Ceftriaxone concentration at the surgical site following systemic and isolated upper limb injection

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Abstract

Background and Aims: This study was conducted to find out the equipotent dose of isolated upper limb injection of ceftriaxone in the upper limb (IUL) surgeries under tourniquet that would attain a peak bone marrow concentration (Cmax) similar to systemic (ST) 1 g injection.

Material and Methods: Patients were allocated into two groups – ST and IUL. ST group (n = 5) received 1 g of ceftriaxone 20 min before tourniquet inflation, and IUL group received calculated dose (n = 5 in each dosage, i.e., 200, 100, 75, and 50 mg) diluted in 50 mL of normal saline distally after tourniquet inflation. Venous and bone marrow samples were collected at various time intervals intra- and post-operatively. Ceftriaxone concentration was analyzed by high-performance liquid chromatography.

Results: There was no significant difference between Cmax following ST 1 g injection and IUL injection with 75 mg (155.8 ± 2.1 vs 158.5 ± 3.1 μg/mL, respectively; P = 0.1). There was significant difference in area under curve (AUC) and t½ between ST 1 g injection and IUL injection with 75 mg of ceftriaxone (AUC 1285 ± 67 vs 784.4 ± 28 μg/mL/h, respectively; P < 0.001), (t½ 5.2 ± 0.5 vs 4.7 ± 0.3 h, respectively; P < 0.001). None of the patients in the ST and IUL groups had post-operative infection up to a period of 1 week duration.

Conclusion: IUL injection with 75 mg of ceftriaxone can be equipotent and as effective as ST 1 g injection in upper limb orthopedic surgeries under tourniquet.

Keywords: Ceftriaxone, pharmacokinetics, tourniquets, upper extremity

Introduction

Infection is one of the most dreaded complications of surgical procedures. Single-dose antibiotic prophylaxis is an effective measure to prevent this complication, provided sufficient concentration of the drug is present at the surgical site.[1,2] Bacterial contamination occurs most frequently when the wound is open. One of the vital factors associated with the efficacy of the antimicrobial prophylaxis is the presence of high concentration of antibiotic in the tissue and blood bathing the wound during the period of surgery. This is the case in majority of the orthopedic procedures, and it explains the well-documented efficacy of cephalosporins such as ceftriaxone, cefuroxime, or cefazolin.[3,4] Ceftriaxone has shown excellent tissue and body fluid penetration after a dose of 1–2 g. Concentration well above the minimal inhibitory concentration (MIC) of most pathogens responsible is detectable for more than 24 h after a single prophylactic dose.[5]

In most institutions, anesthesiologists are expected to assume the responsibility of administering prophylactic antibiotics before...
surgery.\textsuperscript{[6,7]} In orthopedic procedures, prophylactic antibiotics are routinely administered systemically before tourniquet inflation for adequate concentration to reach the surgical site. However, it seems prudent to administer intravenous antibiotic distal to the location of the tourniquet and keep it confined to the surgical site after tourniquet inflation.\textsuperscript{[8]} This study was designed to assess ceftriaxone concentration at the surgical site after tourniquet application and to compare with concentration achieved after systemic (ST) administration.

**Material and Methods**

After obtaining written informed consent and institute ethics committee approval, this study was conducted in 25 patients scheduled to undergo upper limb orthopedic surgeries under tourniquet. American Society of Anaesthesiologists (ASA) physical status 1 and 2 adults between the age group of 20–50 years with closed upper limb fractures of less than 1-week duration with a weight between 45 and 65 kg and height between 150 and 180 cm were included in the study. Patients with hypersensitivity to ceftriaxone, diabetic neuropathy, and patients with any contraindication to tourniquet application such as coagulopathy and peripheral vascular disease were excluded. Surgeries exceeding the tourniquet time were also excluded.

Eligible patients who provided written informed consent were randomly allocated to either ST (1 g) or isolated upper limb (IUL) (200 mg) group. Allocation concealment was done by serially numbered opaque sealed envelope technique. This was a double-blind study in which the person measuring ceftriaxone level and the data analyst were blinded. In the IUL group, trial was started with 200 mg dose (n = 5) and the other lower doses (100, 50, and 75 mg) were sequentially administered to the patients (n = 5 for each dose).

A baseline blood sample was taken from both the groups to ensure that patients were not on any previous antibiotics. Ceftriaxone test dose was given in ward, and after excluding hypersensitivity, patients were shifted into operation theatre. In the operation theatre, an intravenous (IV) cannula was secured in non-operating limb, and a control blood sample was taken from both the groups. Standard ASA monitors such as electrocardiogram (ECG), pulse oximeter, and non-invasive blood pressure (NIBP) were attached, and baseline parameters were recorded. Following induction of anesthesia, for ST group, 1 g of ceftriaxone was injected 20 min before tourniquet inflation. For isolated limb (IUL) group, another IV cannula was secured distal to the closed fracture site under aseptic precautions, and the cannula was secured with adhesive plasters. Following limb elevation and exsanguination, the tourniquet was applied proximal to the fracture site and inflated 100 mmHg above the systolic blood pressure, and the IUL ceftriaxone dose was administered after diluting in 50 mL of normal saline.

Serum samples were collected intra-operatively from opposite limb at 10 min after tourniquet inflation and immediately after tourniquet deflation, and bone marrow samples were collected from the surgical site 30 min after tourniquet inflation. Tourniquet was kept inflated for a maximum duration of 90 min, and surgeries that extended beyond 90 min were excluded from the study. Post-operatively, serum samples were taken at various time intervals till the ceftriaxone concentration reached trace value. All samples were analyzed for ceftriaxone concentration by high-performance liquid chromatography.\textsuperscript{[9]} Postoperatively, patients were followed up for 1 week for incidence of any surgical site infection.

*Post hoc* power analysis was done keeping the sample size as five in each group. The primary outcome used was peak marrow concentration (Cmax) and the effect size was 501 μg/mL. The power is estimated to be 99.1% with an alpha value of 0.05. Data were analyzed using SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). Student’s *t*-test was used to compare the mean between two groups. One-way analysis of variance (ANOVA) was used to compare mean between more than two groups. *P* < 0.05 was considered as statistically significant.

**Results**

All the demographic parameters such as age, height, weight, and body mass index (BMI) passed normality, and one-way ANOVA showed that all the parameters were comparable between the groups (*P* > 0.05) [Table 1]. An isolated limb dosage of 200, 100, and 50 mg produced peak bone marrow concentration (Cmax) of 656 ± 28, 277.7 ± 6.7, and 105.3 ± 2.4 μg/mL, respectively; when compared with ST 1 g injection (155.8 ± 2.1 μg/mL), there was significant difference (*P* < 0.001). IUL injection of 75 mg of ceftriaxone produced peak marrow concentration of 158.5 ± 3.1 μg/mL that closely approximated the peak marrow concentration following ST 1 g injection (*P* = 0.1). Serum concentration of ceftriaxone was plotted against time [Figure 1]. Area under the curve and half life produced by isolated limb injection of 200, 100, 50, and 75 mg were significantly different when compared with ST 1 g group [Table 2]. None of the patients in both ST and IUL groups developed surgical site infection in the first week.
**Discussion**

This study was conducted to find out the equipotent dose of ceftriaxone for the IUL that will achieve a peak bone marrow concentration similar to the peak levels attained following ST 1 g injection in upper limb orthopedic surgeries under tourniquet. The most important finding in this study is that 75 mg of ceftriaxone IV injection in the IUL attains Cmax which closely approximates the Cmax following ST 1 g injection of ceftriaxone and is well above the MIC.

A drug is considered effective when its peak concentration in target tissue tends to remain above the MIC for a sufficient duration. Ceftriaxone has got an MIC range of 16–30 μg/mL, which covers more than 90% of Gram-positive and Gram-negative organisms. The peak marrow concentration (Cmax) following 75 mg of IUL dosage in the study was three- to four-fold above the MIC for a period of more than 12 h. The pharmacokinetics of ceftriaxone as studied by Patel et al. showed that ceftriaxone concentration peaks at 30 min after ST 1 g injection (150.7 ± 14 μg/mL) which was comparable to our study. As there was no previous study done to find out the equipotent dose of ceftriaxone in the IUL, the Cmax following IUL injection in the study cannot be compared.

As an IUL acts as a compartment with specified blood volume, much less ceftriaxone dosage can produce peak bone marrow concentration well above the MIC. The study was initially started with 200 mg of ceftriaxone for the isolated limb, and dose de-escalation was done by one-half and then by one-fourth. Because 75 mg of ceftriaxone in the IUL attains a Cmax similar to following ST 1 g injection, it is equipotent and as efficacious as ST 1 g injection in upper limb orthopedic surgeries under tourniquet. Calculated dose of ceftriaxone was diluted with 50 mL normal saline to fill the entire venous compartment in the IUL and ensure uniform distribution of the drug. Similar volume is used for diluting lidocaine for IV regional anesthesia when used for upper limb surgery under tourniquet.

Ceftriaxone injection is known to produce several adverse reactions when injected systemically. Diarrhea can occur because of alteration of gut flora. The hypersensitivity reaction is one of the most dreaded complications which can be in the form of anaphylaxis, angioedema, and urticaria. None of the patients in the study had any hypersensitivity reaction in the IUL. Ceftriaxone has got low-grade nephrotoxic

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**Table 1: Demographic parameters of patients**

| Parameters      | ST 1 g (n=5) | IUL injection |
|-----------------|--------------|---------------|
| Age (years)     | 35±2.6       | 35±2.7        |
| Sex             |              |               |
| M               | 3 (60%)      | 3 (60%)       |
| F               | 2 (40%)      | 2 (40%)       |
| Weight (kg)     | 55±2.3       | 54.4±2.0      |
| Height (cm)     | 163±3.0      | 164.2±2.5     |
| BMI (kg/m²)     | 20±1.2       | 20±0.9        |

ST=Systemic injection; IUL=Isolated upper limb; BMI=Body mass index; SD=Standard deviation. Values expressed in mean±SD

**Table 2: Ceftriaxone pharmacokinetic comparison**

| Parameters      | ST 1 g (n=5) | IUL injection |
|-----------------|--------------|---------------|
| AUC (µg/mL/h)   | 1285±67      | 924±38*       |
| t½ (h)          | 5.2±0.5      | 4.6±0.4*      |

ST=Systemic injection; IUL=Isolated upper limb; AUC=Area under curve (plot of serum concentration vs time); t½=Time taken for serum concentration to become half the initial value; SD=Standard deviation. Values expressed in mean±SD. *P<0.001 when compared with ST 1 g injection.
potential which can be further exacerbated by renal failure,[13] elderly age, and concomitant use of aminoglycosides. None of the patients in the study had any evidence of renal toxicity postoperatively as the dosage of ceftriaxone is drastically reduced in the IUL, and the drug is confined distal to the tourniquet following IUL injection thereby reducing significant renal exposure.

IUL injection is economical and cost beneficial as very less dose of ceftriaxone is injected. This technique of IUL injection can be beneficial for patients undergoing surgeries for closed fractures, tendon repairs, contracture release, and so on where single dose of preoperative antibiotics is administered and not followed with postoperative antibiotics. Antibiotic administration in the IUL is very effective in reducing both early and late post-operative complications.[1,14] All the patients in both ST 1 g group and IUL groups were followed up for a period of 1 week post-operatively, and none of them had any surgical site infection.

Conclusion

Hence, we conclude that IUL injection of 75 mg of ceftriaxone can be equipotent and as effective as 1 g ST injection in upper limb orthopedic surgeries under tourniquet. The results of this study were applicable only to upper limb closed fractures where the tourniquet was used. However, further clinical trials will be required to determine the equipotent dose in lower limb surgeries under tourniquet application.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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