Local tissue concentrations of cefazolin during total joint arthroplasty: a systematic review

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Background: Periprosthetic joint infections (PJI) following joint arthroplasty are now the leading cause of reoperation and are associated with serious morbidity to the patient, often requiring several staged operations and a prolonged course of parenteral antibiotics. Prophylactic administration of intravenous antibiotics before skin incision is arguably the most important measure to prevent PJI; however, the dose effectiveness of cefazolin in target tissue is not well known. We aimed to identify parameters affecting local tissue concentration (LTC) of cefazolin.

Methods: We performed a literature search using the following keywords: "orthopaedics," "orthopedic," "arthroplasty" and "cefazolin." We included studies that measured LTC of cefazolin from samples obtained during either a total knee or total hip arthroplasty.

Results: Of the 332 records screened, we included 10 studies that described LTC of cefazolin. The included studies evaluated dosing ($n = 7$), procedure type ($n = 3$), body mass index ($n = 1$) and tourniquet utilization ($n = 1$).

Conclusion: Few studies have measured LTC levels of antibiotics (or levels of cefazolin) to validate current recommendations for antibiotic prophylaxis in orthopedic surgery. With infection as the leading reason for early reoperation or revision surgery, the parameters affecting LTC during orthopedic procedures need to be further assessed.

Contexte : Les infections de prothèse articulaire (IPA) suivant une arthroplastie de la hanche sont aujourd'hui la principale cause de réopération; elles sont associées à une grave morbidité chez le patient et nécessitent souvent plusieurs interventions en séquence et une antibiothérapie prolongée administrée par voie parentérale. L'administration prophylactique d'antibiotiques intraveineux avant l'incision cutanée est sans doute la mesure la plus importante pour prévenir les IPA; la dose efficace de céfazoline dans le tissu ciblé n'est toutefois pas connue avec précision. Nous avons voulu déterminer les paramètres modulant la concentration locale tissulaire de la céfazoline.

Méthodes : Nous avons effectué une recherche documentaire à l'aide des mots-clés suivants : « orthopaedics » [orthopédie], « orthopedic » [orthopédique], « arthroplasty » [arthroplastie] et « cefazolin » [céfazoline]. Nous avons aussi inclus des études ayant mesuré la concentration locale de la céfazoline dans des échantillons obtenus dans le cadre d'arthroplasties totales du genou ou de la hanche.

Résultats : Après examen de 332 articles, nous avons inclus 10 études décrivant la concentration locale tissulaire de céfazoline, qui évaluaient la dose ($n = 7$), le type d'intervention ($n = 3$), l'indice de masse corporelle ($n = 1$) et l'utilisation d'un garrot ($n = 1$).

Conclusion : Peu d'études ont mesuré les concentrations locales tissulaires d'antibiotiques (ou de céfazoline) afin de valider les recommandations actuelles sur l'antibioprophylaxie en chirurgie orthopédique. Les infections étant la principale cause de réopérations ou chirurgies de révision hâtives, les paramètres modulant la concentration locale tissulaire au cours des interventions orthopédiques doivent faire l'objet d'une évaluation plus poussée.

Despite numerous advancements in orthopedics, surgical site infection remains one of the most common and serious complications. Infection involving a joint arthroplasty portends a poor prognosis and usually requires revision surgery and prolonged parenteral antibiotics. Prosthetic joint infections (PJI) are serious complications of joint arthroplasties, with hip and knee prostheses most frequently affected. In Canada, the incidence of infections is 1.64% for hip arthroplasties and 1.52% for knee arthroplasties.[1–4]

Associated with serious morbidity, PJIs often require several reoperations and consume substantial health care resources. Treatment of a single PJI has been shown to cost about $50 000.[3,4] Optimizing patient risk factors, managing the operating room environment, using proper skin preparation and using antibiotic prophylaxis effectively are all intended to prevent this devastating complication.[5,6] Preoperative antibiotic prophylaxis is one of the most important strategies used to lower the risk of PJI.[7,8] Cefazolin is the antibiotic of choice in arthroplasty procedures because of its broad-spectrum effect on methicillin-sensitive *staphylococci* and *streptococci* and its relatively low cost.[7,9] However, there is limited modern evidence to support dosage recommendations for use of cefazolin in arthroplasty PJI prophylaxis. As stated in various international guidelines on surgical prophylaxis,[10–12] patients undergoing implant surgery are often not included in research providing the basis for dosage recommendations.

In evidence-based and protocolized medicine, the trend is moving toward increased weight-based dosage of β-lactam drugs for surgical procedures. In addition, redosing during longer procedures is now considered paramount in surgical prophylaxis recommendations. However, these recommendations are often based on pharmacokinetic extrapolations and not on actual local tissue concentration (LTC) data. It is necessary to reach concentrations of prophylactic antibiotics that surpass the targeted pathogen's minimum inhibitory concentration (MIC) of 1 μg/mL for at least the time between incision and wound closure for prophylactic antibiotics to prevent infections.[13] Achieving four-fold (4 μg/mL) MIC in tissue is recommended for halting the specific pathogen.[14] Cefazolin achieves its highest peak bone concentrations 40 minutes after parenteral application with a serum half-life of 108 minutes and bone half-life of 42 minutes.[15,16] Since medications are not equally distributed throughout the body, it is critical to know that an antibiotic obtains adequate concentrations not only in serum, but also in the local tissues at the surgical site.[17] Compared with conventional methods, modern techniques using liquid chromatography and mass spectrometry can accurately measure antibiotic concentration in tissues like fat and bone.[18]

We sought to provide a comprehensive summary of reported studies of LTC of cefazolin in total knee and total hip arthroplasty. We explored the parameters that influence LTC of cefazolin including route of administration, type of procedure, body mass index (BMI) and use of a limb tourniquet.

METHODS

Search strategy and data collection

We conducted this review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[19] We searched the National Library of Medicine (PubMed) and MEDLINE (Ovid) using a combination of keywords including "orthopaedics," "orthopedic," "arthroplasty" and "cefazolin." Studies retrieved from the searches were combined into a library on Endnote X9 which then underwent deduplication. Two authors (M.M. and J.M.) independently reviewed the search entries using strict inclusion and exclusion criteria. Studies were first screened by title and abstract. The remaining studies then underwent full text screening, and any discrepancies between reviewers were resolved through consensus. Eligible studies then underwent data extraction. No date restrictions were applied, and only studies written in English were included. To be eligible for inclusion, study participants had to have received cefazolin before skin incision for either total knee arthroplasty (TKA) or total hip arthroplasty (THA) and the LTC of cefazolin had to have been measured from samples obtained during the procedure. Data extracted from eligible studies included author, year, study title, study type, total number of participants, mean age, procedure, cefazolin dose, technique, infection rate and LTC.

RESULTS

Included studies

Our review included 10 studies that reported on the use of cefazolin in TKA and THA (Figure 1). These studies evaluated 4 different variables: dosing and route of administration, procedure type, BMI and tourniquet utilization. Variations in LTC of cefazolin were compared based on these factors. There were 7 studies that evaluated the change in LTC according to the dose and route of cefazolin administration. Three studies reported the effect of the type of procedure on LTC of cefazolin. One study assessed the effect of weight or BMI on LTC. One study reported the effect of timing of tourniquet inflation on LTC.

Dosing and route of administration

Of the 7 studies that reported on the doses or routes of cefazolin administration (Table 1), LTC measures of bone, serum or fat at 1 g or 2 g of cefazolin were compared. Williams and colleagues,[20] Angthong and colleagues[16] and Sharareh and colleagues[21] compared 1 g of cefazolin with 2 g of cefazolin. In each study, there was a greater concentration of cefazolin in the bone samples from the group who received 2 g of cefazolin. Serum and bone LTC ranged from 17.3 to 210 μg/mL and 5.9 to 44.1 μg/g, respectively. Moreover, Williams and colleagues[20] observed a greater concentration of cefazolin in the serum of the group who received 2 g when compared with the
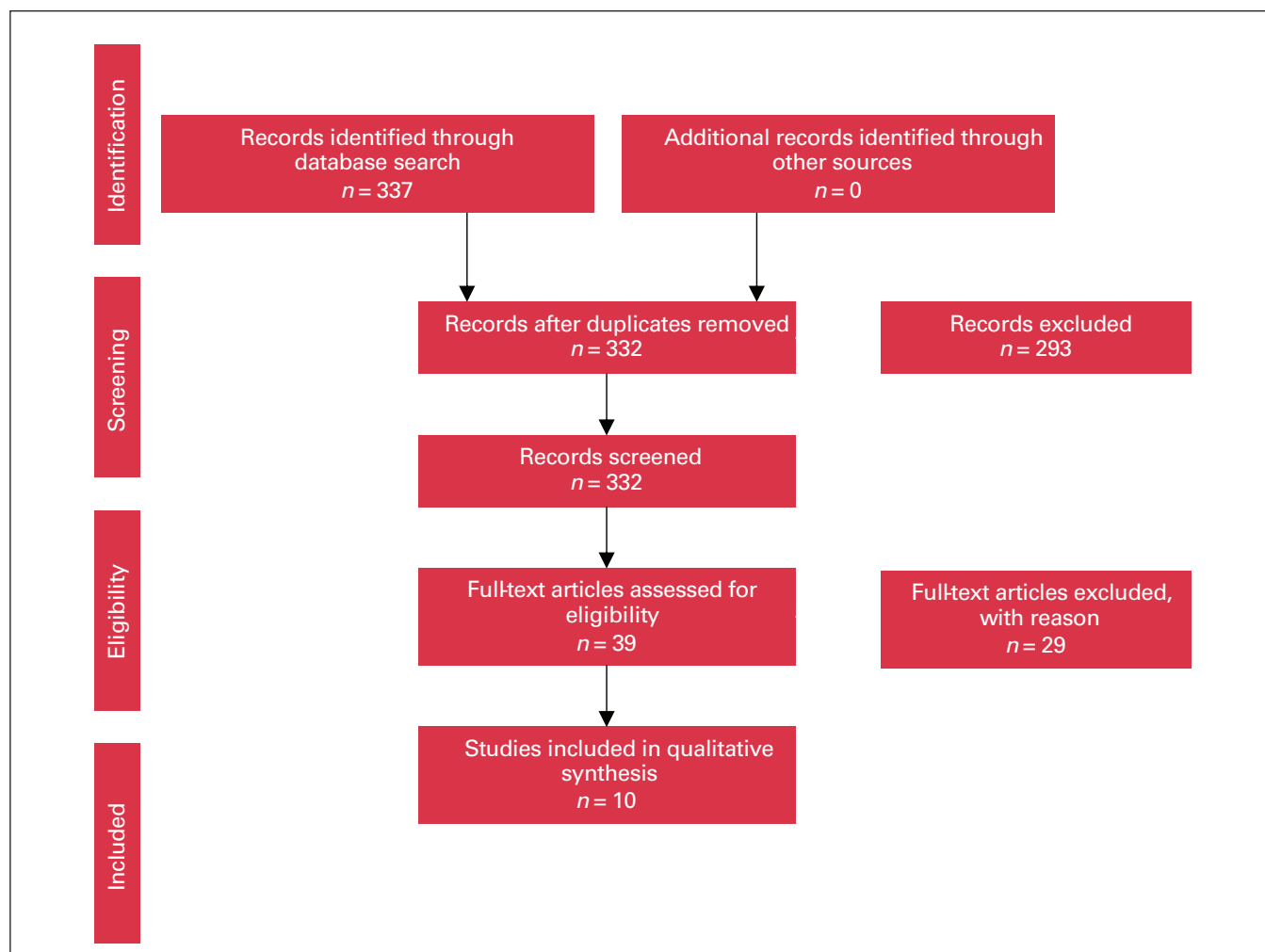
Fig. 1. Selection of studies for inclusion in our review, based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

group who received 1 g. Angthong and colleagues[16] found that there was a greater accumulation of cefazolin in the distal femur than in the proximal tibia in the group who received 2 g. Cunha and colleagues,[22] Polk and colleagues[23] and Rivera and colleagues,[24] who studied the tissue concentration of only 1 dose of cefazolin, reported that the serum concentration of cefazolin was always greater than the bone concentration. Interestingly, Young and colleagues[25] examined the difference in tissue accumulation when cefazolin was given through different routes of administration. When comparing intravenous (IV) with intraosseous (IO) administration of cefazolin, they found that in the fat and bone samples, IO administration yielded significantly greater LTC than IV administration.

Procedure type

Three studies compared LTC in patients undergoing THA and TKA. All 3 studies observed a difference in bone LTC (Table 2). Concentrations observed were quite variable among studies, but the trend was similar. Bryan and colleagues,[26] Yamada and colleagues[27] and Sharareh and colleagues[21] all found greater LTC of cefazolin in bone samples from patients who underwent THA than in those who underwent TKA. There were no observed differences in serum concentrations between procedures.

Body mass index

Only 1 study evaluated the effect of BMI on LTC of cefazolin in patients undergoing arthroplasty (Table 3). Sharareh and colleagues[21] gave 1 g of cefazolin if the patient weighed less than 70 kg and 2 g of cefazolin if the patient's weight was greater than 70 kg. No notable difference was observed in LTC between BMI groups.

Tourniquet utilization

Only 1 study assessed LTC based on the timing of tourniquet inflation (Table 4). Friedrich and colleagues[28]

Table 1. Effect of cefazolin dosing and route of administration on target-site concentration					
Study (level of evidence)	Group	Tissue	Technique	Tissue concentration,* (SD)	Above MIC
Cunha et al.[22] (prospective study) n = 71			Disc diffusion		
	1 g	Serum (peak)		210 (NR)	Yes
		Bone (peak)		30 (NR)	Yes
Polk et al.[23] (prospective study) n = 20			HPLC		
	1 g	Serum		42 (5.0)	Yes
		Bone		7.7 (4.8)	Yes
Williams et al.[20] (prospective study) n = 23			Disc diffusion		
	1 g	Serum		51.7 (NR)	Yes
		Bone		5.9 (NR)	Yes
	2 g	Serum		98.3 (NR)	Yes
		Bone		14.9 (NR)	Yes
Young et al.[25] (randomized control trial) n = 22			HPLC		
	1 g IV	Fat		10.6 (NR)	Yes
		Bone		11.4 (NR)	Yes
	1 g IO	Fat		186 (NR)	Yes
		Bone		130 (NR)	Yes
Angthong et al.[16] (prospective study) n = 21			HPLC		
	1 g	Bone femur		22.6 (8.7)	Yes
		Bone tibia		21.4 (11.4)	Yes
	2 g	Bone femur		44.1 (25.8)	Yes
		Bone tibia		35.5 (5.1)	Yes
Sharareh et al.[21] (prospective study) n = 34			HPLC		
	1 g	Bone		5.0 (3.1)	Yes
	2 g	Bone		8.3 (5.6)	Yes
Rivera et al.[24] (prospective study) n = 22			HPLC		
	2 g	Serum		17.3 (range 11.2–33.2)	Yes

HPLC = high-pressure liquid chromatography; IO = intraosseous; IV = intravenous; MIC = minimum inhibitory concentration; NR = not reported; SD = standard deviation.
*Serum = µg/mL; bone = µg/g.

compared the differences in LTC in soft tissue, bone and serum when waiting 1 minute, 2 minutes and 5 minutes to inflate the tourniquet after administration of cefazolin. Waiting 5 minutes to inflate the tourniquet had the greatest area under the concentration curve for soft tissue, bone and serum.

Discussion

Despite routine use of prophylactic antibiotics, PJI remains a serious issue in arthroplasty. Cefazolin is well suited for the most common PJI pathogens, having bactericidal activity against most Gram-positive organisms, aerobic Gram-negative bacilli and anerobic Gram-positive organisms.[29] Despite many institutional differences worldwide, the standard preoperative dose is 1 g, and the dose increases to 2 g for patients weighing more than 80 kg and for procedures with tourniquet inflation.[30,31] However, dosage recommendations and corresponding efficacy remain unclear, partly because of the unknown distribution of drugs throughout the body and actual LTC. Sufficient LTC of an antibiotic is required for optimal infection prevention by achieving MIC of 1 µg/mL. The LTC can vary owing to several parameters such as BMI,

dose, route of administration, procedure type and tourniquet inflation. Knowing the LTC of cefazolin during TKA or THA will facilitate optimization of antibiotic prophylaxis and help reduce the incidence of PJI.

Of the more than 300 studies screened, only 10 reported the LTC of cefazolin in TKA and THA. Most of the study groups used mass spectrometry to quantify LTC, with some variations in their extraction protocol. Data from the studies were retrieved and used to evaluate the target parameters: dosing and route of administration, procedure type, BMI and tourniquet usage. Of the 7 studies that observed the effect of dosing on LTC, it was found that 2 g of IV cefazolin yielded a greater LTC in the bone and in the serum than a 1 g dose. Young and colleagues[25] reported greater LTC with an IO administration protocol, but clinical reduction of PJI has yet to be proven to outbalance the inconvenience and applicability of such a protocol. Among the studies that evaluated the difference in LTC when comparing THA and TKA, LTC sampling tended to achieve greater bone concentration of cefazolin in THA than TKA, while maintaining similar serum concentration. We observed a twofold increase in proximal femur (THA) bone LTC compared with THA sampling across all 3 studies. Other than the

Table 2. Effect of procedure type on target-site concentration

Study (level of evidence)	Group	Tissue	Technique	Tissue concentration,* (SD)	Above MIC
Bryan et al.[26] (prospective study) n = 48			HPLC		
	THA	Serum		53.4 (18.9)	Yes
		Bone		1.6 (1.4)	Yes
	TKA	Serum		66.7 (35.2)	Yes
		Bone		0.6 (0.57)	No
Yamada et al.[27] (prospective study) n = 43			HPLC		
	THA	Serum		177.2 (68.1)	Yes
		Bone		32.3 (15.2)	Yes
	TKA	Serum		166 (38.5)	Yes
		Bone		16 (10.4)	Yes
Sharareh et al.[21] (prospective study) n = 34			HPLC		
	THA	Bone		11.5 (6.7)	Yes
	TKA	Bone		6.0 (3.6)	Yes

HPLC = high-pressure liquid chromatography; MIC = minimum inhibitory concentration; SD = standard deviation; THA = total hip arthroplasty; TKA = total knee arthroplasty.
*Serum = µg/mL; bone = µg/g.

Table 3. Effect of BMI on target-site concentration

Study (level of evidence)	Group	Dosing	Technique	Tissue concentration,* (SD)	Above MIC
Sharareh et al.[21] (prospective study) n = 34			HPLC		
	BMI < 25	1 g if < 70 kg		8.05 (4.90)	Yes
	BMI 25–30			6.7 (4.43)	Yes
	BMI 31–35	2 g if > 70 kg		8.4 (6.9)	Yes
	BMI > 35			8.57 (3.4)	Yes

BMI = body mass index; HPLC = high-pressure liquid chromatography; MIC = minimum inhibitory concentration; SD = standard deviation.
*Serum = µg/mL; bone = µg/g.

Table 4. Effect of tourniquet utilization on target-site concentration

Study (level of evidence)	Group	Tissue	Technique	Tissue concentration,* (AUC)	Above MIC
Friedrich et al.[28] (prospective study) n = 24			HPLC		
	1 min	Soft tissues		224 (21–408)	Yes
		Bone		200 (79–617)	Yes
		Serum		4699 (1328–8266)	Yes
	2 min	Soft tissues		387 (133–533)	Yes
		Bone		182 (93–277)	Yes
		Serum		5170 (1301–26 272)	Yes
	5 min	Soft tissues		671 (489–2395)	Yes
		Bone		235 (61–1804)	Yes
		Serum		6044 (2944–16 542)	Yes

AUC = area under the serum concentration curve; HPLC = high-pressure liquid chromatography; MIC = minimum inhibitory concentration.
*Serum = mg*min/L; bone = µg × min/g.

effect of tourniquet inflation to explain such a trend, research groups should consider evaluating if vascularity of different bony regions affects LTC during surgery. In addition, Sharareh and colleagues[21] evaluated the effect of BMI on bone LTC, showing there was no statistical difference in concentrations of cefazolin in bone between the different BMI groups. The average bone concentration was consistent with other studies, ranging between 6.7

and 8.6 µg/mL. Although morbid obesity is considered a modifiable risk factor for PJI, there is presently a lack of consensus regarding a BMI threshold above which the high risk of PJI outweighs the benefits of surgery. More research should focus solely on particularities of antibiotic prophylaxis in the context of obesity to optimize LTC and hopefully reduce infection rates in these patients. Finally, there was only 1 study that assessed the effect of a

tourniquet on LTC. Waiting 5 minutes before inflating the tourniquet after cefazolin infusion had the greatest tissue penetration in soft tissue, bone and serum compared with waiting 1 or 2 minutes before inflating the tourniquet; however, longer wait times were not evaluated. To our knowledge, no studies to date have assessed LTC during a TKA with and without a tourniquet.

Limitations

Our review had several limitations that could be addressed in future research. A substantial range and variations in LTC were observed across all 10 studies. These discrepancies could be explained by evolution of extraction techniques over the last 30 years. Standardizing techniques, parameters and patient population was not possible here. Another limitation is that infection rate was not considered as a primary outcome. Having LTC as our main outcome limited the number of included studies in our review. Our primary search was intended to observe LTC in all orthopedic procedures, but no studies outside of arthroplasty procedures fit our inclusion criteria. This led us to narrow our search and focus solely on TKA and THA. Furthermore, PJI occurs in the context of a complex combination of preoperative, operative and postoperative factors. Although extensive research is conducted on PJI prevention, this review focused on and highlighted the paucity of studies showing levels of LTC and on whether usual antibiotic prophylaxis practices in orthopedics achieve required MIC for common microorganisms.

This systematic review did highlight several gaps in our understanding of LTC of cefazolin that would help us optimize antibiotic prophylaxis. Although all included studies used the premise that prophylactic antibiotics should be completely infused within 60 minutes before the surgical incision, no study looked at the effect of different preoperative time intervals on LTC throughout the surgery. Cefazolin achieves highest peak bone concentrations 40 minutes after parenteral application with a serum half-life of 108 minutes and a bone half-life of 42 minutes.[20] By using the given pharmacokinetics of cefazolin and a mathematical model, Bicanic and colleagues[31] inferred that parenteral application of cefazolin should be no longer than 30 minutes before incision (tourniquet inflation) and no less than 10 minutes before tourniquet inflation, if given in bolus to achieve maximal blood and bone LTC. This must be further studied with dedicated LTC measurements based on different administration courses. Furthermore, the duration of LTC is not well studied and could help guide the timing for redosing. Another parameter that should be further assessed is BMI as it is considered a modifiable risk factor for PJI in the arthroplasty literature, with the risk for infection increasing gradually as BMI increases. In this review, only 1 study assessed the change in LTC with BMI. As obesity rates continue to rise worldwide, it is paramount to understand the change in LTC to optimize antibiotic prophylaxis and hopefully prevent adverse outcomes.

We found a single study analyzing the effect of timing of tourniquet inflation on LTC. No studies assessed the effect of performing a TKA with or without a tourniquet on LTC. Tourniquet inflation during TKA is commonly used to reduce bleeding in the surgical field, thereby facilitating exposure and cementation. However, this reduced circulation in the limb may also reduce antibiotic distribution and clearance in the periincisional tissues. Recently, improved immediate pain and functional outcomes of TKA without a tourniquet have been suggested.[32] The effect of TKA surgery without a tourniquet on LTC should be explored.

CONCLUSION

We highlighted a paucity of studies that measured levels of LTC to validate the current recommendations for antibiotic prophylaxis for arthroplasty surgery. Future studies evaluating the parameters highlighted in our review are essential considering that PJI will remain the leading source of early reoperation or revision surgery in arthroplasty and that prophylactic antibiotics are the single most effective preventative measure.

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