Cefazolin should be administered maximum 30 min before incision in total knee arthroplasty when tourniquet is used

Goran Bicanic \(^a,^b\), Kresimir Crnogaca \(^b\), Katarina Barbaric \(^b\), Domagoj Delimar \(^a\)

\(^a\) Department of Orthopaedic Surgery, University of Zagreb School of Medicine, Clinical Hospital Centre Zagreb, Salata 6-7, 10000 Zagreb, Croatia
\(^b\) Department of Orthopaedic Surgery, Clinical Hospital Centre Zagreb, Salata 6, 10000 Zagreb, Croatia

**Abstract**

Periprosthetic infection is regarded as one of the most feared complications following total knee arthroplasty, developing in 0.4–2% of patients. *Staphylococcus aureus* and *Staphylococcus epidermidis* are credited for more than half of all infections. Cefazolin is the most commonly used antibiotic drug in arthroplasty antibiotic prophylaxis worldwide. Guidelines and studies recommend that prophylactic antibiotics should be completely infused within 60 min before the surgical incision. Cefazolin achieves highest peak bone concentrations 40 min after parenteral application with serum half-life of 108 min and bone half-life of 42 min. Respecting the given pharmacokinetics of cefazolin and theoretical mathematical model we hypothesise that parenteral application of cefazolin should be in time period not longer than 30 min before incision (tourniquet inflation) and not less than 10 min before tourniquet inflation if given in bolus. This new regime would provide maximal blood concentration of the cefazolin and almost maximal bone concentration of the cefazolin at the beginning of the operation and at the beginning of the tourniquet inflation.

Article history:
Received 14 October 2013
Accepted 16 March 2014

**Introduction**

Total knee arthroplasty is safe, efficient and successful procedure, which restores function thus increasing the quality of life to the patients suffering from knee osteoarthritis [1–3]. There is an annual increase in total knee arthroplasty procedures and estimated increase is from 450,000 procedures in the year of 2005 to 3.48 million procedures in the year of 2030, around 673% [4]. Although very successful procedure, complications do occur. One of the most feared complication is periprosthetic infection which develops in 0.4–2% of patients [5]. Periprosthetic infection is source of repeated procedures, prolonged hospitalization, poor final functional status, increased morbidity, poor quality of life and increased cost of treatment [6–8]. *Staphylococcus aureus* and *Staphylococcus epidermidis* cause more than half of periprosthetic infections [5,9–12]. *S. epidermidis* is a growing issue as being one of the most resistant pathogens in the world as well as showing increase in prevalence among periprosthetic infection isolates [9,12]. Antibiotic prophylaxis is part of the routine preoperative preparation of patients and is credited for decrease in probability of periprosthetic infection [9,13–16]. It’s objective is creating a hostile environment in blood and tissue that will inhibit or eliminate pathogens that could contaminate the wound throughout the procedure. Hostile environment for the pathogens is achieved through minimal inhibitory concentrations (MIC) in tissue. Minimal inhibitory concentration is not the same for all pathogens and depends on the specific antibiotic and specific pathogen. Minimal inhibitory concentrations for sensitive coagulase-negative *S. epidermidis* range from 0.5 to 1.0 µg/ml in bone [17–19]. Achieving fourfold MIC in tissue is recommended for halting the specific pathogen [20]. Chosen antibiotic has to be efficient against pathogens which are most likely to contaminate the wound, must have good tissue penetration and minimal toxicity [13,21]. First or second-generation cephalosporine meets the needed criteria and should be administered for routine perioperative surgical prophylaxis. Cefazolin is antibiotic of choice in arthroplasty procedures in orthopaedic surgery [9,13,15,19,21,22]. It achieves highest peak bone concentrations of all first generation cephalosporines, 40 min after parenteral application with serum half-life of 108 min and bone half-life of 42 min [17–19,23,24]. Guidelines and studies recommend that prophylactic antibiotics should be completely infused within 60 min before the surgical incision [13,14,19,23–25]. Total knee arthroplasty procedure has at least two specificity that raise concern in regard to the recommended optimal timing of preoperative antibiotic prophylaxis. Tourniquet is used which disables additional application of antibiotic once the tourniquet is on. This means that complete dose of antibiotic should be infused prior to...
tourniquet establishment and at that time peak antibiotic concentrations must be secured. Key moment of procedure is cementing the endoprosthesis which takes part about 40–100 min after the incision and at that time peak antibiotic concentration in bone should be achieved and retained [17–20,24]. Failure to preserve tissue concentrations above MIC would increase the risk of peri-prosthetic infection [26]. The problem is when we take in account that the bone half life of cefazolin is 42 min and if cefazolin is administered 60 min before tourniquet inflation at the start of the operation we will have between 25% and 50% of possible antibiotic concentration in bone. Furthermore, the most important moment of the operation is cementing the endoprosthesis (this permanently covers all open bone surfaces), and when taken into account that this occurs at fastest around 40 min from beginning of the operation this is another half life time of cefazolin and theoretical concentration in the bone drops to 10–25% of maximal concentration (or even lower if the surgeon is slower).

**Hypothesis**

Respecting the given pharmacokinetics of cefazolin (highest peak bone concentrations 40 min after parenteral application with serum half-life of 108 min and bone half-life of 42 min) and theoretical mathematical model we hypothesise that parenteral application of cefazolin should be in time period not longer than 30 min before incision (tourniquet inflation) and not less than 10 min before tourniquet inflation if given in bolus.

This new regime would provide maximal blood concentration of the cefazolin and almost maximal bone concentration of the cefazolin at the beginning of the operation and at the beggign of the tourniquet inflation. This new regime would allow the bone concentration to drop from maximal concentration to around 50% at the time of endoprosthesis cementing which is maximal theoretical possibility when tourniquet is used.

**Evaluation of the hypothesis**

Cefazolin has bactericidal activity, broad spectrum of action, covers gram-positive organisms and clinically important aerobic gram-negative bacilli and anaerobic gram-positive organisms. Standard preoperative dose is 1 g but for procedures when tourniquet is used as well for the patients with 80 kg or more the dose is doubled and is 2 g applied intravenously. Ho et al. showed that 2 g of cefazolin offers protection for all surgical procedures lasting up to 5 h regardless of BMI [27]. Other studies also show that additional dose of cefazolin is not recommended in procedures lasting up to 3–4 h and with intraoperative blood lost of 1500–2000 ml [28–31]. Williams et al. demonstrated that direct correlation between cefazolin concentration in serum and bone does not exist and that peak bone concentration is achieved 60 min after administration [19]. Yamada et al. showed that cefazolin does not achieve minimal inhibitory concentration for resistant S. epidermidis during arthroplasty procedures when administered by the guidelines recommended [32]. Ideal timing of tourniquet onset should be as early as peak inhibitory concentrations in tissue are obtained and before the decline in antibiotic concentrations occur. Steinberg et al., and van Kasteren et al., already showed decrease of surgical site infections when antibiotics are administered within 30 min before incision [24,33]. Friedman and Friedman showed that with administering cefazolin 5, 2, and 1 min before tourniquet inflation adequate bone concentrations can be achieved [17,18]. Such results are confirmed by Bannister who demonstrates effective inhibitory concentrations of cephalosporines if given 5 min before the inflation of tourniquet [34].

**Consequences of the hypothesis**

In author’s opinion, proposed new regime of administering preoperative antibiotic prophylaxis with cefazolin will have enormous positive consequence in total knee arthroplasty, when tourniquet is used, by obtaining higher antibiotic concentrations in bone thus possibly reducing the number of periprosthetic infections. Higher antibiotic concentrations in bone will be obtained throughout the whole procedure up till the cementing of the endoprosthesis. The surgeon will be allowed to work in safer environment even in prolonged procedures with tourniquet used. Practical implications are: reduced number of repeated procedures, reduced hospitalization time, better final functional status of patients, decreased morbidity, improved quality of life and significant decrease in cost of treatment.

**Conflict of interest**

The authors declare no conflicts of interest.

**References**


