

Intramedullary antibiotic perfusion for the control of fracture-related infection early after osteosynthesis

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Abstract

Background

In our hospital, cases of bone and soft tissue infections have been treated with continuous local antibiotic perfusion, which allows for continuous circulation of antibiotics throughout the infected lesion. We call this treatment “intramedullary antibiotic perfusion (iMAP)” for bone infection, such as fracture-related infection (FRI), and “intra-soft tissue antibiotic perfusion” for soft tissue infection. Many cases are treated with both modalities. To introduce “iMAP,” this study focused on FRI patients treated with only iMAP and reviewed their treatment outcomes.

Methods

We included ten patients who developed FRI early after osteosynthesis and were treated with CLAP, between 2004 and 2017. The iMAP needles were inserted near the deep-seated infected lesion, and an aminoglycoside antimicrobial was continuously administered slowly. Intravenous and oral antibiotics were administered after CLAP. Patient characteristics, age, pathogenic bacteria, used antimicrobials and duration of administration, concentrations of antimicrobial agents in blood and drainage fluid, fracture union rate, implant retention rate, duration of follow-up, and complications were evaluated.

Results

The mean patients’ age was 59.9 years, and the mean follow-up was 2.5 years. The affected bones were the tibia (8 patients), humerus (1 patient), and fibula (1 patient). Internal fixation was performed at an average of 7.5 days after the injury. Deep infections developed on average 29.9 days after the operation. Pathogenic bacteria included methicillin-susceptible *Staphylococcus aureus* in six patients, methicillin-resistant *Staphylococcus aureus* in two patients, and were unknown in two patients. CLAP was performed with astromicin, arbekacin, or gentamicin. The average duration of iMAP was 17.1 days. Antimicrobial concentrations were adjusted to appropriate levels. In all patients, the deep infection was eradicated while preserving the implants, and fracture union was achieved without any complications.

Conclusions

iMAP is a novel local drug delivery system allowing high concentrations of antimicrobial agents without systemic adverse effects. It is a useful option in the treatment of FRI where implant retention is desired.

Background

Fracture-related infection (FRI) is one of the most common complications of osteosynthesis [1]. In particular, patients who developed FRI in the early period after osteosynthesis require concurrent eradication of infections and treatment of fractures, making it difficult to structure therapeutic strategies. It is often necessary to remove the implants to eradicate infections; however, removing them before fracture union can lead to instability at the fracture site. Therefore, if possible, it is desirable to eradicate

infections while preserving the implants, at least until fracture union. The bacterial biofilm formed around the implant is one of the factors that hinder FRI treatment [2–4]. Moreover, antimicrobial agents at concentrations of 100 to 1,000 times the minimum inhibitory concentrations (MIC) have been required to eradicate the biofilm, which is defined as the minimum biofilm eradication concentration (MBEC) [5–7]. Nevertheless, delivering the agents locally to the MBEC level by intravenous administration without systemic adverse effects is difficult. Another factor impeding the treatment of FRI is the inability of agents to reach the tissues with poor blood flow or dead cavities. In many FRI cases, infections spread to the surrounding soft tissues, and simultaneous treatment for the soft tissue infection is often required.

In our hospital, such difficult-to-treat bone and soft tissue infections were treated using continuous local antibiotic perfusion (CLAP), in which antibiotics are continuously circulated throughout the infected lesion. We call the treatment for FRI “intramedullary antibiotic perfusion (iMAP)” and for soft tissue infection “intra-soft tissue antibiotic perfusion,” and many cases are treated with a combination of both. iMAP is a treatment method that delivers a sufficient local concentration of the agent by eluting a daily dose of antibiotics in a small amount of saline and injecting it continuously at low speed using a bone marrow needle placed near the infected lesion. The injected agent is infiltrated into the infected site and is then drained through a drainage tube. This system is expected to eradicate the infections without the removal of implants and generate a pathway for localized perfusion of antibiotics, continuously circulating an effective concentration of the agent throughout the infected lesion. To introduce the methods, concepts, and therapeutic efficacy of iMAP, one of the treatment modalities for CLAP, this study focused on FRI patients treated with only iMAP and reviewed their treatment outcomes.

Methods

This study was approved by the institutional review board of our hospital. Written informed consent was obtained from all patients whose clinical course or images are presented in this manuscript.

Subjects

Patients who developed FRI early after osteosynthesis and were treated with only iMAP, between 2004 and 2017, were enrolled as participants. To exclude patients with chronic osteomyelitis, patients with FRI within 9 weeks after the initial internal fixation were only included [8].

Data collection

Patient characteristics, including age, sex, and comorbidities, pathogenic bacteria, administered antibiotics (iMAP, intravenous, and oral), duration of administration of each agent, fracture union rate, implant retention rate, duration of follow-up, and complications were evaluated. When possible, the

concentrations of antibiotics in the blood and drainage fluid were measured. The latter was used as a reference for local concentration.

Continuous local antibiotic perfusion by iMAP

The iMAP method is depicted in Fig. 1. iMAP was initiated as soon as deep infections were suspected by clinical findings, such as pus-like discharge from the wound, swelling, redness, and local heat of the affected limb. A not-loosened implant was retained to prevent the fracture from becoming unstable. A bone marrow puncture needle with a 3-mm outer diameter was used for iMAP (iMAP needle). Two holes of 3-mm diameter were made in the bone nearby the infected lesion, and highly concentrated antibiotics were continuously injected at 2 mL/h through two inserted iMAP needles using syringe pumps. A drainage tube of the leachate around the fracture site was placed subcutaneously. Based on our experience, we consider local administration as ideal for bactericidal agents because higher concentrations can be achieved. Since aminoglycoside is a bactericidal agent with a long history of clinical and basic evidence and has been reported to have a superior bactericidal effect against biofilms formed by methicillin-resistant *Staphylococcus aureus* (MRSA) [9, 10], we used aminoglycoside antibiotics for iMAP. The iMAP needles were withdrawn when the local and hematological findings indicated resolution of the infection. We selected and changed the intravenous and oral administration of agents with reference to the results of bacteria sensitivity for antibiotics and continued those administrations after removal of iMAP needles as a standard protocol to treat osteomyelitis.

Results

Data from 10 patients (eight men, two women) were collected. The mean age at the time of fracture operation was 59.9 (range, 22–80) years, and the mean follow-up duration was 2.5 (1.0–5.0) years. Comorbidities included diabetes mellitus (three patients), hepatitis C (one patient), chronic renal failure requiring dialysis (one patient), and epilepsy (one patient). The affected bones were the tibia in eight patients and the humerus and fibula in one patient each. Open fractures were present in three patients. Osteosynthesis was performed in seven patients by plates and in three patients by intramedullary nail. The initial internal fixation was performed at an average of 7.5 (0–27) days after the injury. Deep infections developed on average of 29.9 (14–63) days after the initial internal fixation.

A summary of the characteristics of the 10 patients is presented in Table 1. The pathogenic bacteria were methicillin-susceptible *Staphylococcus aureus* (MSSA) in six patients, MRSA in two patients, and unknown in two patients. Antibiotics administered through iMAP were astromicin (800–1000 mg/day), arbekacin (150 mg/day), and gentamicin (60–300 mg/day) in three, one, and eight patients, respectively; the average duration of iMAP was 17.1 (range, 8–28) days. A summary of administered antibiotics is shown in Table 2. In all patients, the deep infections could be eradicated with the implants preserved, leading to fracture union. During the observation period, there were no complications or recurrence of infection, and no patient required arthrodesis and amputation of the affected limb. The blood

concentration of gentamicin needed to be adjusted in one of the patients (patient 7 in Table 2). The transition of gentamicin concentration in the blood and drainage fluid of the patient is shown in Fig. 2. The gentamicin concentration in the blood was adjusted to an appropriate level by promptly slowing down the rate of gentamicin administration. By contrast, the concentrations in the drainage fluid, used as a reference for local concentration, were maintained at a high level throughout the administration period.

Case presentation 1 (patient 1 in Table 1)

The patient was a 75-year-old woman with diabetes mellitus. She sustained left closed tibial and fibular distal shaft fractures in a traffic accident (Fig. 3a). Pre-injury activities of daily living were T-cane gait exercises. We performed open reduction and internal fixation (ORIF) for both fractures using locking plates on the 5th day after the injury (Fig. 3b). On the 14th postoperative day, purulent discharge was observed from the surgical wound (Fig. 3c), and deep infection to the implant and fracture site was considered; thus, emergency surgery was performed on the same day. A subcutaneous pocket filled with necrotic tissue and infected fluid was curetted. A drainage tube was placed subcutaneously, and iMAP needles were inserted proximal and distal to the fracture site in the tibia (Fig. 3d). We confirmed that the injected saline through the iMAP needles was properly drained through the tibial fracture site to the drainage tube. A solution of 120 mg of gentamicin in 50 mL saline was injected locally at 2 mL/h from two iMAP needles in a sustained manner using syringe pumps, with the implants preserved (Fig. 3e). The pathogenic bacterium was MSSA. Local findings improved promptly after the initiation of iMAP, and iMAP needles were removed 14 days after insertion. Intravenous and oral administration of antibiotics was continued for 4 weeks and 8 weeks after iMAP needle removal, respectively. At 1 year after surgery, no signs of infection recurrence were observed, and fracture union was achieved. The patient was able to walk with a T-cane as before the injury (Fig. 3f).

Case presentation 2 (patient 5 in Table 2)

The patient was a 22-year-old man with hepatitis C who could walk independently before the injury. He was injured in a traffic accident and was diagnosed with right closed tibial and fibular shaft fractures (Fig. 4a). ORIF with an intramedullary nail was performed for the tibial fracture on the 9th day after the injury (Fig. 4b). High-grade fever was observed on the 14th day after internal fixation, and localized swelling with heat was noted around the fracture area and the knee. Purulent discharge was observed upon the puncture of both areas (Fig. 4c). The infection was suspected to have spread to the knee joint via an intramedullary nail, and emergency surgery was performed on the same day. Two incisions were made around the fracture site, and curettage was performed. After placement of the subcutaneous drainage tube, iMAP needles were inserted in the proximal and distal parts of the fracture area (Fig. 4d). Bone marrow infusion was started at the same dose as in Case 1, and purulent leachate was drained. Two drainage tubes were placed in the knee joint after intra-articular irrigation during arthroscopy (Fig.

4e). The pathogenic bacterium was MSSA. Local findings improved promptly after iMAP was applied, and the iMAP needles were removed 27 days after insertion. Intravenous and oral administrations of antibiotics were continued for 2 weeks and 8 weeks after iMAP needle removal, respectively. There were no signs of recurrence of infection at 5 years after the treatment. Fracture union was achieved, and the patient could walk without pain (Fig. 4f).

Discussion

FRI after osteosynthesis is usually difficult to treat. Especially in early postoperative cases in which implant retention is desirable, the biofilm formed around implants and soft tissues with poor blood flow may hinder treatment. Bacteria existing within biofilms have been reported to be significantly less susceptible to antibacterial agents because their structural features prolong the penetration of agents by many orders of magnitude [11, 12]. Effective antimicrobial concentrations are generally assessed by MIC; however, MBEC is required to prevent the growth of biofilm, which is reported to be 100–1000 times the MIC depending on the type of bacteria [5–7]. However, high blood levels of antibiotics can cause systemic side effects, and extremely high concentrations of antibiotics have been reported to inhibit the replication of osteoblasts and cause cell death [13]. In this study, no patient exhibited systemic side effects. The fracture union was achieved in all cases, suggesting that cell death due to exposure to high concentrations of antibiotics, a concerning prognostic factor, did not occur, and biological viability at the fracture site was preserved. Therefore, we believe that iMAP can safely deliver high concentrations of antibiotics to infected lesions.

The bactericidal effects of aminoglycoside antibiotics are dose-dependent and are easier to maintain at a constant concentration than the time-dependent agents. A previous study reported that local aqueous aminoglycoside administration in combination with systemic antibiotics is effective in reducing infection rates in open fractures [14]. Thus, in our practice, we were initially using astromicin as the first-line antibiotic and arbekacin as the choice for resistant bacteria. After astromicin became unavailable in the market, we chose gentamicin as the first choice, the concentration of which can be measured in the blood. *Staphylococcus aureus* is known to be the most common pathogenic bacteria in postoperative surgical site infections in the orthopedic field [15, 16], with MRSA infections being especially difficult to treat. High concentrations of gentamicin are effective in eradicating biofilms formed by *Staphylococcus aureus*, including MRSA [9, 10], and the MBEC of gentamicin is lower than that of linezolid and vancomycin [9]. Although gentamicin at high blood concentrations is known to be associated with a risk of nephrotoxicity and ototoxicity [17], its concentration can be adjusted easily and safely during treatment by changing the dose of the syringe pump according to the measured blood concentration. The gentamicin concentration in the blood required some adjustment in one of our patients; it was possible to promptly reduce the gentamicin concentration in the blood to an appropriate level by slowing down the rate of gentamicin administration. A study reported that exposure to high concentrations of gentamicin does not inhibit the activity and proliferation of osteoblasts or endothelial cells, which are essential for fracture union [18].

Therefore, we consider that gentamicin is suitable as an antibacterial agent for this treatment and thus selected it as a single protocol for CLAP, regardless of antimicrobial susceptibility. Nevertheless, since the target of CLAP is the local infected lesion, systemic administration of antibacterial agents should be combined with intravenous and oral administration of agents depending on the results of antimicrobial susceptibility. Antibiotic-loaded bone cement has previously been used as an effective method of treating implant-associated infection [19, 20]. In this method, however, local concentrations of the antibiotics rise for the first few hours and sharply decline within the next few days. Although the local concentration is several times higher than the MIC for about one month after bone cement placement [21, 22], this is far below the MBEC required to inhibit biofilm formation. Some authors have reported that the slow release of antibiotics from bone cements could cause bacterial biofilm formation on the surface of antibiotic-loaded bone cement [23, 24]. By contrast, CLAP can maintain the required local concentration of the antibiotics by monitoring the concentration in the drainage fluid and adjusting it accordingly. To monitor gentamicin concentrations in the drainage fluid, gentamicin levels were kept high throughout the administration period, suggesting that sufficient local concentrations were maintained during the application of CLAP. As another advantage, CLAP can approach the site of infection from a distance and does not require the placement of artifacts directly into the lesion. Negative-pressure wound therapy with instillation in combination with local infusion is an efficient local perfusion method for agents and has been reported to be effective in controlling infection in cases of posttraumatic osteomyelitis and infections associated with implants [25, 26]. We expect that the combined use of negative-pressure wound therapy and iMAP will be efficient in guiding locally administered antibiotics through the infected lesion and into the drainage tube according to the pressure gradient.

This study had one limitation. During the initiation of this treatment, due to the absence of protocol to measure the concentrations, data about agent concentration were not available for some patients. The current treatment protocol is to measure the concentration in all patients.

Conclusions

We treated FRI with CLAP by iMAP early after osteosynthesis and could eradicate infections while preserving implants in all patients. As a novel drug delivery system, CLAP has the advantage of being able to distribute high concentrations of antibiotics locally, making it a useful option in the treatment of FRI.

Abbreviations

CLAP

Continuous local antibiotic perfusion

FRI

Fracture-related infection

iMAP

Intramedullary antibiotic perfusion

MBEC

Minimum biofilm eradication concentration

MIC

Minimum inhibitory concentrations

MRSA

Methicillin-resistant *Staphylococcus aureus*

MSSA

Methicillin-susceptible *Staphylococcus aureus*

ORIF

Open reduction and internal fixation

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of our hospital. Written informed consent was obtained from all patients whose clinical course or images are presented in this manuscript.

Consent for publication

Patients provided signed informed consent forms regarding the publication of their data and photographs.

Availability of data and materials

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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No funds were received in support of this work.

Authors' contributions

AM and TO were the major contributors to writing the manuscript. HM1, HM2, TF, KO, RK, and TN conceived the study and were involved in the study design and coordination. All authors read and approved the final version of the manuscript. AM is the guarantor of this work and, as such, had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Not applicable.

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Tables

Table 1 Summary of the characteristics of the 10 patients

Case	Sex	Age	Duration of follow-up (year)	Affected bone	Open fracture (Y/N)	Method of osteosynthesis	Any diseases under treatment	Duration between injury and initial internal fixation (day)	Duration between initial surgery and occurrence of deep infection (day)
1	F	76	1.0	Tibia	N	Plate	DM, HT, DL	5	17
2	M	42	3.4	Tibia	Y	Plate	None	9	37
3	M	80	1.7	Tibia	Y	Plate	None	0	14
4	M	72	2.5	Fibula	Y	Plate	DM	27	37
5	M	22	5.0	Tibia	N	Intramedullary nail	Hepatitis C	9	22
6	F	68	3.6	Tibia	N	Plate	CRF	3	34
7	M	66	2.9	Tibia	N	Plate	DM	4	63
8	M	73	1.9	Tibia	N	Plate	None	8	40
9	M	26	1.0	Humerus	N	Intramedullary nail	Epilepsy	3	22
10	M	75	1.7	Tibia	N	Intramedullary nail	None	7	18

DM diabetes mellitus, *HT* hypertension, *DL* dyslipidemia, *CRF* chronic renal failure

Table 2 Summary of antimicrobial agents used in the 10 cases

Case	Pathogenic bacterium	Antimicrobial agents					
		iMAP	Administration period (day)	Transvenous	Administration period (week)	Oral	Administration period (month)
1	MSSA	GM	17	SBTPC	6	SBTPC	2
2	Unknown	ASTM	13	-	-	-	-
3	Unknown	ASTM → GM	14	SBTPC → CEZ	2	SBTPC	7
4	MRSA	ABK	12	CEZ → VCM	8	LVFX	8
5	MSSA	GM	27	SBTPC → FMOX	6	LVFX	2
6	MSSA	GM	22	SBTPC → TEIC → CEZ → IPM/CS	6	LVFX	2
7	MSSA	ASTM	28	SBTPC → CEZ	6	LVFX	1
8	MSSA	GM	13	SBTPC	6	CCL	1.5
9	MRSA	GM	17	VCM → TEIC	4	CFDN	3
10	MSSA	GM	8	SBTPC	2	SBTPC → CFPN- PI	7

iMAP intramedullary antibiotic perfusion, *MSSA* methicillin-susceptible *Staphylococcus aureus*, *MRSA* methicillin-resistant *Staphylococcus aureus*, *GM* gentamicin sulfate, *ASTM* astromicin, *ABK* arbekacin sulfate, *SBTPC* sultamicillin tosilate hydrate, *CEZ* cefazolin sodium, *VCM* vancomycin hydrochloride, *FMOX*, flomoxef sodium, *TEIC* teicoplanin, *IPM/CS* imipenem/cilastatin sodium, *LVFX* levofloxacin hydrate, *CCL* cefaclor, *CFDN* cefdinir, *CFPN-PI* cefcapene pivoxil hydrochloride hydrate

Figures

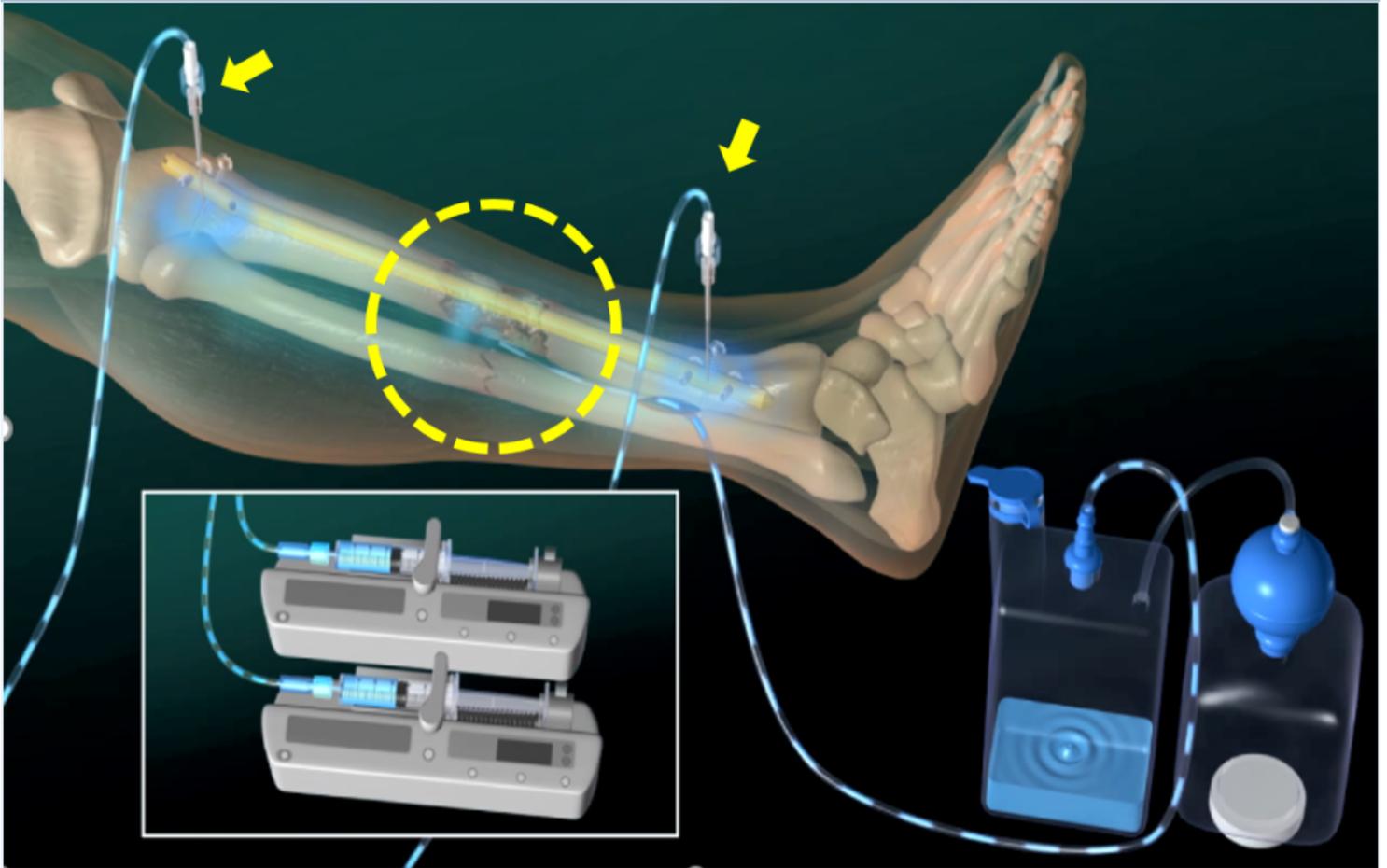


Figure 1

Intramedullary antibiotic perfusion (iMAP). Two bone marrow needles (yellow arrows) were inserted proximal and distal to the fracture site in the bone, and a small amount of highly concentrated antibacterial agent was continuously infused using a syringe pump. The leachate was drained from a drainage tube placed subcutaneously. The construction of a local perfusion pathway for antibiotics allows for the sustained circulation of high concentrations of antibiotics throughout the infected lesion (yellow-dotted circle)

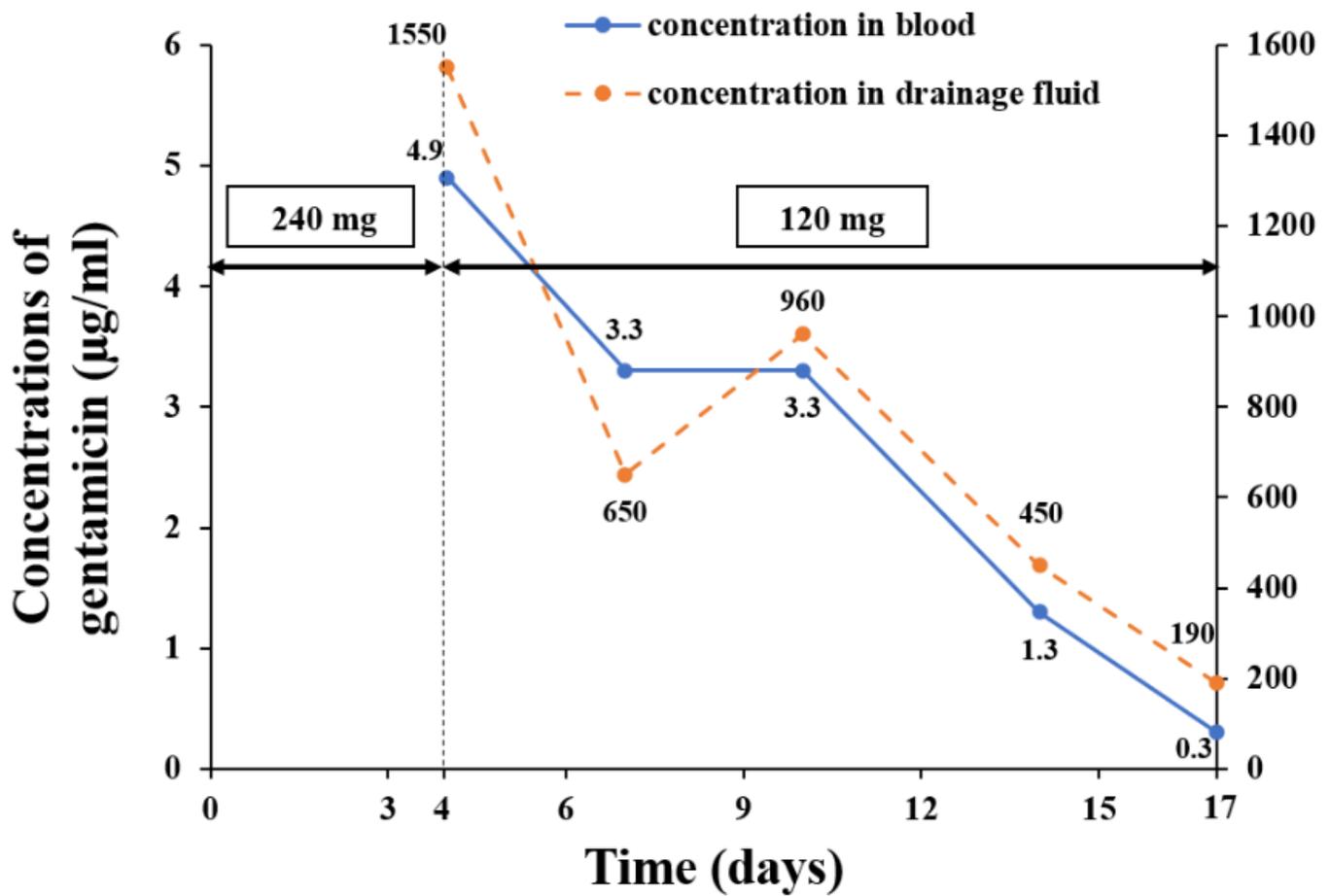


Figure 2

Transition in gentamicin concentration in patient 7. The straight line shows the concentration in the blood, and the dotted line shows the concentration in the drainage fluid. Daily doses of gentamicin through iMAP are shown in frames. We started the administration of gentamicin at 240 mg/day through iMAP; however, as the blood concentration of the agent on the 4th day was very high (4.9 µg/mL), we changed the administration dose to 120 mg/day. Consequently, the gentamicin concentration in the blood promptly declined. By contrast, the concentration in the drainage fluid remained high, suggesting that a sufficient concentration was maintained locally.



Figure 3

Clinical images of patient 1. (a) Anterior-posterior and lateral radiographs taken immediately upon the patient's arrival at our hospital. (b) Anterior-posterior and lateral radiographs of the left tibia and fibula just after osteosynthesis with locking plates. (c) Photograph of the left lower leg at the onset of deep infection; purulent discharge was observed from the surgical wound (red circle). (d) Photograph of the left lower leg just after the insertion of bone marrow needles. (e) Anterior-posterior and lateral radiographs of the left lower leg while undergoing treatment with iMAP. (f) Anterior-posterior and lateral radiographs at 1 year after the injury; fracture union was achieved.

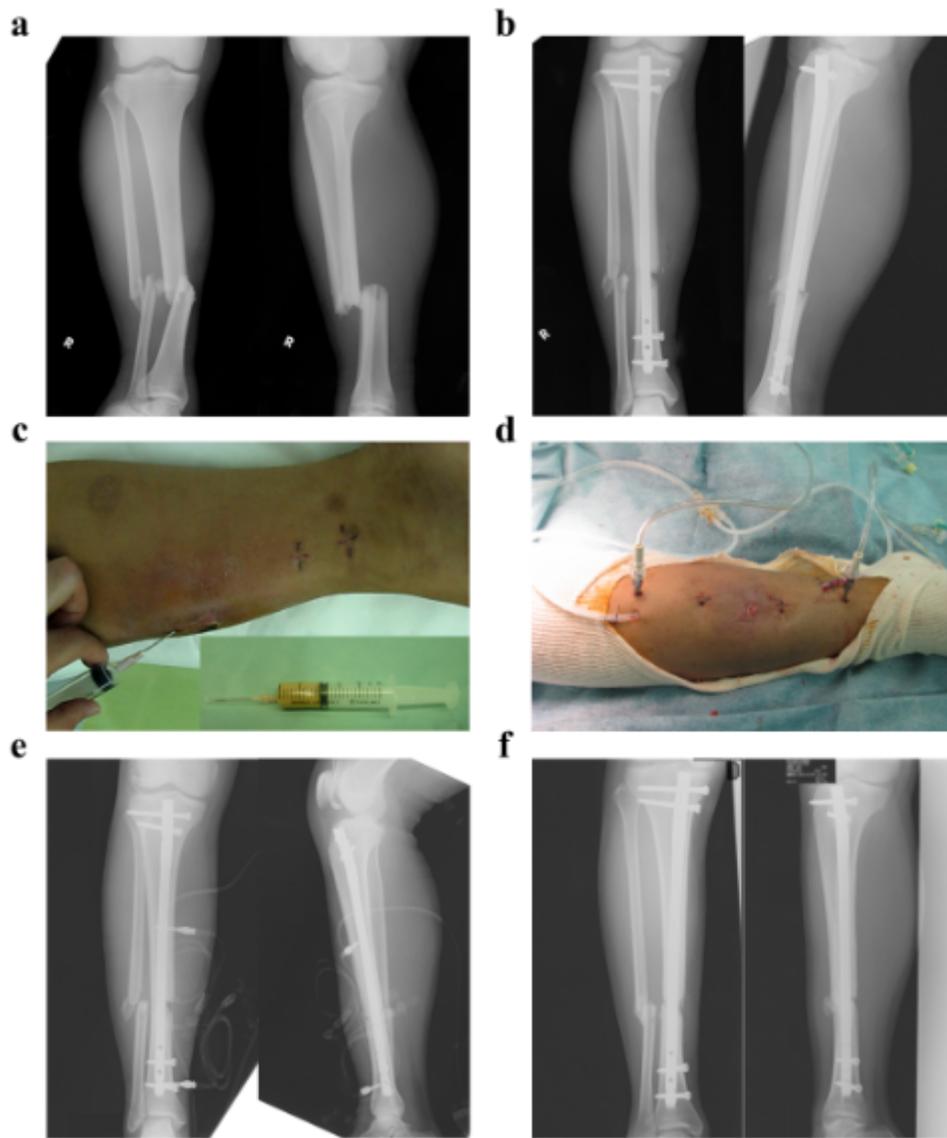


Figure 4

Clinical images of patient 5. (a) Anterior-posterior and lateral radiographs taken immediately upon the patient's arrival at our hospital. (b) Anterior-posterior and lateral radiographs of the left tibia just after osteosynthesis with an intramedullary nail. (c) Photograph of the left lower leg at the onset of deep infection; localized swelling with a feeling of heat was noted, and purulent discharge was obtained by puncture. (d) Photograph of the left lower leg just after the insertion of bone marrow needles. (e) Anterior-posterior and lateral radiographs of the left lower leg while undergoing treatment with iMAP. (f) Anterior-posterior and lateral radiographs at 1 year after the injury; fracture union was achieved.