Local and systemic antibiotic prophylaxis and infection control during major joint arthroplasty

Summary of the PhD Thesis

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1. Introduction

Postoperative deep infection is perhaps the most feared complication of orthopaedic interventions. It is also the most common nosocomial infection. The value of antibiotics in preventing wound infection is the subject of much debate but, many, if not most, surgeons use prophylactic antibiotics for operations because the most effective protection is prevention. In case of elective surgeries administration of antibiotics seems to be the most effective method of prophylaxis. The antibiotics are usually given systemically from just before the operation and for a few days after. In addition, antibiotics are administered by the local application as a perfusion and/or added to the bone cement.

In 1970 Buchholtz and Engelbrecht proved that pulverized antibiotic mixed to the bone cement has a potential to dissolve and thus provide prophylaxis after solidification of the cement. Since then, based on the results obtained from a great number of patients, combined local and systemic antibiotic prophylaxis seems to be the most effective way of infection control. Polymethyl-metacrylate bone cements release the contained antibiotics and have been used in numerous ways (cement beads for infected cavities, spacer blocks in infected revision prosthesis surgeries) to prevent, or to treat bone infections. Although the exact details of the elution of antibiotics are not fully understood polymethyl-metacrylate bone cement has been used in more than 1. 000. 000 joint replacements a year world wide.

In the thesis I give an overview of the opportunities of different antibiotic prophylactic methods, report about my experimental *in vitro* and *in vivo* results and publish our clinical data gathered related to the clinical surveillance and infectious

incidence rates at the Department of Orthopaedic Surgery of Medical School of University Pécs.

2. Goals

One of the principal goals was to create an effective and reproducible *in vitro* assay to measure the activity of various antibiotics released from the bone cement. The dynamics of the release of the most commonly used drug (gentamicin sulphate) from different types of bone cements were also studied using this technique to determine the duration of the elution of antibiotics from the bone cement after mixing them together and the therapeutic influence of the eluted antibiotics.

In the United States tobramicin is the most frequently used antibiotic for local prophylactic purpose. However, in Europe for prophylactic purposes adding gentamicin-sulphate to the bone cement is the most preferred combination (1 gram of gentamicin to 40 grams of bone cement) during primary prosthesis implantation. The influence of the manual mixing of gentamycin-sulphate on the effect of elution was also investigated.

Further experiments were performed *in vivo*, to obtain reliable data on the antibiotic concentration levels in humans. It is mandatory to know whether the antibiotic concentration in the periprosthetic space is above the Minimal Inhibitory Concentration (MIC), thus being effective, or in the event of it being below MIC this may trigger antibiotic resistance or play a role as a substrate in the biofilm formation process.

The elution properties of the antibiotics years after the initial mixing were also examined.

Antibiotic containing saline has been used, and continues to be used for defrosting the deep frozen allogenic tissue during the tissue transplantation. The antibiotic resorbtion capacity of different transplantation tissues was measured in relation to time.

The goals of the clinical studies were to reveal the incidence of certain infections and determine the predictive value of fever in the postoperative infections

3. Materials and Methods

3.1 In vitro measurements

The principal aim was to analyse the in vitro effectiveness of the antibiotics emitted from bone cement used in orthopaedic surgery. The bone cement-antibiotic complex chosen for analysis is the most popular complex selected for use by European orthopaedic surgeons as well as in our department. This cement is also available on the commercial market prepared with or without antibiotic, therefore it appeared to be sensible to compare the effect of the mixing technique on the emission features.

3.1.1

The goal of the first study was to establish an *in vitro* microbiologic monitoring system which measures the time related dynamics of antibiotic emission from acrylic bone cement and its bactericidal efficacy. Palacos R® and Orthofix R® cements containing gentamicin sulphate were tested. The *in vitro* emission-dynamics of cement-gentamicin sulphate complex was analysed by plate diffusion method for eight days after mixing.

3.1.2.

In this experiment we have used the previously established *in vitro* plate diffusion method to investigate the maximum duration of the elution of the antibiotics from the cements in which were added either 1,5g of cefuroxim, or 1,4g of gentamicin sulphate or 1,2 g erythromycin. The examined strain was the *Bacillus subtilis*.

3.1.3.

The effect of the preparation and mixing technique of the antibiotics on the elution features were also investigated. Two random groups of total hip replacement patients were created. Each group contained 10 patients using CMW2 bone cement containing gentamicin sulphate in the same dose. In group I, the antibiotic was mixed by the manufacturer industrially. In group II, the antibiotic was added and mixed by ourselves manually during the surgery. The elution properties of the complexes were measured and compared.

3.2. In vivo measurements

3.2.1. The investigation of the antibiotic release from bone cement in vivo in the early postoperative period

Our goal was to examine the in vivo characteristics of gentamicin-Palacos-R® combination and to describe the binding and dissolving properties of gentamicin in the early postoperative period. We also aimed to define the concentration of gentamicin sulphate in the periprosthetic space within 48 hours after the surgery in order to investigate the relationship to the MIC (minimal inhibitory concentration) to evaluate the effectiveness of local antibiotic prophylaxis. Due to the fact that aminoglycosid concentrations depend on the fat and glyceride content of the human body, effects of age, sex, and Body Mass Index (BMI) were also examined. There were 10 patients enrolled to this study who underwent a total hip replacement. At the end of the operation two silicon drains were left behind in the patients. Samples were taken from the drain bottles at various time intervals and antibiotic concentrations were measured using fluorescent-polarization-immunoassay method.

3.2.2. Measurement of long term antibiotic release *in vivo*

The goal of this study was to explore the time scale of the antibiotic elution from bone cement in humans. During revision operations the previously implanted Palacos-R® bone cement which contained 1,48g gentamicin sulphyte was removed. These samples were than measured according to their antibiotic activity.

3.2.3. The in vivo long term systemic effect of antibiotic loaded bone cements

Nine patients were enrolled to this study where the local and systemic effects of the antibiotic loaded bone cement were examined. During revision surgery due to aseptic loosening samples were taken from blood, urine, synovial fluid and three different layers of periprosthetic tissue for determination of the antibiotic concentration measured by fluorescent-polarization-immunoassay method.

3.2.4. Measurement of antibiotic elution from allogenic tissue samples from tissue bank

Routinely, during the defrosting process of deep frozen allogenic tissue allografts are put into a sterile solution containing antibiotics at room temperature. The aim was to determine the absorbtion-emission potential of these allogenic samples during the defrosting process. gentamicin sulphate emission was measured at intervals of 24, 48 and 72 hours.

3.3. Infection control in the orthopaedic surgery

3.3.1. Infection control in the orthopaedic routine

A prospective clinical study was conducted in order to determine the clinical effectiveness of the combined systemic and local antibiotic prophylaxis based on our orthopaedic practice. The aims of this study were:

- Determine the incidence and type of infectious complication after orthopaedic operations
- Analyze the effectiveness of the antibiotic prophylactic regime
- Improve the quality of clinical surveillance and incorporate it into the every day clinical practice
- The financial impact of the proper clinical surveillance

3.3.2. The importance of postoperative fever after total hip replacement

The goal of this retrospective clinical study was to establish the genuine value of fever as a significant clinical symptom in the postoperative infection. 177 patients were

enrolled in this study, all of whom received the routine antibiotic prophylaxis (24 hour systemic, i.v. second generation cephalosporin + local antibiotic added to the bone cement) and developed at least 38°C temperature. The temperature, onset, duration and characteristic of the fever were recorded along with the antibiotic treatment (if given) and the final outcome as an infection or cure.

4. Results

4.1. *In vitro* analysis of the antibiotic release of the bone cement

4.1.1. Biological measurements of antibiotic levels using the plate diffusion method

An inhibition zone of 23-27 mms was developed around the standard solutions. The inhibition zone around the antibiotic free inoculation sites was not measurable. The size of the 24 hour inhibition zone proved to be the same, regardless of type of bone-cement and the method of administration of the antibiotics. The emission of antibiotic was highest for the first day and declined quickly in a logarhythmic fashion. This pattern was more or less identical in each of the three cases. The difference between the various groups was only visible after between four to six days. All of the bone-cements showed some antibiotic activity even after eight days.

4.1.2. Long term *in vitro* analysis of the bone-cements containing different antibiotics.

Our results show that at the end of the first day, the first week and the first month the highest amount of gentamicin was released from Palacos® R and the least amount of erythromycin was released from Surgical Simplex P®. Comparing the three bone-cement – antibiotic complexes in this period only a minimal emission was observed. Two months later this insignificant difference disappeared, the size of the inhibition zones were identical. Measurements after one year revealed a very small, equal, but still detectable emission in all three complexes.

4.1.3. Effect of preparation technique on the dissolution ability of the antibiotics.

24 hours after the mixing of the bone-cement the release of gentamicin from the industrial combination was far exceeded by the emitted amount of the manually prepared combination.

The average value of the manually mixed combination exceeded, by 2.5 times, the mean emission value of the industrial preparation. This difference was statistically significant ($p<0.05$).

4.2. *In vivo* measurements of antibiotic levels.

4.2.1. Short term *in vivo* analysis of antibiotic emission.

After 6, 24 and 48 hours the gentamicin concentrations decreased to 2.642, 1,256, and 0.682 μg/ml respectively. At the same time we could observe a logarythmic decrease in the antibiotic levels in our patients after 48 hours. The BMI had no significant effect on the antibiotic levels. If patients were ranked by decreasing volume of drained fluid it was clearly visible that the less fluid that was drained the higher the mean gentamicin concentration was measured. Gender, age and side of the operation had no effect on the dissolution of the gentamicin.

4.2.2. Long term *in vivo* analysis of antibiotic emission.

According to our observations the size of the inhibition zones depends on the bulk and surface of the bone-cement piece, not on the time of the addition of the antibiotics. All bone-cements showed some antibiotic activity after an average of 9.2 years. Even the oldest bone-cement – antibiotic complex (12 years old) showed a significant inhibition zone. The larger, intact, bone cement demonstrated a smaller inhibition zone, contrary to the deliberately resurfaced bone-cement, (although smaller in size) which demonstrated a bigger inhibition zone. The smaller, thicker sample was able to release more antibiotic due to longer term retention.

4.2.3. Long tern *in vivo* analysis of the systemic effect of antibiotic containing bone-cements.

We could detect gentamicin in the urine of only three cases at the time of revision surgery, 77 months after the primary operation. In one patient a detectable amount of gentamicin was observed, which was well below the valid lower limit. None of the periprosthetic tissue preparations showed any trace of gentamicin.

4.2.4. Antibiotic essay from allograft samples.

The allogenic grafts absorbed antibiotics from the isotonic saline solutions containing 20 mg/ml gentamicin and then released it gradually. We could detect quite a difference in the behaviour of the different grafts. Absorbtion was the highest in the soft-tissue graft, followed by the spongious bone. The smallest absorbtion-release was seen in the corticospongious graft. In relation to the dynamics of the release a significant difference was observed as well. The spongious bone-graft released the antibiotic for about 48 hours in a high concentration, but after this period of time the release decreased. The corticospongious graft emitted gentamicin at a much lower level, but with the same dynamics. The graft made of the patellar tendon released the antibiotics well above the level of that of the bone-grafts, but by the second and third day the emitted amount was well below the level of that of the bone-grafts.

4.3. Clinical infections and their control in orthopaedics

4.3.1. Effectiveness of clinical infection control in orthopaedics

From 1st January, until the 31st December 1996 1316 operations were carried out in our department. In twenty (1.5 %) cases a microbiologically confirmed infection was observed. There was a 3,4 % occurrence related to hip operations, a 4.9 % occurrence in spinal operations and 1.4 % in other categories. There were no associated infections registered in knee operations (arthroscopies, prosthesis, etc.). In our cases the rate of Gram-positive infections were higher then the average published in the scientific literature. However, in line with the literature data, Staphylococcus aureus and coagulase negative Staphylococcus aureus were the two most common pathogen.

Methycillin resistant Staphylococcus aureus (MRSA) infection was not detected. Due to adopting a more considered approach towards antibiotic therapy and prophylaxis regime, we were able to save 8000 EUR compared to the previous year's budget when we were not undertaking such a study.

4.3.2. The significance of postoperative fever following hip prosthesis implantation.

In the immediate postoperative period out of the recruited 117 patients, 69 (35%) developed a temperature higher than 38 ºC. Only four patients had a temperature higher than 39 ºC, with the highest reading at 39.4 ºC. An identifiable cause was evident in only nine patients. In four cases the haematoma developed at the site of operation might have had caused the fever, whereas in one case respiratory tract infection was diagnosed along with the haematoma in the postoperative period. In none of these cases was it necessary to evacuate the haematoma surgically, therefore we defined the elevation of body temperature as „absorbtion fever". In two cases urinary infection and cholecystitis could have been the cause of the fever. In three cases serous oozing was seen from the operative site, from where microbiologically confirmed infection was diagnosed from a swab. Apart from these nine cases no specific cause of fever was identified in 60 patients.

4.3.2.1. Appearance and duration of the postoperative fever.

In 68 % of the 69 patients with fever the temperature increased within the first 48 hours, in 5 patients on the day of operation (7%), in 25 patients (36 %) on the first day, and in 17 patients (25 %) on the second postoperative day.

4.3.2.2. Association between the fever and administration of antibiotics.

We analysed those patients in whom there was no clear clinical specific cause of fever. In those patients receiving antibiotics the duration of the fever was on average 4.1 days. On the contrary, those patients not receiving antibiotics had a fever for only 1.7 days. In these patients 76 % ceased to have an elevated body temperature without antibiotic therapy within 48 hours.

4.3.2.3. Association between the fever and wound infection.

Out of 177 patients examined only four had detectable antibiotoc agents (2 cases S. aureus, 2 cases S. epidermidis), three of them had fever in the postoperative period, one had no fever at all (S. epidermidis). In the patients with temperature the fever started on day 2, 3 and 14 and ceased within 3, or 4 days.

4.3.2.4. Association between the fever and blood transfusion.

129 patients (76 %) needed blood transfusion in the first 24 hours. Within this group a second transfusion was given to 32 patients (25 %) in the next 48 hours. 49 patients (38 %) receiving a transfusion developed a temperature whilst this only occurred in 11 patients not being transfused (27%).

5. DISCUSSION

In our *in vitro* experiments of short term antibiotic emission measurements we concluded that this method is useful to detect the emission and quantitative monitoring of the antibiotics. According to our results the gentamicin mixed into the bone-cement is capable of emission in a detectable amount eight days after the procedure and exert a bactericid effect regardless of the type and mixture of the bone-cement.

In our *in vitro* experiments we also focused on the question of long-term antibiotic emission of bone-cements used in our department. We also examined the implanted bone-cements *in vitro* and how the emission profile changes over the long term (one year post-implantation and years after the primary operations during revisions when the bone-cement fragments were removed). Regardless of the type of the bone-cement – antibiotic complex emission was detectable a year later using our standard method. The analysis of the bone-cement samples retrieved during the revision-operations showed a significant emission even 12 years after the mixture using the *in vitro* method. Comparing the samples with different surfaces we concluded that the

antibiotics are dissolved from the superficial layers of the bone-cement over time and deeper layers are capable of retaining it in a much higher concentration for a prolonged period time. This does not explain the exact emission mechanism, but the background might well be diffusion or a passive „washout" from the pores of the bone-cement. There is still no unanimous literature regarding this phenomenon. The *in vitro* and *in vivo* studies aimed at the gentamicin emission stipulate that the antibiotic, after being evenly distributed within the bone-cement is emitted by simple diffusion through the microfractures and small cavities of the bone-cement. The types of emission (superficial dissolution, dissolution through the microfractures, diffusion from the matrix) may well play different roles in different periods of time. The disadvantage of the manually mixed cement might be an unevenly dispersed antibiotic, that in regard of dissolution might vary. The industrially manufactured complex might emit the antibiotics in a more even fashion, but we have to consider the potential drug-interactions (the powder component of the bone-cement – antibiotic complex) resulting from the long exposure time and the development of inactivation during storage

Our results show that 24 hours following mixing, the antibiotics were capable of doubling their emission rate into the environment. Others believe that the emission is primarily determined by the amount of added antibiotics. Although the quantity of the added antibiotics needs to be restricted because of the potential *in vivo* systemic side-effects and a change in the mechanical properties of the bone cement.

During our experiments we found some antibacterial effect in the fragments implanted a long time ago (there was a visible inhibition zone around the bone-cement fragments), which is proof that the bone-cement long after implantation is inhibiting the multiplication of the bacteria even if only in the immediate surrounding area, but certainly on its surface. Our results show a logarythmic, decreasing of the dissolution of the gentamicin over time *in vivo*. Based on the average values of the 6

and 24 hour fractions of the samples from the wound exudates we can state that these data correlate with the systemic minimal inhibition concentration (MIC≥1μg/ml), so they exert a prophylactically efficient systemic effect in relation to the Staphylococcus strains. In the samples obtained later the antibiotic concentrations decreased below the MIC value, so the question of resistance arises. The average of the dissolved gentamicin concentration was in indirect proportion to the overall volume of the wound exudates. Based on this, in the event of significant postoperative bleeding the possibility of an insufficiency of the local antibiotic prophylaxis and necessity of the modification of the systemic antibiotic prophylaxis arises.

During the joint replacements in our department we examined the significance of the presence or absence of fever, as this was the considered one of the best infection indicators in the postoperative period. We concluded that fever is only a natural response to the surgical stress as part of the acute phase reaction, as suggested by literature. Since fever is not necessarily a predictive sign of infection, the infection must be assessed by other diagnostic methods, for example, C-reactive protein (CRP) seems to be the most accurate indicator. In order to analyse and decrease the postoperative infection as one of the perioperative complications we did an infection-control surveillance over a year in our department. The 3.4 % superficial infection rate in hip operations detected by us is higher than published data, but it is our firm belief that observing the CDC guidelines our results are more realistic and therefore suitable for international comparison. In the year of infection-control only one case of deep infection was registered in our department which can be considered outstanding even in international comparisons and significantly better than those experienced over the previous two years. Therefore a significant improvement was observed in this area in the period of infection-control. According to our analysis the infective agent in wound infections were Gram-positive bacteria with a high number of coagulase-negative Staphylococci. Using the method we managed to decrease the cost

significantly. It is clear from our results that wound infection increases the length of stay by 8 days, this naturally increases the cost of treatment. The 16 % decrease in the amount of the antibiotics used and the saving of 8000 EUR can be considered as a direct financial benefit of the infection-control.

The most important results of the thesis.

As the aim of the thesis we examined the storing and emitting parameters of different bone-cement – antibiotic complexes – with a special regard to the most frequently used gentamicin-cement complex in our department and in the whole of Europe – *in vivo* and *in vitro*. Through clinical studies the effectiveness and efficiency of the combined prophylactic methods and some predictive signs (e.g. fever) were evaluated. The results considered as novel are listed below:

1. We managed to evaluate a standard, reproducible *in vitro* method that can be used to assess the emission properties of different bone-cements. This method, compared to other *in vitro* detecting precision methods (HPLC, FPIA, etc) did not only reveal the numerical values of the concentrations, but referred to the amount of the emitted „biologically active" antibiotics. In this regard, highly different opinions emerged. The possible cause of the differences might be the versatility and lack of accuracy of the assessing methods, therefore we emphasised the importance of managing to establish a simple, accurate and reproducible method.
2. We have found that the bone-cement, used by us, is capable of emitting antibiotics possessing antibacterial capability. However, the release decreases exponentially but a detectable amount of antibiotics is present even a year after mixing *in vitro*.

Regarding emission levels, there was no significant difference between the various types of bone cement-antibiotic complexes. However, a significant difference was

found regarding the mixing methods. The „home-made" bone-cement released significantly higher amount of antibiotics compared to the industrial mixture.

3. In the *in vivo* experiments we concluded that the amount of antibiotics in the wound exudates were above the therapeutic range after 24 hours (MIC), and in large proportion of cases this level was reached even after 48 hours. The level of this was merely determined by the volume of the drained exudates rather than the BMI. Therefore, we can conclude that the surrounding area of the prosthesis contains a higher than MIC level of antibiotics, definitely for two days postoperatively.

4. Our long term studies revealed that bone-cement fragments removed during revision are capable of emitting antibiotics even without „fresh" broken surface years after implantation. In the case of resurfacing (formation of „new" surface) the release of antibiotics increases significantly and can exceed the therapeutic level.

5. We captured the absorption and emission characteristics of antibiotics in different allogenic tissues routinely used in the orthopaedic tissue transplantation, which formerly was not addressed in the literature.

6. By establishing of infection-control in our department we described precisely the incidence of wound and deep infections and the types and distribution of the infective agents. There has been no national data available up to now and the international data are not particularly comparable in this regard because of different technical conditions.

7. Due to the continuous control the rate of deep infections was decreased below 1 %, and using a conscious and not unnecessary antibiotic regime we did it in a way that the cost of antibiotics was highly reduced.

8. During the clinical studies we found that fever, as an established symptom referring to a possible infection of the operative area was detected in 35 % of our patients, but real, proven deep infection was seen only in 2.3 %. In case of short fevers, lasting for less than 24 hours, antibiotic treatment is not necessary without

other signs of infection. It is important to recognise that even with deep infections fever is not always present, therefore even when fever is not present we should still consider the possibility of a deep infection.

Since the treatment of periprosthetic infections is particularly difficult, takes a long time and is costly, the importance of decreasing the infection rate through preventative measures is extremely significant. The concept of antibiotic mixed with the implanted bone-cement goes back to the work of Buchholz and Engelbrecht in the seventies and has been a well-accepted method in orthopaedics ever since. The systemic antibiotic prophylaxis is part of the everyday routine, by which orthopaedic surgeons wish to prevent the unwanted suppurations.

I hope and believe that with this work that I have conducted over the last twelve years I have contributed to a better understanding of the antibiotic prophylaxis in the orthopaedic practice. I sincerely hope and believe that my results support our daily activity of protecting our patients and providing them with the best possible clinical care.

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