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Prophylactic Topical Gentamicin after Open Reduction and Internal Fixation of Long Bone Fractures in Orthopedics

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Abstract: The present study aimed to evaluate the efficacy of adding local Gentamicin to the systemic regimen, in patients undergoing open reduction and internal fixation of a single long bone fracture. Randomized double blind placebo controlled trial conducted from April, 2005 to October, 2006. Shahid Mohammadi Hospital, Bandar Abbass, Iran, Hormozgan University, main hospital for Hormozgan province. One hundred and twenty patients were randomized to equal groups (60 patients each). In both groups, 1 g of Cefazolin was administrated intravenously before surgery and repeated every 6 h for 48 h. In the case group 160 mg of Gentamicin in liquid form was added to the wound too. The primary endpoints to be evaluated were superficial and deep infection rates in both groups, suspected by clinical presentation and confirmed by laboratory tests. All of the patients were followed up for 4 months and many of them for one year. Superficial infection was found in 12 patients of the control group. Three of them progressed to deep infection. Deep infection occurred without superficial infection in two patients of the control group. All of the infections occurred in the first three months of the operation. In the case group only three superficial and no deep infections were found. Both superficial and deep infection rates were significantly lower in the case group ($p<0.05$). The follow-up period for all of the patients was not long enough because of noncompliance. The results can not be generalized to all surgical operations. Rate of infection can be diminished by adding local Gentamicin as a prophylactic agent to the standard systemic antibiotic regimen.

Key words: Infection, gentamicin, orthopedic surgery

INTRODUCTION

Infection after orthopedic operations is one of the most disastrous complications in orthopedic surgery, remaining a dangerous and devastating event despite the best efforts at sterility and prophylactic use of antibiotics. In light of the enormous population of patients with orthopedic implants, even a currently low risk of infection, estimated to be in the range of 0.5-5% for total joint replacements or 1 to 5% for fracture treatment, has to be considered very relevant for its serious consequences (Campoccia *et al*., 2006, Cleveland, 2003). Although the efficacy of systemic use of antibiotics has been proved in this setting in several studies and is in common use nowadays (Cleveland, 2003; Schurman *et al*., 1978; Buckwalter *et al*., 1995), the risk is not completely abolished since these operations are performed on tissues with poor blood supply and aside from this the use of metallic devices and the occasional need for bone graft addition are important factors, (Cleveland, 2003, Buckwalter *et al*., 1996; Nelson *et al*., 1982). So use of prophylactic local antibiotics has gained significant notice nowadays and many studies have been performed on the topic. Many of these studies have used polymethyl methacrylate (PMMA) mixed with antibiotics and most of them have been carried out on patients with open fractures (Eckman *et al*., 1988; Keating *et al*., 1996; Osternann *et al*., 1993). Some other studies have evaluated the effect of local antibiotics (mainly gentamicin) on chronic osteomyelitis and they have been proved to be effective in these cases (Rouse *et al*., 2006; Cornell *et al*., 1993; Evens and Nelson, 1993; Henry *et al*., 1993). It has been suggested that local gentamicin has no adverse effect on the adjacent bone and soft tissues and on the bone healing process (Nelson *et al*., 1982; Eckman *et al*., 1988; Keating *et al*., 1996; Osternann *et al*., 1993), though this is controversial (Isefuku *et al*., 2003). The present study

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was designed to evaluate the effectiveness of the practice of local (topical) antibiotic application as a prophylactic measure in patients with closed fractures undergoing open reduction and internal fixation of their fracture.

MATERIALS AND METHODS

The study was a prospective randomized placebo controlled double-blinded clinical trial performed on 120 patients undergoing open reduction and internal fixation of their fractured long bone in Shahid Mohammadi Hospital, Bandar Abbass, Iran, Hormozgan University (Main hospital for Hormozgan province) from April 2005 to October 2006. The study protocol was approved by the faculty of education and research of Hormozgan University of medical sciences. Eligibility criteria were as follows:

- Male or female more than 18 years of age.
- Willing and able to give informed consent
- Single closed long bone fracture classified as class I or II Winquist-Hansen with regard to comminution. The exception was the patients with forearm fractures (both bones, radius or ulna) that were included in the study and their fracture was assumed as single bone fracture.
- Absence of systemic or chronic disease, pathologic fracture, pregnancy, or previous steroid treatment.
- Absence of head, chest or abdominal trauma
- Open fractures graded as, equal or higher than type II in Gustillo-Anderson classification or fractures with compartment syndrome were excluded from the trial.

One hundred and twenty patients were so randomized into control and case groups, of which the case group patients were treated with 160 mg of gentamicin, added locally to the surgical wound at the termination of the operation and before closure, while the control group received placebo.

Both groups received prophylactic intravenous antibiotic (1 g of cefazolin) before the operation which continued for 48 h postoperatively. Plate and screws were used for fixation of all fractures, except for femur fractures in which open intramedullary nailing without locking was possible, noticing the fracture geometry (closed locked intramedullary nailing was not possible at the time of the study because of unavailability of armamentarium). All of the surgical procedures and follow up visits were performed by one surgeon (Z.A.), who was not aware whether the patient had received gentamicin or placebo.

The patients were discharged from the hospital on the 4th or 5th postoperative day. All of the patients were followed up on a routine basis: 2 weeks after the operations for wound inspection and suture removal, 4 weeks later for control radiograms and union assessment, 6 weeks later (3 months after the operation) for taking control radiograms and probable discontinuation of limb protection if the union was complete, then in 1 month intervals for assessment of union, the general condition of the patient and any probable suggestion. After this the patient was visited a year after operation. In addition the patient was visited out of the program in case of any unexpected complications. Although the aim of the study protocol was to follow all of the patients for at least 1 year, this proved to be extremely difficult and actually impossible. Although all of the patients enrolled in the trial were followed for 6 months, after this the percentage decreased gradually, so that at 1 year despite the best efforts only 85 of them could be visited or contacted. As no cases of infection could be detected after 3 months of operation in the group that completed the 1 year follow up, we took it for granted that after 3 months of the operation the other group too had no infection case within. Despite this the results regarding the infection rate can be applied only to the first 6 months of the operation, which is the major limitation to the study. The patients were closely observed for any signs of local or deep infections. Superficial infection was diagnosed if the patient developed redness, swelling, tenderness or wound discharge associated with a positive culture of the wound (Cleveland, 2003; Hanssen *et al*., 1999; Pollock, 1984; Gingrass *et al*., 1964). Deep infection was diagnosed in case of deep abscess formation (limb swelling, pain, fever and pus drainage from the wound, directly or on aspiration with a positive culture) (Cleveland, 2003; Hanssen *et al*., 1999; Pollock *et al*., 1984; Gingrass *et al*., 1964).

RESULTS AND DISCUSSION

The demographics of the patients are demonstrated in the Table 1 and the surgical operations they underwent in the Table 2. All of the cases of infection were observed in the first 3 months after the operation. Twelve cases of superficial infection occurred in the control group of which 9 patients responded to local care, antibiotic treatment and debridement. Three patients developed deep wound infection despite the best efforts at treatment. Wound cultures revealed *S. aureus* in two and *E. coli* in one. The other infecting organisms in this

Table 1: Patients' age and sex distribution

Groups	Mean age (Y/0)	Male	Female
Control group	30.0±2.21	46	14
Case group	28.0±7.36	48	12
Total	29.0±7.04	94	26

Table 2: Distribution of the surgical operations within the two groups

Groups	Femur (plate and screws)	Femur (IM Nail)	Tibia (and fibula)	Humerus	Forearm
Control group	15	11	20	6	8
Gentamicin group	14	10	23	8	5

group were *S. aureus* in 8 and *S. epidermidis* in one. Two patients of this group developed deep infection without evidence of superficial wound infection. The infecting organisms in these two patients were *Proteus vulgaris* and *Escherichia coli*.

In the study group 3 superficial infections were found, all responding to debridement and intravenous antibiotic treatment. The infecting organism proved to be *S. epidermidis* in two and *S. aureus* in one. No cases of deep infection, primary or after presentation with superficial wound infection were found in this group.

All of the deep infections occurred in patients with tibia or femur fractures in whom the fracture had been fixed with plates and screws. But two cases of superficial infection were found in patients with humerus and forearm fractures, both in the control group.

Although it was not the aim of the study, an attempt was made to detect the patients that their fracture had progressed to nonunion. Among the patients that completed the one year follow up period 8 cases of established nonunion were found, 5 in the control and 3 in the case group. Three of these occurred in patients with deep infection, all in the control group. Among the patients who were followed up to complete union of their fracture, the mean healing period was 4.3 months for both groups.

Statistical analysis revealed that both superficial and deep infection rate was significantly lower in the case than the control group (Chi-square $p<0.05$). Again the overall infection rate (superficial and deep) was significantly higher in the control than the case group (Chi-square $p= 0.01$). No statistically significant difference was found between the two groups with regard to rate of union or union time.

Infection is a devastating complication after orthopedic surgical procedures, especially after open reduction and internal fixation of fractures, as it may lead to infected nonunion, the management of which may be extremely difficult and expeditious, (Cleveland, 2003). Considering the time, morbidity and expenses of this complication, every effort must be made to reduce its prevalence and to date many studies have been made to find the risk factors for infection after surgery and how to control them. These studies have resulted in preoperative evaluation of the nutritional status of the patient to the development of new ventilation devices for the operation rooms, (Rouse *et al*., 2006; Cleveland, 2003). But there may be simpler, less expensive and still effective ways to control infection.

The use of topical antibiotics in orthopedic surgery has been very limited. However the effectiveness of topical antibiotics has been shown well enough *in vitro* (Eckman *et al*., 1998) and in the surgical literature (Kamath *et al*., 2005; Savitz *et al*., 1998; Lidwell *et al*., 1984) to justify their consideration in orthopedic procedures. The present study was designed and conducted to evaluate the efficacy of topical (inside the wound) antibiotics in prevention of wound infection in one of the common orthopedic procedures i.e., open reduction and internal fixation of the fractures. In the present study we used gentamicin in the liquid form. It proved to be effective, at least in short term in decreasing the rate of infection.

As stated previously the effect of local gentamicin on bone healing is controversial and though many studies have shown that it has no adverse effects, at least one has suggested probable ones. In the present study, the rate of union and the mean time to union was not different between the two groups. In fact we chose gentamicin, because it is not expensive and is accessible easily. On the other hand many of the infecting organisms isolated from orthopedic wounds are gram negative organisms nowadays and aminoglycosides constitute a good first choice for these.

Most of the previous studies have assessed the efficacy of local antibiotics in combination with some preservative material, such as PMMA or bone graft substitute. Aside from the expense, some of these materials have to be removed from the wound necessitating a second procedure and at least theoretically when devoid of antibiotic act as a foreign body, predisposing to possible infection.

We included only patients with closed fractures or open type I Gustillo-Anderson fractures for two reasons; first the patients with open fractures of higher degrees would undergo different surgical operations based upon the size of their wounds and devices available and most importantly the training of the surgeon, which theoretically would create bias in the study. Second and more important was the fact that the wounds would be left open in most open fractures and this would attenuate the concentration of topically applied antibiotics.

Grading wound complications is difficult, particularly the diagnosis of definite wound infection. Lidwell *et al.* (1984) divided the wound into four grades: No evidence of sepsis, possible wound sepsis, minor wound sepsis and major wound sepsis. He based his classification on the following signs: abnormal redness, a gaping wound, sinus formation, hematoma, discharge, abscess formation, pyrexia, raised ESR beyond 8th day and isolation of bacteria. Others have defined wound infections as an inflamed wound with positive bacterial growth or other criteria. We did not choose very strict criteria for diagnosis of infection so that actually no false negative cases would have been included in our results; however the problem is that in this manner we diagnosed a higher than usual rate of infection in our case series. Though this may be of little significance, as the criteria were the same for both groups.

The results of present study are by no means conclusive: the patients enrolled in the study were selected carefully with regard to the operation that they had to undergo. The efficacy of this measure in ORIF of closed fractures, although a common procedure, can not be generalized to all surgical procedures and especially to any operative fracture treatment. Despite all of these we believe that the results are promising and hopefully further studies on the topic can be very helpful in prevention of infection in orthopedic procedures.

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