Successful Treatment of Intractable Facial Osteomyelitis with Autologous PRP and Gentamicin

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Abstract

**Background:** Osteomyelitis is one of the most challenging medical conditions as failure of antibiotics is common and surgical removal remains the only option. In facial osteomyelitis, alternative successful treatment strategies are important as excessive surgery leads to mutilation. This study presents local application of platelet rich plasma in combination with gentamicin as a treatment regimen for patients with intractable facial osteomyelitis.

**Methods:** Three patients with chronic osteomyelitis previously treated with surgical debridement, antibiotics and hyperbaric oxygen therapy without success received individual treatment with autologous activated platelet rich plasma with gentamicin addition. Application was performed locally once a week for a total period of 6 weeks.

**Results:** All patients reported a reduction in pain, redness and swelling already after the second treatment. Radiologic control via cone beam computed tomography after the last treatment showed an increase in trabecular and cortical structure, as well as a reduction of periosteal reaction. Furthermore, all patients showed improved soft tissue healing without any scarring. Relapse of disease was not observed 6-12 months after the last treatment.

**Conclusion:** Activated platelet rich plasma in combination with gentamicin is a promising novel approach for the control of difficult to treat facial osteomyelitis.

Introduction

Osteomyelitis is caused by infecting microorganisms leading to inflammation and destruction of the bone [1,2]. It presents one of the most challenging conditions and can be classified as follows: acute, chronic, diabetic related or implant related [3,4]. Depending on the localization, osteomyelitis can develop to a devastating condition. If the craniofacial skeleton is affected, infection may even harm critical neurovascular structures [4]. Typical infection presents within the medullary cavity and extends through the Haversian canals [5]. The most common route of infection is transdermal invasion and migration of pathogens through the subdermal soft tissue into the bone [6]. The majority of the cases occur after trauma. However, with a rising number of transdermal implants, the number of iatrogenic infections also grows. For example, osteomyelitis can develop as a threatening condition after anchor fixation for nasal epithesis in tumour patients [7].

The low rates of self-healing and the poor response to systemic antibiotic treatment make this condition difficult to treat [2]. Initially, it threatens the patient’s aesthetic appearance and, if progressive, also threatens his or her life. The underlying pathophysiology is based on the development of a bacterial biofilm on the surface of the implant. The bacteria on these biofilms have a lower replication rate and slower metabolism compared with bacteria in free cellular culture [8]. This results in a reduced effectiveness of intravenous antibiotic therapies [8]. Debridement resulting in the complete removal of infected and devitalized soft tissue and bone and local application of antibiotics often remains the only treatment option [9]. In facial bones, this approach is massively invasive and results in mutilation.

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of appearance severely affecting the daily life of the patient. Antibiotic beads are favoured due to their long-term release of the active compound. Especially for the treatment of osteomyelitis, gentamicin beads are commonly used [9]. However, the need of a second operation for removal is a major drawback of this treatment.

Despite of the radical removal of the affected tissue and the local long-term delivery of antibiotics [10], this measure often fails to cure osteomyelitis. Therefore, diverse alternative treatment options were developed to give hope to these patients. Among these, biological therapies combining the antibiotic therapy with stimulation of wound healing as well as osteoblastic activity via growth factors presents one promising approach. Platelet rich plasma (PRP) can be obtained from peripheral blood via centrifugation, and contains a high amount of platelets as well as a plethora of bioactive factors important for wound healing and tissue repair [11,12]. Autologous PRP has been used for several decades in Orthopaedics. Negative side effects such as induction of cancer have not been observed hitherto [11,13-15]. However, the clinical effect of PRP in osteolytic diseases has been discussed controversially and contradictory results have been obtained in animal as well as in human studies [13,16,17].

The purpose of this case study was to determine the clinical effectiveness of a combined application of autologous PRP and gentamicin to patients with intractable, facial chronic osteomyelitis.

**Study Design**

Three patients with chronic osteomyelitis of the nasal root have been treated. All patients had been previously treated with surgery and local as well as systemic antibiotic therapy without any benefit. The treatment with PRP in combination with gentamicin was approved by the institutional ethical committee. Written consent was obtained from each patient and they were informed about the possibility of side effects (e.g., (re)-activation of cancer, progression of disease and treatment failure).

**Patient 1**

Patient 1 is a 53 year old female and was successfully treated for a T4 squamous cell carcinoma of the nasal sinus that was initially diagnosed in 2007. For cancer treatment, complete removal of the soft tissue of the nose as well as of the nasal cartilages and bone (nasal ablation) and functional neck dissection on the left side were performed in the same year. Neither lymph node nor distant metastases were identified. For midface reconstruction, she received magnetic bone-anchored implants for the fixation of a nasal epiphysis. In September 2015, she presented to our emergency ward and complained about redness, swelling and pain in the area around the bone anchor. Cone beam computed tomography (CB-CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) verified the diagnosis of osteonecrosis. Antibiotic therapy, implant removal and resection of the destructed bone were performed. Furthermore excessive debridement of the affected bone with local application of antibiotics has been initiated. Despite these therapeutic measures, progression of osteomyelitis was observed affecting the left sided maxilla (Figure 1 and 2). Thus, a maxillectomy was discussed. However, the patient refused this intervention. She was offered the combined local application of PRP and gentamicin as alternative treatment. The first treatment bout was performed under general anesthesia. In order to achieve the best outcome, a debridement of the necrotic bone and tissue was performed (Figure 3, left picture). Thereafter, peripheral blood was obtained by venous puncture and centrifuged in special tubes (Regentube-BMC, Regenlab, Swiss) at 5000 rpm for 5 minutes. The supernatant (platelet poor plasma, PPP) was used for re-suspension of the mononuclear fraction containing the platelets as recommended by the manufacturer. The resulting supernatant (platelet rich plasma, PRP) was collected in one part of a double syringe. The other part was filled with calcium gluconate at an overall volume concentration of 30% and 135.6 mg gentamicin sulfate (corresponding to 80mg active gentamicin). The use of the double syringe enables the simultaneous instillation of this dilution with the PRP. Calcium gluconate induces thrombin activation and activates the platelets. Upon activation, platelets release the factors stored in the alpha, dense and lysosomal granules. Thus, a gelatinous matrix containing gentamicin and the factors stored in the platelets is created directly after instillation within the infection area (Figure 3, right picture). The following treatments included repeated transdermal application of PRP, calcium gluconate and gentamycin application once weekly without debridement for 7 times. To document the grade of the osteomyelitis, MRI and CB-CT were performed after 3 and 6 months.

**Patient 2**

A 42 year old female patient presented in our clinic in January 2016 with a chronic destructive infection of the radix of the nose. She showed swelling and redness of the radix. The affected area was very tender on palpation. The diagnosis of chronic osteomyelitis was obtained 4 years ago at another clinic. There was no history of trauma or foreign body implantation. Skin or immune diseases were ruled out. Therefore, the origin of the osteomyelitis remains unclear. Based on this diagnosis, she has been treated in several other centres with intravenous antibiotics as well as with surgical resection of the affected bone and local implantation of antibiotic beads without any success. After further surgical treatment in our clinic and hyperbaric oxygen therapy without any positive effect, we offered her treatment with local PRP and gentamycin.

After ethical approval and written informed consent of the patient, we performed an open rhinoplasty in February 2016 to enable the complete debridement only of the necrotic bone and fibrous tissue. Subsequently, PRP, calcium gluconate and gentamycin were applied. This application of the PRP/antibiotic mixture was repeated every second week as described for Patient 1. The patients received a total of 5 local PRP/antibiotic treatments. The effectiveness of this procedure was documented via CB-CT 3 and 6 months after the first treatment.
Figure 1: Cone beam CT scan of a patient with chronic osteomyelitis before treatment with PRP
Cone beam CT (a) as well as sagittal (b) and coronal (c) MRI scans from Patient 1 with chronic osteomyelitis after ablation of the nose and removal of the magnetic anchor are shown. Degradation of the trabecular bony structure is visible in CBCT (*). In the MRI, there is an increase in signalling in the osteomyelitic bone (*).

Figure 2: PET-CT scan of a patient with chronic osteomyelitis before treatment with PRP
The PET-CT shows an over-accumulation of positrons within the affected bone, demonstrating the expansion of osteomyelitis. Within this picture, the patient still wears her anchor bodies and nasal prosthesis.
Patient 3

A 78 year old female patient presented in our clinic with the history of multiple sinus operations due to progressive granuloma development. As pathophysiological aetiology, a Wegener’s granulomatosis was evaluated. Not only invasion in the sinuses but also in the orbit developed over time. As a consequence of massive granuloma invasion in the orbit, enucleation of the eyeball and orbital soft parts was performed alio loco. In the following, osteomyelitis of the orbit and frontal sinus occurred. Treatment was performed via surgical removal of the affected bone with antibiotic treatment. This therapy has not achieved the intended results and the patient was referred to our clinic. She was offered treatment with PRP. After ethical approval and written informed consent of the patient, we performed an open frontal sinus surgery in August 2016 for debridement of the necrotic bone in order to maintain facial structures. Subsequently, a mixture of PRP, calcium gluconate and gentamicin were applied intraoperatively. This application of the PRP/antibiotic mixture was repeated every second week as described for Patient 1. The patient received a total of 5 local PRP/antibiotic treatments. The effectiveness of this procedure was documented via CB-CT 3 and 6 months after the first treatment.

Results

The histopathological analysis of the removed tissue revealed achronical osteomyelitis with active portions in Patient 1 and 3. In Patient 2, a chronic osteomyelitis with active segments was found in addition to a rare accumulation of fibrotic and myotic tissue. Genetic analysis showed an increase in the gamma chain of the T-cell receptor. This correlates to a polyclonal lymphocyte proliferation without evidence of monoclonal proliferations. These findings supported the diagnosis of a benign inflammatory myofibroblastic tumour in addition to chronic osteomyelitis.

Directly after treatment, none of the patients complained about pain, sensory discomfort or reduced olfactory functioning. After one week, both patients noted slight discomfort. They described it as a pressure, comparable to light pain sensation. However, none of the patients needed any pain medication and the discomfort disappeared. After around 1 month, both patients noticed a reduction of skin sensitivity and an overall increase in well-being. The skin showed no scars due to the injection procedure. The redness of the skin was reduced with each treatment. There was no sign of subdermal scarring or unintended osteoblastic proliferation.

All patients received CB-CT scans to determine a possible progression of osteomyelitis. None of the treated patients showed a progression due to radiological aspects. All patients showed regular trabecular structure of the bone with reorganization of cortical bone.

Patient 1 presented with a dehiscence at the dental region 22 approximately two weeks after initial treatment. It has to be mentioned that she continues wearing her nasal epithesis by gluing it to the skin, since she wanted to remain presentable despite ablation of the nose. The dehiscence might therefore be the result of continuous local irritation due to the epithesis. Primary closure of the wound was not possible due to missing tissue and increased tension of the wound margins. The dehiscence was therefore treated with local application of the gelantine solution (PRP, calcium gluconate and gentamicin). Within one week, the dehiscence was covered with intact mucosal epithelium and the procedure was continued until complete regeneration of the tissue. After 7 treatments with platelet rich plasma and gentamycin, the trabecular structure of the maxilla reorganised. There is no sign of further osteomyelitis in the performed CB-CT (Figure 4).

Patients 2 and 3 developed after 5 treatments an even skin surface without redness, scarring or humps despite being prone to developing excessive scarring and hypertrophic osteoblastic reaction. They confirmed the perception of the
first patient, describing a mild pressure of the bone within the first three treatments. In addition, a general increase of wellbeing was noticed by the patients with reduced fatigue and reduced hot flashes in the affected area. CB-CT confirmed the local results and showed a regression of the osteomyelitis without any signs of inflammatory myofibroblastic tumor in patient 2. In addition, a reorganisation of vivid bone was demonstrated.

Patient 3 furthermore showed a soft tissue closure of an over years existing fistula of the orbit to the sinus. Within the orbit, vascularized mucosa developed with an overall reduction of signs of infection.

**Discussion**

This is the first study to report successful treatment of osteomyelitis of the facial area with regeneration of destructed bone architecture and soft tissue using PRP and gentamicin. This treatment led to improvement of chronic osteomyelitis in cases in which conventional treatment failed. The procedure was well tolerated and can be also performed in an ambulant setting. Taking the growing pressure on economics in human health care in consideration, this therapy reveals an effective but low cost procedure for the treatment of patients with osteomyelitis. As autologous material is used, there are no risks of rejection.

Platelet rich plasma contains several growth factors like platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), transforming growth factor β (TGFβ), vascular endothelial growth factor (VEGF) and endothelial growth factor (EGF) [11,12,18].

Depending on the environment, these growth factors can also induce stem cell proliferation as well as chondrogenic and osteoblastic differentiation [19].

Platelet-derived growth factor and TGF-β support chondrocyte proliferation, proteoglycan synthesis, as well as generation of type-1 collagen [18]. Type-1 collagen is essential for elastic properties and guarantees the formation of tensile strength cartilage [20].

Reorganization of the trabecular structure of the maxilla was demonstrated after treatment in the first patient and may be accounted to the growth factors listed above. The osteogenesis observed after local application of PRP may be a synergistic effect of growth factors, cytokines and progenitor cells that are present in PRP. Progenitor cells are located mainly in the bone marrow and, to a lesser degree, also in the peripheral blood. By preparing PRP, the low proportions of progenitor cells that are present in the mononuclear fraction were also injected into the affected area. The excellent blood supply of the nose may aid in the homing of endogenous mesenchymal and hematopoietic progenitor cells to the area of damage. Wen et al. demonstrated recently that PRP induces the expression of genes such as ALP, OPN, RUNX2 and COL-1 that are regulating osteoblastic differentiation [21]. Thus, we assume that the reorganisation of the trabecular structures in this patient might be the result of osteogenic induction in resident cells or in cells transplanted with the PRP. An osteoinductive effect of PRP has been shown also in periodontal trabecular defects [22]. Wang et al. showed a successful treatment of a patient with chronic osteomyelitis of the foot [23]. They proposed that the PRP stimulates cell proliferation and enhances soft-tissue repair, vessel reformation and collagen synthesis, which is usually down-regulated in chronic wounds [23]. The observation in the two cases presented herein corroborates the results of Wang et al. Even the soft tissue defect recovered quickly after treatment with PRP and scar less healing was observed without excessive fibrous tissue formation. This may be due to the immunological abilities of PRP [11,12,18].

A significant amount of leukocytes that are able to combat infection are present in PRP [11,24,25]. The main components of PRP, however, are platelets.

Thus, they are composed of a cell membrane and contain the cytoplasm of megakaryocytes filled with granules, mitochondria and mRNA [26]. Although they lack genomic DNA and were usually not classified as cells, recent evidence accumulates to the notion of platelets as metabolically active cells [25]. They express receptors connected to a functional signalosome, contain several transcription factors and release several soluble factors [25,26]. Since they are involved in different processes such as autocrine and paracrine stimulation, pathogen recognition, lymphocyte modulation and endothelial activation, it has been recently proposed to acknowledge platelets as immune cells [25,26].
In addition to the osteomyelitis in the second case, a rare presentation of myofibroblastic proliferation led to uncontrolled growth of fibrotic tissue with degeneration of the surrounding cartilage and bone through pressure and reduced blood perfusion. This condition mainly occurs in the lung and affects especially children and young adults. It is discussed if the nasal occurrence can be described as a mucosal variation of the facial granuloma [27]. Their aetiology still remains unclear since their first description in 1937 [28]. Pain sensation due to the chronic infection was effectively reduced by the use of PRP in the treated patients and this effect has been observed previously by other groups [9,29]. The exact mechanism of pain reduction by PRP is not known. It may be associated with the neuroprotective growth factors that may aid to lessen missense in the wound area. A neuroprotective effect of PRP has been demonstrated recently after traumatic peripheral nerve injury [30]. Neuroprotection is desirable especially in the nose for the preservation of nerve fibres responsible for olfaction, nasal cleaning, foreign body reaction and chemical alert for toxic substances [31-33]. However, application of recombinant growth factors is challenging due to their difficult pharmacokinetics and a low half-life time. Thus, the use of PRP is recommended for the provision of a variety of endogenous growth factors as an alternative to the application of recombinant growth factors. In order to warrant a high amount of growth factors, a fresh blood sample for the isolation of PRP is required for each treatment. In the herein presented case study, both patients reported suppression of pain with steady sensibility in the affected area.

Gentamicin is a known ototoxic substance. However, local treatment seems not to result in blood concentrations that are critical for inducing damage to the hair cells resulting in hearing impairment. This assumption is in consistence with observation of patients treated locally with gentamicin beads without the development of any hearing loss [8]. However, hearing tests during the treatment period were performed regularly showing unchanged hearing in the two patients. Therefore this treatment can be considered safe in terms of a putative ototoxicity.

Success of treatment was judged based on patient evaluation and radiologic control. For the latter, magnetic resonance imaging (MRI) [2], computed tomography (CT) or cone beam CT were used [34-36]. Typical signs for osteomyelitis are osteolytic areas in sclerotic zones, loss of trabecular pattern, cortical degradation and periosteal reaction [34]. As the second patient presented with an additional inflammatory myofibroblastic tumor, the diagnosis was very difficult and mainly based on histopathology. However, typical signs such as solid masses with unclear margins and lobulated shapes, hypointense or slightly hyperintense T2 signals, as well as strong enhancement in the contrast-enhanced images can be seen in MRI [37] and cone beam CT or standard CT scan [38,39].

As cone beam CT is more convenient for the patients and allows a better resolution for osteomyelitis [34], we prefer cone beam CT over MRI. Biopsies are considered the gold standard of osteomyelitis detection [40,41]; however, they are much more invasive and bear the risk of reoccurring infection.

The experience with PRP is wide [11,14,15,17,23,41] and no tumour formation has been shown yet [42-43]. Although it may be suitable to treat also patients with malignancies in their medical history, this treatment should be limited to severe cases of osteomyelitis with imminent danger of loss of their midface or other vital structures. In order to judge the residual risk of accelerated recurrence of malignancy, further investigations with long-term follow up are necessary. In addition, exact definition of outcome measures is important in order to judge the success of the treatment.

**Conclusion**

Platelet rich plasma (PRP) is widely used and showed great sufficiency and safety. Using autologous PRP with gentamicin as a local therapy showed great benefits in the treatment of osteomyelitis in our patients. PRP appears to be an easy to use and cost effective treatment for patients with osteomyelitis after insufficient surgical and antibiotic treatment.

**Ethics approval**

This study has been approved by local ethic board as compassionate treatment. A study number is therefore not required. All patients gave their informed consent for treatment and publication of data in verbal and written form.

**Consent for publication**

All patients gave their informed consent for this treatment as well as for publication of the data including individual details and images.

**References**


