective and limited to a homogeneous group of patients.

The antibiotic of choice should be highly specific against the bacteria usually seen in post-operative neurosurgical wound infections, mainly staphylococcus aureus and epidermidis, enterobacter, propionibacterium and a few other gram-negative bacteria[2, 6, 8]. Further it should reach the surgical region in sufficient concentrations, that is, it should easily permeate into soft tissue and bone. If possible it should also penetrate into the cerebrospinal fluid.

According to these criteria cefotiam, a well known cephalosporin of the second generation was submitted to this trial. It has a very broad antibiotic spectrum including staphylococci, betalactamase producing bacteria and gram-negative bacteria. Cefotiam penetrates soft tissue and bone and it is of low toxicity and has few side effects[4]. It is widely used for intra-operative prophylaxis in other surgical specialities.

The aim of this study was to determine whether prophylactically given cefotiam could reduce the rate of deep wound infections including meningitis, abscess and bone flap infections in craniotomies.

Materials and Methods

From October 1985 to September 1987 all consecutive patients undergoing trepanation in the Neurosurgical University Clinic Freiburg were submitted to this prospective and randomized trial. Randomization was achieved in advance by computerized random lists for the administration of cefotiam separately for each of the three operating-tables. Burr hole trepanations and shunt operations were not included in the randomization scheme. Patients operated on more than once in this period were counted separately at every new occasion, except for immediate re-operation for p.o. complications. The total number of trepanations performed was 918. Cefotiam was administered in a 2 g single dose with induction of anaesthesia, only in 5 cases with extremely prolonged operations (> 12 h) a second dose was used to top up.

The result turned out to be 459 patients with intra-operative cefotiam and 459 cases as control group.

The surgical procedure was standardized: The hair of the patient was totally shaved with an electrical razor on the day before the operation and again immediately before the operation with a razor blade in the region of the skin incision which was prepared with a polyvidone-iodine solution. The patient's head was secured in a Mayfield clamp. All trepanations were performed with a free bone flap with the flap kept in polyvidone-iodine solution for the time of the intracranial procedure. At the end of the operation the bone flap was re-implantated and fixed with absorbable threads and the burr holes were filled with bone dust. All operations were performed under the operating microscope.

Data from the operation and the early post-operative period were taken from a special study protocol containing the main surgical data and the usual clinical reports including the anaesthetist's protocol. Late results were obtained by a questionnaire sent to the patients six months after the operation with a return rate of 71%. Further sources for clinical data were the out-patient-clinics' reports (8.4%), clinical reports from other units and the telephone (9.3%). Follow-up informations were not available in 7% only. These patients lost to follow-up had no infection during their stay in the hospital. The post-operative period investigated for wound infections was at least six months.

Data analyzed in particular were: personal data, past medical history, actual diagnosis and treatment, details of operation, intensive care and medical treatment, antibiotic therapy and infection, the post-operative course and the late result. Data collection and evaluation was computer-based (DBASE III+) employing 118 singular items per case.

Statistical analysis was based on the confirmation of structural equality and comparability of the treated and the control group followed by the chi^2-test with double sided p.

Three groups of patients had to be secondarily excluded from the study. These were: Patients with pre-operative infectious diseases and/or further pre- or intra-operative antibiotic therapy (n = 48), patients with an obviously contaminated operative site, in detail: CSF-fistulae and frontal fractures (n = 27), operations employing a trans-sphenoidal approach (n = 88) and patients from other clinics (n = 44) leaving the neurosurgical clinic immediately after the operation, most of which were pediatric patients.

Results

Valid Cases

711 out of 918 cases fulfilled the final entry criteria. 356 belonged to the cefotiam group (= 50.1%), 355 to the control group (= 49.9%).

The equal distribution in the cefotiam and the control group is shown for the age in Fig. 1, for the diagnosis in Fig. 2 and for the localization of the operative approach in Fig. 3. The average duration of the operation was 5 hrs 12 min in the control and 5 hrs 23 min in the treated group. The cefotiam group included 44.4% male and 55.6% female patients, the control group 44.2% and 55.8%, respectively.

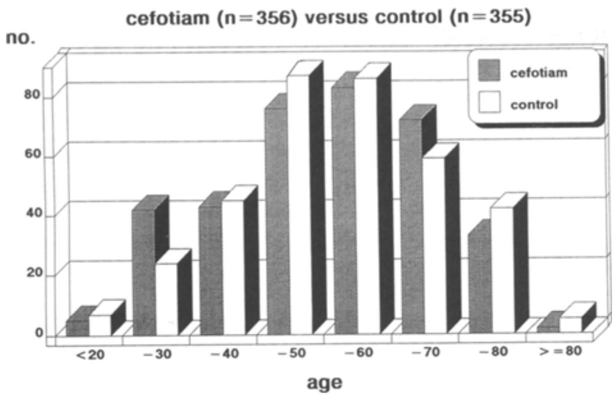

Fig. 1. Distribution of age

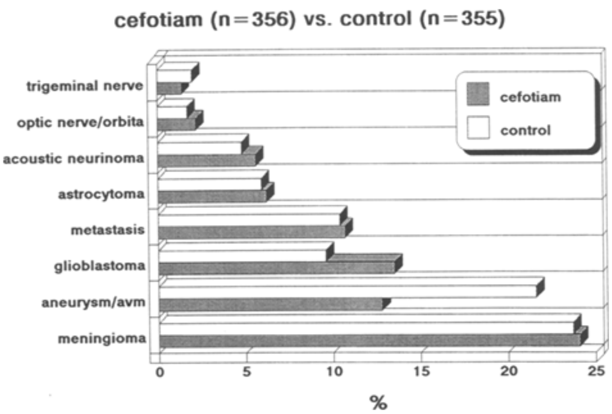

Fig. 2. Distribution of the main diagnoses

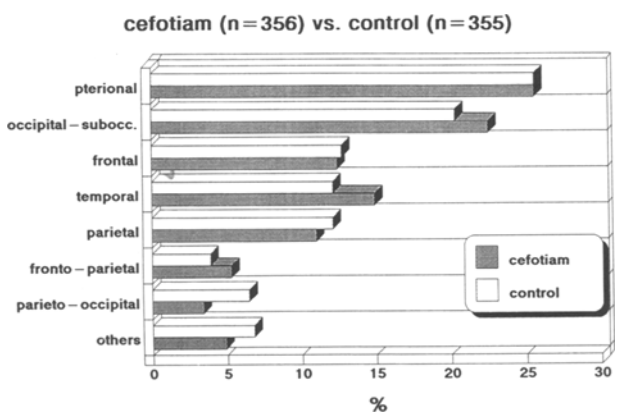

Fig. 3. Rates of operative approaches

Wound Infections

In our study wound infection is defined as deep wound infection requiring further surgical treatment and/or bacterial meningitis with clinical symptoms and bacterial contamination of CSF. Superficial infections of the wound alone were omitted. The results are shown in Table 1.

Table 1. *Post-operative Wound Infections*

Post-operative wound infections	Patients			
	Cefotiam n = 356		Control n = 355	
	n	%	n	%
No follow-up	28	7.9	22	6.2
Bone flap infection alone	1	0.3	18	5.1
Meningitis +/− superficial wound infection	5	1.4	9	2.5
Bone flap infection + CSF-fistula + meningitis	1	0.3	4	1.1
Shunt-sepsis	3	0.8	–	–
Abscess in tumour-bed	–	–	1	0.3
Infected (palacos) cranioplasty	1	0.3	–	–
Infected cyst	1	0.3	–	–
Total infections*	12	3.4%	32	9.0%

* Difference significant with $p < 0.005$.

The rate of bone flap infection alone was in the cefotiam group, 1 out of 356 cases (0.3%), and in the control group, 18 out of 355 (5.1%), which is statistically significant for $p < 0.005$.

The single patient with bone flap infection in the cefotiam group was a 50 years old man with a recurrent oligodendroglioma grade II. As an intra-operative problem difficult haemostasis was reported. Post-operatively the patient was on dexamethasone, 18 days after the operation he developed a bone flap infection and the bacterium identified was enterobacter aerogenes. The patient was treated with fosfomycin, the bone flap was removed and the patient recovered.

In the group of the 18 control patients with bone flap infection the average age was 53 years, 8 were female and 10 male. Their diagnoses were 6 meningiomas, 4 metastases, and 1 of each of the following: glioblastoma, epidermoid, astrocytoma, acoustic neurinoma, optic nerve compression, cavernoma, haemangio-pericytoma and re-operation for haemorrhage. 28% out of those 18 patients had a malignant tumour compared to 25.3% out of all 711 valid cases, suggesting that in our study malignancy does not increase the risk of bone flap infections. Two patients had post-operative local radiation. Out of the 18 patients 6 (33%) none had corticosteroids (defined as pre-operatively less than 12 mg/day dexamethasone for 4 days or 48 mg/day for 3 days, post-operatively less than 24 mg/

day for 4 days or 48 mg/day for 3 days or dose equivalent), 4 patients (22%) had corticosteroids only post-operatively and 7 patients (39%) were pre- and post-operatively under corticosteroids compared to only 14% out of all 711 valid cases, which suggests an influence of an extensive corticoisteroid treatment on the risk of aquiring a bone flap infection. The microbiological results were 9 cases with staphylococcus aureus (50%), 6 staphylococcus epidermidis (33%), 4 propionibacterium acnis (22%) and 2 enterobacter cloacae (11%). One of the 18 patients was severely medically impaired (pulmonary and renal insufficiency), after removal of the bone flap he went into coma and died later on. Two patients were severely disabled and 15 patients recovered completely or were slightly impaired. The antibiotics used were mainly cefotiam and fosfomycin.

The rate of bone flap infections with a secondary CSF-fistula and/or meningitis was 1 (0.3%) in the cefotiam versus 4 (1.1%) in the control group. The cefotiam treated patient was a 61-year old male with an acoustic neurinoma, he had no corticosteroids and developed a bone flap infection 3 weeks post-operatively, a CSF-fistula was found and the microbiological result was staphylococcus epidermidis. He was re-operated upon and recovered almost completely. The details of the control group were as follows: One of the control group cases was female, 59 years old, operated on for an aneurysm, she was on dexamethasone, developed a meningitis and bone flap infection on the 10th post-operative day, was re-operated on and remained severely disabled. One was a 62-year old male with an aneurysm and hepatic failure, besides the meningitis and bone-flap infection he developed a sepsis and pneumonia, was re-operated on the 10th day and died later. The third patient was a 74 years old male with a meningioma, he developed a meningitis, bone flap infection, sepsis and pneumonia, was re-operated upon and remained severely disabled. The fourth patient was a 54 years old female with a glioblastoma and diabetes. She had a bone flap infection with CSF-fistula 6 weeks after the operation, she was re-operated on and recovered completely.

Regarding the rate of post-operative bacterial meningitis alone only a small insignificant difference of 5 out of 356 cefotiam treated patients (1.4%) versus 9 out of 355 control patients (2.5%) could be observed. Aseptic post-operative meningitis was not considered as a post-operative infection[1]. One meningitis due to a lumbar drain was recorded, this patient had a lumbar drain because of a subarachnoid haemorrhage due to a ruptured aneurysm, was operated upon for the aneurysm and had a meningitis and sepsis 5 days post-operatively. The single case with an infected (palacos) cranioplasty was one out of 5 patients operated for a cranioplasty. The palacos used contained gentamycin in all cases.

The overall wound infection rate including all kinds of post-operative deep wound infections as shown in Table 1 was 11 out of 356 cases (3.1%) in the cefotiam versus 32 out of 355 cases (9.0%) in the control group. This main result is statistically (chi^2-test) significant for $p < 0.005$.

For all 44 patients with deep wound infections 16 different antibiotics were employed post-operatively. In cases of bone flap infections mainly cefotiam and fosfomycin were used. One patient developing meningitis after transmission to another hospital experienced at least 6 different antibiotics within a very few days and without having an antibiogramm performed. He belonged to the control group.

Other Post-operative Infections

There were 14 cases of post-operative sepsis. Five (1.4%) occurred in the cefotiam group with one fatal outcome, 9 (2.5%) in the control group with 3 fatal results ($p < 0.01$). In 40% of the cases staphylococcus epidermidis was found. There was one case of proteus sepsis and one of pseudomonas both occurring in the cefotiam group. 42 cases of pneumonia were found, 14 (3.9%) in the cefotiam and 28 (7.9%) in the control group ($p < 0.05$).

Special Risk Groups

Several subgroups of patients were investigated to evaluate a special risk of infection and special effectivity of cefotiam. The rates of post-operative wound infections in the control cases of some subgroups are given in Table 2. Each subgroup was examined for comparability even if no special figures are given.

Table 2. *Post-operative Wound Infections in High Risk Groups*

Risk factors	Patients				
	Control		Cefotiam		Total
	n	%	n	%	n
Malignant tumour	7	8.4	0	0	180
Pre-operative steroids	13	17.6	3	3.8	152
Post-operative steroids	13	9.6	4	2.9	271
Severe internal disease	8	13.3	2	3.2	122
Re-operations	7	9.1	5	4.7	183

Statistically age did not contribute to the wound infection risk, the average age of patients with or without infection was 51 years. It was attempted to evaluate the time spent pre-operatively on intensive care units but due to frequent transmissions from other hospitals pre-operative intensive care times could not be evaluated. Post-operative intensive care was of course longer in cases with infection, due to the infection itself. Therefore the duration of intubation and intensive care and the central venous lines were not further evaluated.

Parietal trepanations (n = 82) were chosen as the cleanest group because there is no risk of opening any paranasal air sinus. There was no wound infection in the cefotiam group (n = 39) and 3 (7%) in the control group (n = 43). This is only slightly below the main group results.

180 patients were operated on for a metastasis or a malignant tumour of the brain. 97 (54%) were in the cefotiam group, 83 (46%) in a control group, 61% and 68% respectively had post-operative cerebral radiotherapy and 44% and 37% respectively had pre-operative steroids. In the cefotiam group no patient developed a wound infection, in the control group 7 patients (8%) developed a deep wound infection. The difference was statistically significant with $p < 0.02$.

Considering the immuno-supressing effects of corticosteroids as shown in the cases of bone flap infections, data were investigated for the influence of pre-operative and post-operative administration of dexamethasone on the infection rate. Pre-operative dexamethasone therapy was defined by a minimum dose of 12 mg/day for a minimum of 4 days or 48 mg/day for a minimum of 3 days (or dose equivalent). Total number of thus treated patients was 152, 78 (51%) were cefotiam treated and 74 (49%) were controls. The wound infection rates were 3 out of 78 (4%) in the cefotiam treated versus 13 out of 74 (18%) in the control group ($p < 0.01$), which indicated a twice as high infection risk compared to the control group.

In the case of severe concomitant medical disease, such as diabetes, renal, hepatic and cardiac insufficiency, alcohol abuse, asthma and others (n = 122) the wound infection rate was 2 out of 62 cefotiam treated cases (3%) versus 8 out of 60 control cases (13%) with $p < 0.05$. Consequently, severe medical disorders increase the risk of post-operative wound infection from 9% to 13%.

In cases of re-operations no statistical difference could be detected (4.7% vs 9.1%).

Excluded Group of Transnasal-Transsphenoidal Operations

In this excluded group 32 out of 81 patients (40%) were in the cefotiam group and 49 (60%) were controls. In the cefotian group 2 patients (6%) had meningitis. One was a 61 years old patient with a hypophyseal adenoma who was operated upon 3 times within 2 days, 3 weeks post-operatively he had a CSF-fistula and meningitis. The other patient was 81 year old and had a recurrent hypophyseal adenoma. He was operated and re-operated on for bleeding in the tumour bed, a few days later he had pneumonia, meningitis and sepsis and died due to cardiac failure.

In the control group 4 patients (8%) had a post-operative meningitis. Two patients showed no special risk, one was diabetic and the fourth was 79 years old, he died post-operatively of a fulminant meningitis and pneumonia. No statistical evaluation is possible.

Discussion

Post-operative wound infections are a widely discussed problem in surgery. Additionally in neurosurgery the rate of post-operative wound infection seems to be higher when compared to general surgery[5]. The infection rate ranges between 2 and 8%[2, 3, 7, 8, 10, 12, 14, 18]. The two main deep wound infections following trepanations are bone flap infections and meningitis leading to prolonged hospitalization, surgical revisions, possible neurological impairment or death.

There are only few controlled and randomized studies which demonstrate a beneficial effect of antibiotic prophylaxis[2, 7, 10, 19, 20]. This stimulated us to undertake a large controlled study focussed on this topic. Considering the low rates of post-operative infections the study was designed to be large enough to achieve a significant result.

As to the methods employed in this study, it is a randomized, controlled and prospective trial on the basis of 918 consecutive patients, whereas other controlled study numbers range between 150 and 400 patients with the exception of the trial by Young and Lawner[20] comprising 846 patients. The surgical procedures were standardized. Comparability of the treated and the control groups could be shown. The careful statistical analysis was based on the X^2-test with double sided p.

The entry criteria of this study were comparatively strict. Only major craniotomies were included, other procedures such as burr hole trepanations, stereotactic and spinal surgery were excluded. Especially spinal surgery contains a lower risk of infection in[3, 6, 19, 20] comparison with craniotomies. Shunt implantations were excluded because the implantation of the foreign material and the connection of the ventricles with the atrium or the peritoneum causes a completely different situation with far higher infection rates[9]. Patients with CSF-fistulae or frontal fractures were excluded as contaminated cases and patients operated on by a transnasal approach were excluded and evaluated separately. Furthermore, patients with any other pre-operative infection or antibiotic therapy and outpatients were excluded.

By these restrictions the patients formed a homogeneous group and only clean or clean contaminated (paranasal sinuses opened) major craniotomies were included. On the other hand the controlled and randomized studies by Geraghty[10], Young and Lawner[20], Winkler[19] and Djindjian[7] include spinal surgery, only the study by Blomstedt[2] in 1988 is restricted to craniotomies. Consequently the comparability of these studies is limited.

On the basis of previously performed antibiograms in our clinic and the pharmacological properties[4] of cefotiam, this antibiotic was considered appropriate to reduce the rate of post-operative wound infections.

Compared to several other studies[10, 14, 15, 20] the use of only one antibiotic has the advantage of less side effects and less costs. Furthermore the use of combinations of antibiotics is discussed as the reason for more and more resistant bacteria. In our study on the cephalosporin cefotiam no case of allergy or serious side effect was observed with 918 patients. Other controlled studies on one prophylactic antibiotic only were by Blomstedt[2] on vacomycin, by Djindjian[7] on oxacillin and by Winkler[19] on the cephalosporin ceftriaxone. Vancomycin can have serious side effects and is recommended for severe infections with staphylococci where other antibiotics have failed. Oxacillin on the other hand is especially effective against staphylococci, which cause most of the trouble in neurosurgical wound infections[6].

The results of the non-treated group in our study are in agreement with the literature. Generally the wound infection rate in neurosurgical procedures ranges from 2 to 8% with spinal surgery and shunt procedures included[3, 8, 10]. In the study of Blomstedt[2] on craniotomies the infection rate of the untreated group is 8%, ours is 9%.

Of course it has to be considered, that every hospital has its own bacterial spectrum and this restricts the choice of the antibiotic for every clinic.

The randomized and controlled trials which have to be compared with our results are the following: Geraghty[10] performed a trial employing the "Malis" regime of gentamicin, vancomycin, and irrigation with streptomycin including 407 patients with cranial and spinal procedures. The wound infection rate was lowered from 3.5% to 0.5%. The trial of Young and Lawner[20] consisted of 846 patients, 250 of which had major craniotomies. By use of cefazolin together with gentamicin the deep wound infection rate in craniotomies could be reduced from 4.5% to 0%. In the study by Blomstedt[2] with 360 clean craniotomy cases the bone flap infection rate in supratentorial surgery was reduced from 6.2% to 1.6% by means of vancomycin. Djindjian[7] in his study on the effect of oxacillin with 400 cases including spinal and stereotactic procedures showed that the deep wound infection rate was reduced from 4.9% to 0.6%. Finally, Winkler[19] in his study on 159 patients including spinal and cranial surgery tested ceftriaxon with the first administration during induction of anaesthesia and a second dose the next morning. The numbers of wound infection were 2 versus 4 cases, but the numbers of pneumonias were 1 versus 10 cases.

With a reduction of the deep wound infection rate from 9% to 3.1% the results of our study show a significant effect of a single dose of cefotiam with the induction of anaesthesia. The rate of bone flap infections alone was extremely low in the cefotiam group (0.3% versus 5.1%), and together with the bone flap infections with CSF-fistula and/or meningitis it was 0.6% versus 6.2% in the control group, a reduction of 90%. These results are comparable to the results obtained with vancomycin (1.6% versus 6.2%) by Blomstedt[2] or those by Young and Lawner[20] with cefazolin plus gentamicin (0% versus 4.5% in craniotomies only), but they are achieved their results with one antibiotic only with very little side effects. With the exception of the "re-operated" patients the prophylactic effect of cefotiam in the special risk groups was even more impressive than in the total group.

The development of post-operative sepsis and post-operative pneumonia was also significantly lowered, which leeds to the assumption, that most bacteria are introduced during anaesthesia and operation. But this was not further analyzed.

Thus, it can be concluded, that cefotiam is in clean and clean contaminated trepanations effective in the prevention of deep wound infections.

Addendum

This investigation on antibiotic prophylaxis was undertaken at the Freiburg University Clinic when the author and co-author worked there in the neurosurgical department.

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