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■ INFECTION

Wound fluid ceftriaxone concentrations after local application with calcium sulphate as carrier material in the treatment of orthopaedic device-associated hip infections

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Aims

There is a considerable challenge in treating bone infections and orthopaedic device-associated infection (ODAI), partly due to impaired penetration of systemically administrated antibiotics at the site of infection. This may be circumvented by local drug administration. Knowledge of the release kinetics from any carrier material is essential for proper application. Ceftriaxone shows a particular constant release from calcium sulphate ($CaSO_4$) in vitro, and is particularly effective against streptococci and a large portion of Gram-negative bacteria. We present the clinical release kinetics of ceftriaxone-loaded $CaSO_4$ applied locally to treat ODAI.

Methods

A total of 30 operations with ceftriaxone-loaded $CaSO_4$ had been performed in 28 patients. Ceftriaxone was applied as a single local antibiotic in 21 operations and combined with vancomycin in eight operations, and in an additional operation with vancomycin and amphotericin B. Sampling of wound fluid was performed from drains or aspirations. Ceftriaxone concentrations were measured by liquid chromatography with tandem mass spectrometry (LC-MS/MS).

Results

A total of 37 wound fluid concentrations from 16 operations performed in 14 patients were collected. The ceftriaxone concentrations remained approximately within a range of 100 to 200 mg/l up to three weeks. The median concentration was 108.9 mg/l (interquartile range 98.8 to 142.5) within the first ten days. No systemic adverse reactions were observed.

Conclusion

Our study highlights new clinical data of locally administered ceftriaxone with $CaSO_4$ as carrier material. The near-constant release of ceftriaxone from $CaSO_4$ observed in vitro could be confirmed in vivo. The concentrations remained below known local toxicity thresholds.

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Article focus

- Local antibiotic application may enhance drug delivery at the site of infection of bone and orthopaedic device-associated infections (ODAIs).
- The release kinetics of ceftriaxone from calcium sulphate ($CaSO_4$) used as local antibiotic application to treat bone and ODAIs are documented.

Key messages

- The ceftriaxone concentrations remained approximately within a range of 100 to 200 mg/l up to three weeks.
- The concentrations remained below local toxicity thresholds.
- The nearly constant release of ceftriaxone from $CaSO_4$ observed in vitro could be

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confirmed in vivo, release being limited by dissolution of the carrier material.

Strengths and limitations

■ A range of ceftriaxone concentrations could be determined, nevertheless interpatient variability remained quite variable.

■ Only a rather limited amount of measurements were available for analysis, sampling having not been performed systematically but instead as treatment imposed and allowed.

■ Samples were available solely from hip wounds, while dissolution of the carrier material and release of the added antibiotic may differ at other sites.

Introduction

Bone infections and orthopaedic device-associated infections (ODAIs) are notably difficult to treat. One of the reasons is the impaired penetration of systemically administered antibiotics at the site of the infection, worsened by reduced activity against biofilm.[1-4] Antibiotic drug delivery may be enhanced in bone and joint infections by local administration.[5-8] Interesting release kinetics have been documented particularly for vancomycin with polymethylmethacrylate (PMMA) bone cement as well as with calcium sulphate ($CaSO_4$) as antibiotic carrier materials.[5-8] Even intermittent direct intra-articular administration is associated with high joint fluid concentrations of vancomycin.[9] The choice of antibiotics is limited due to local toxicity and stability issues.[10-12] The release of aminoglycosides from available carrier materials is relatively short and associated with emergence of resistance.[5,13-16] Adequate options to treat Gram-negative bacteria are therefore limited.[6]

Ceftriaxone appears to have a nearly constant release from $CaSO_4$ in vitro.[12,17] Furthermore, it has excellent activity against streptococci and covers a large portion of Gram-negative bacterial species, offering interesting new treatment options.[18-21] We aimed to study the release kinetics of $CaSO_4$ loaded with ceftriaxone in various ODAIs when local application of the well-established vancomycin-loaded $CaSO_4$[8,22] was not deemed adequate.

Methods

Patients with ODAI treated with antibiotic-loaded $CaSO_4$ were identified from a prospectively collected database.[8,14] Between October 2013 and August 2022, $CaSO_4$ (Osteoset; Wright Medical Technologies, USA) loaded with ceftriaxone (2 g in ten cases, 4 g in 19 cases, and 6 g in one case) was used in 30 operations (21 hip periprosthetic joint infections (PJIs), two femur fracture-related infections (FRIs), one pelvis FRI, three knee PJIs, two shoulder PJIs, and one elbow PJI) performed on 228 patients (16 male, 12 female; median age 71.6 years (range 49.5 to 97.1)). In 21 cases, ceftriaxone was applied as the only local antibiotic. In eight cases, ceftriaxone was combined with vancomycin (2 g in 25 ml $CaSO_4$), and in one case with both vancomycin and amphotericin B (2 g in 25 ml $CaSO_4$ and 450 mg in 75 ml $CaSO_4$, respectively).

The preparation of the $CaSO_4$ pellets has been described elsewhere.[8,17] Briefly, 2 g of ceftriaxone powder was added per package of 25 ml Osteoset fast cure, adding sterile water for a total liquid volume of 13 to 15 ml, instead of the standard 7.8 ml provided in the set, for the dough to be hydrated enough for mixing and moulding.[17] The total volume exceeded the volume of the moulds provided in each set, although the surplus was nevertheless implanted, even if irregularly formed.

Sampling of wound fluid was performed if available or necessary. When drains were in place, fluid was collected over the shortest possible period of time to obtain samples at a specific timepoint. Drains were not maintained for more than five days. Wound fluid aspirations were performed only at reoperations or in case of clinical need. The samples were collected in serum separator tubes and frozen at -80°C until analyses by liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) as described previously.[12] The limit of quantification (LOQ) for ceftriaxone was 0.5 mg/l.[17]

Results

A total of 37 wound fluid concentrations of ceftriaxone were available from 116 operations (15 hip PJIs and one proximal femur FRI) performed on 114 patients (eight male, six female; median age 69.5 years (range 50.4 to 97.1)). In 12 operations, ceftriaxone was the sole antibiotic added to $CaSO_4$. A combination of ceftriaxone and vancomycin was applied in four cases, of which one also had amphotericin B added. Detailed data are summarized in Table I. All wound fluid samples were collected from the hip, except in one patient treated for FRI of the femur, with sample collection performed over a drain maintained for three days. All samples were collected from the wound cavity of the hip joint or around the proximal femur. Examples illustrating the distribution of the $CaSO_4$ pellets are shown in Figure 1.

The ceftriaxone concentrations measured in the wound fluid over time are illustrated in Figure 2. In one case, marked on the figure, concomitant systemic treatment with ceftriaxone interfered. The concentrations remained approximately within a range of 100 to 200 mg/l over a period of up to three weeks. The highest concentrations were observed between five and 12 days postoperatively, with one exception (385.2 mg/l on day 17 at revision due to secondary wound oozing attributed to the dissolution of $CaSO_4$). Over the first ten days, median ceftriaxone concentration was 108.9 mg/l (53.6 to 200; interquartile range (IQR) 98.8 to 142.5) in 16 operations. In three operations, wound fluid could be sampled after a longer follow-up on days 56, 63, and 91, respectively, as aspirations were performed to rule out persistence of infection.

No systemic adverse reactions (toxicity or hypersensitivity) related to ceftriaxone were observed. In one

Table I. Details of the 16 operations, performed in 14 patients, in whom ceftriaxone concentrations were measured in the wound fluid after application of ceftriaxone-loaded calcium sulphate to treat various orthopaedic infections. Only samples from the hip were included in the analysis. The one case of fracture-related infection of the proximal femur had a similar pellet distribution as in the cases of hip periprosthetic joint infection.

Operation no.	Sex	Age, yrs	Organ	Problem	Procedure	$CaSO_4$, ml	Ceftriaxone, mg	Vancomycin, mg	Amphotericin B, mg
1	M	50.4	Proximal femur	FRI	Debridement and hardware removal	75	4,000	2,000	0
2	F	68.2	Hip	PJI	Resection arthroplasty	50	4,000	0	0
3	F	82.7	Hip	PJI	Resection arthroplasty	50	4,000	0	0
4	M	69.5	Hip	PJI	DAIR	50	4,000	0	0
5	F	82.3	Hip	PJI	DAIR	25	2,000	0	0
6	M	75.3	Hip	PJI	DAIR	50	4,000	0	0
7	M	71.1	Hip	PJI	Two-stage exchange with spacer	50	4,000	0	0
8	F	70.2	Hip	PJI	Two-stage exchange without spacer	50	4,000	0	0
9	F	56.7	Hip	PJI	Two-stage exchange with spacer	75	6,000	0	0
10	M	57.1	Hip	PJI	DAIR	50	4,000	0	0
11	M	57.1	Hip	PJI	DAIR	50	2,000	2,000	0
12	Identical 11	Identical 11	Hip	PJI	DAIR	125	2,000	2,000	450
13	M	67.0	Hip	PJI	DAIR	75	4,000	2,000	0
14	M	72.1	Hip	PJI	DAIR	50	4,000	0	0
15	F	73.2	Hip	PJI	One-stage exchange	50	4,000	0	0
16	M	97.1	Hip	PJI	DAIR	50	4,000	0	0
Total	7 × M 6 × F	Median 69.5 (50.4 to 97.1)	All hip or proximal femur	1 × FRI 15 × PJI	N/A	1 × 25 11 × 50 3 × 75 1 × 125	3 × 2,000 12 × 4,000 1 × 6,000	10 × 0 4 × 2,000	12 × 0 1 × 450

Cases 11 and 12 were from the same patient and hip, from two revisions performed 11 days apart, whereas case 10 was the same patient but from the contralateral hip. The quantities of ceftriaxone ranged from 2,000 to 6,000 mg. In four cases, vancomycin-loaded ceftriaxone-loaded calcium sulphate had been added concomitantly, in addition to amphotericin B in one case.

$CaSO_4$, ceftriaxone-loaded calcium sulphate; DAIR, debridement, antibiotics and implant retention; F, female; FRI, fracture-related infection; M, male; N/A, not applicable; PJI, periprosthetic joint infection.

case (4%), $CaSO_4$ had been removed secondarily due to persistent wound oozing (11 days postoperatively).

Discussion

This study provides to the best of our knowledge the first in vivo data of ceftriaxone concentrations released in wound fluid from $CaSO_4$ used as carrier material (Figure 1). Results over time up to three months after implantation were available from 16 operations for PJI of the hip and FRI of the proximal femur. Systemic administration of ceftriaxone interfered in only one case. Considering known serum trough and tissue concentrations,[23] inclusion of this one case does not change the conclusions of this study. These observations confirmed a continuous release, as observed in vitro, probably driven by the slow dissolution of the carrier material (Figure 1).[17] Concentrations remained mainly within a range of 100 to 200 mg/l for at least three weeks. While a certain effect of the ceftriaxone

released from $CaSO_4$ may be expected on any biofilm formed in ODAI, the required time and concentration profiles necessary for biofilm eradication, rather than just reduction, remain unknown to the best of our knowledge.[24–26]

Ceftriaxone-loaded $CaSO_4$ appears to have a particular and outstanding release profile, with constant concentrations persisting for some weeks (Figure 1).[17] As a beta-lactam antibiotic, and consequently highly soluble compound, ceftriaxone would be expected to elute rapidly from the matrix of the carrier.[12,27,28] However, the concentrations observed do not follow the exponential decrease observed in aqueous solution at body temperature without any carrier material.[12,27,28] Persistent high local concentrations over some weeks indicate a slow release, most probably limited by dissolution of the carrier material (Figure 1).[29,30] From clinical experience, dissolution appears to happen faster within well-vascularized muscles around the hip and within
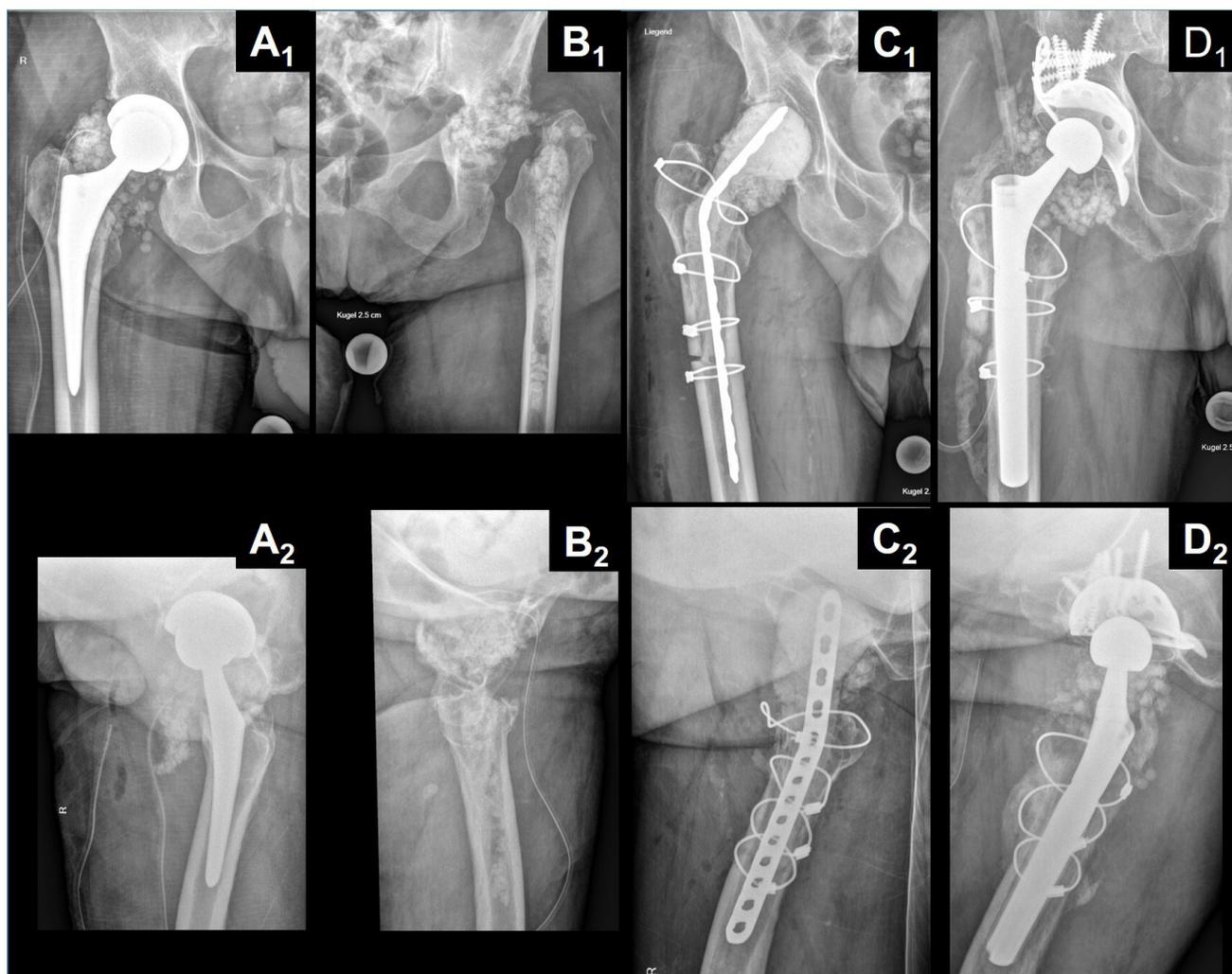
Fig. 1

Examples of applications of ceftriaxone-loaded calcium sulphate ($CaSO_4$). Ceftriaxone concentrations were measured in wound fluid in each of these patients. Note that in all cases the $CaSO_4$ pellets were packed in the hip wound cavity or around the proximal femur. Even if the procedures differed, soft-tissue exposure and dissolution of the pellets were similar. Anteroposterior views of the affected hip are provided In the upper row, and corresponding axial views are provided in the lower row. All images correspond to postoperative radiographs. a) After debridement, antibiotics and implant retention (DAIR) procedure in the case of periprosthetic joint infection (PJI) after primary total hip arthroplasty (THA) in a 69-year-old male. b) After the first stage of a two-stage exchange without spacer in the case of PJI after primary THA in a 70-year-old female. c) After the first stage of a two-stage exchange with spacer in the case of PJI after primary hemiarthroplasty in a 71-year-old male. d) After a DAIR procedure as salvage in the case of PJI recurrence after a two-stage exchange in a 66-year-old male.

the thigh than in case of application within a medullary cavity, or closer to the ankle.

As a beta-lactam antibiotic, time above the minimal inhibitory concentration (MIC) of ceftriaxone determines antibacterial activity.[31–33] Continuous exposure would be ensured by the release observed from $CaSO_4$ (Figure 1). However, the activity of ceftriaxone against staphylococci is slightly reduced in presence of albumin, a protein that binds to this drug with a high affinity.[18,19,34,35] High local drug concentrations may however compensate for protein binding, which may be saturated with an exponential increase of ceftriaxone observed from 10 mg/l upwards.[34,35] While wound fluid albumin concentration is unknown in the early postoperative phase, native joint fluid and periprosthetic joint fluid, as well as wound fluid from chronic wounds, have a lower albumin content than serum.[36–38] Considering the concentrations observed, very high activity may be expected against streptococci (MIC < 0.1 mg/l).[18,20,21] Streptococci may be identified in up to 12% of chronic osteomyelitis cases,[39–41] and cause up to 12% of PJIs.[42–46] Staphylococci cause the vast majority of ODAIs as well as most cases of osteomyelitis,[39–41,43–46] but may show resistance to this antibiotic, particularly coagulase-negative staphylococci.[20,21,42] Ceftriaxone does not suffer from an inoculum effect with Gram-positive bacteria.[18] Gram-negative bacteria may be identified in up to 45% of chronic osteomyelitis cases,[39–41] and cause up to 12% of PJIs[42–46] and 15% of FRIs.[44] While ceftriaxone
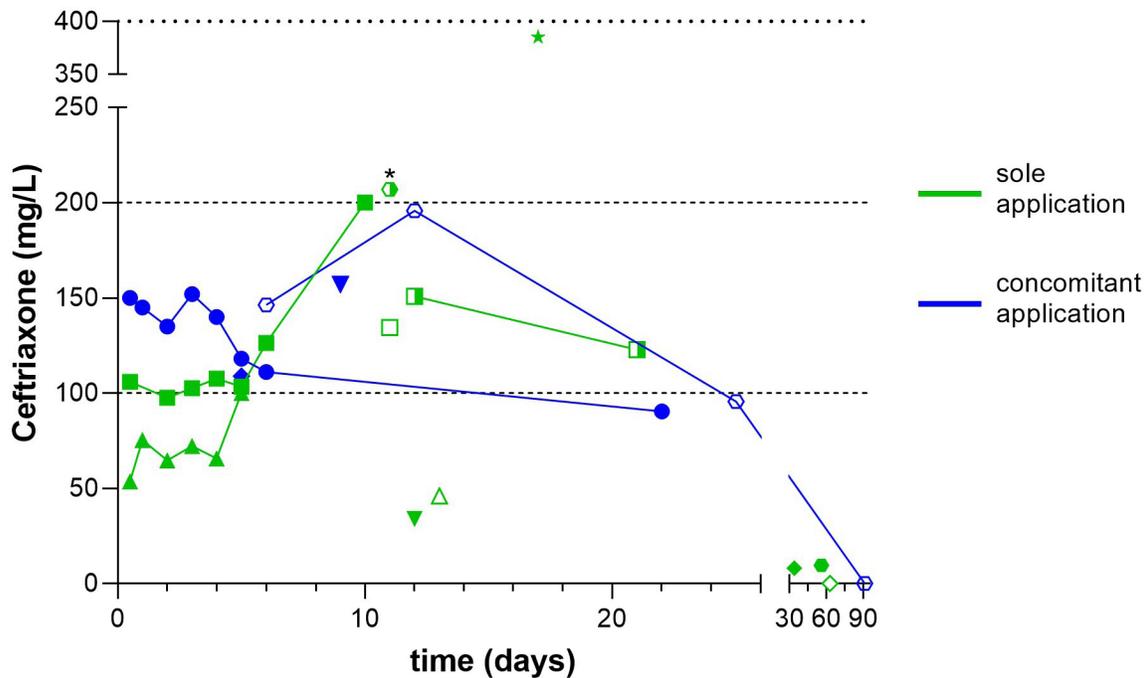
Fig. 2

Ceftriaxone concentrations measured in wound fluid over time after 16 operations with ceftriaxone-loaded calcium sulphate to treat orthopaedic device-associated infection. Each symbol indicates one concentration following a given operation. Different symbols are used to illustrate results from the different patients. Four operations were followed by serial concentration measurements (linked) and ten operations were followed by a unique concentration measurement. Concentrations after sole application of ceftriaxone are shown in green (n = 10), while concentrations after concomitant application of ceftriaxone and vancomycin, or ceftriaxone, vancomycin and amphotericin B are shown in blue (n = 4). In one case, marked with a black asterisk, systemic administration of ceftriaxone interfered, but sampling was performed shortly before the next dose. Considering known trough and tissue concentrations, approximately 30 mg/l may be deduced from the measured value of 206.8 mg/l.[23]

has an antibacterial spectrum enlarged to Gram-negative bacteria, there are potential issues with resistance.[20,21] Non-fermentative Gram-negative bacilli are usually not sensitive to ceftriaxone.[20,21,47] All Gram-negative bacilli carry variants of the AmpC gene, an inducible cephalosporinase.[48] The high concentrations of Ceftriaxone locally released may not suffice to overcome these resistances, despite being of a competitive type. Therefore, other antibiotics may have to be preferred or added to successfully treat such bacterial species.

Samples were frozen at -80°C until assaying, to prevent degradation of ceftriaxone during storage.[12,27,28] LC-MS/MS was used to measure ceftriaxone concentrations, as described elsewhere.[12,17] This method is independent of the protein matrix of the samples.[49] Therefore, the protein matrix has no influence on the measurement, contrary to the fluorescence assays commonly used in clinical chemistry, which are calibrated to the protein content of serum. However, wound and joint fluid has another protein content.[36–38] While the chosen assay had not been validated formally for wound fluid, results may be considered as reliable due to the independence of the protein matrix.[49] Samples were collected both from drains, particularly those from the first three days, and by aspiration. Precipitation of the drug may happen within the drains, resulting in falsely low results. However, all results remained within the

same range (Figure 1), making such a sampling issue unlikely. One sample reached a high peak of 385.5 mg/l at day 17. This sample was collected at revision due to persistent wound oozing induced by $CaSO_4$, a known issue with this carrier material.[50] In this case, a more rapid degradation of $CaSO_4$ may have happened for an unknown reason, with consecutive secretion and high ceftriaxone concentrations.

Cell toxicity is limiting any local application of drugs.[10,11] Toxicity of ceftriaxone is both concentration- and time-dependent.[11] Nevertheless, the release from $CaSO_4$ remains far below long-term toxicity thresholds observed in vitro.[11] No systemic toxicity is to be expected from local application of a single dose of 2 to 6 g of ceftriaxone, as the slow release process is associated with low systemic exposure, and the single dose is within or close to the highest recommended daily dosage (4 g).[17,18,20,21] Ceftriaxone is primarily eliminated by hepatobiliary pathways.[18] Therefore, an accumulation in case of renal failure is not an issue. Hypercalcaemia may, however, be an issue, particularly in case of renal impairment, and may require limiting the total amount of $CaSO_4$ carrier material.[51] The implantation of $CaSO_4$ may be associated with prolonged wound drainage. In a recently published systematic review, the risk of prolonged wound drainage was estimated at 3.8%.[52] With one patient from this study reoperated for

prolonged wound drainage, the risk in this cohort was 4%. Uncontrolled infection may also cause prolonged wound drainage and require reoperations, a risk mitigated by the local application of antibiotic-loaded CaSO$_4$.[22] Placement of a subcutaneous suction drain may allow the skin to heal without prolonged oozing, without aspirating relevant quantities of the antibiotic placed in the depth of a hip. As mentioned, we remove this drain on day 5 at the latest.

Despite interesting release kinetics observed clinically,[5,6,8] local application of antibiotics in the treatment of bone and joint infections remains a matter of debate. A recently published large study even showed a negative effect of local application of antibiotics in the treatment of PJI.[53] This, however, may have been due to application of inappropriate antibiotics as well as poor carrier materials.[22,54] The historically used standard carrier material PMMA is non-resorbable and may serve as substrate for biofilm formation, despite active antibiotic drug release.[55,56] PMMA may have to be removed for mechanical reasons, thus requiring reoperations with consecutive supplementary risks negating any advantages of local delivery.[57] The most commonly applied aminoglycosides may simply be inadequate for local application. Release of these small, very hydrophilic molecules may be too fast, resulting in a high initial burst with potential toxicity, whereas the concentrations drop too fast towards subtherapeutic values.[5,13,14,16] In addition, the mode of action of these antibiotics may be inadequate for local delivery, as it requires an oxygen-dependent active transport against the proton gradient, which is particularly unfavourable for treating bacteria with low metabolic activity in an acidic environment.[58] The addition of antibiotic-loaded CaSO$_4$ to standard of care did greatly improve outcomes in two studies examining debridement, antibiotics and implant retention procedures in hip[22] or knee[54] PJI, but had no effect in two other studies.[59,60] A potential explanation is insufficient quantities or concentrations. Another hypothetical explanation is the type of CaSO$_4$ used, as both studies with a positive effect used Osteoset, whereas the other two studies used Stimulan (Biocomposites, UK). Ceftriaxone-loaded CaSO$_4$ may be particularly useful in case of PJI caused by streptococci, considering their sensitivity to this antibiotic and the currently subpar outcome of the standard treatment.[20,21,61]

In conclusion, this study provides new clinical data on ceftriaxone wound fluid concentrations when locally applied with CaSO$_4$ as carrier material to treat orthopaedic infections. The near-constant release of ceftriaxone from CaSO$_4$ observed in vitro could be confirmed in the clinical application (Figure 1).[17] Furthermore, the concentrations are below the local toxicity threshold and therefore are not expected to have any negative impact on regenerative capacity of the tissues. First clinical results for antibiotic-loaded CaSO$_4$ are encouraging,[22,54] but further studies are necessary to determine the ceftriaxone time-concentration profiles necessary for eradication of the various bacteria causing ODAIs and their associated biofilm.

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