Biomaterials in infection treatment

Summary

In this thesis we explore different aspects of the treatment of infection in the field of orthopaedic surgery. In order to improve treatment options and outcome of this difficult problem, a novel biomaterial sparked our interest as it has to potential to combat infection in a very specific way that is not related to the classic antibiotic approach : bioactive glass S53P4 (BonAlive®, BonAlive Biomaterials Ltd, Turku, Finland). This is of much importance nowadays since we are facing ever more problems with antimicrobial resistance (AMR). Apart from the antibacterial mechanism, bioactive glass has several other properties that render it very attractive for bone void filling in comparison to other available biomaterials. The introduction of bioactive glass S53P4 in our department for the treatment of chronic bone infection led to the different studies incorporated in this thesis.

In ***Chapter 2*** we describe indications and contra-indications of the use of different biomaterials in infections. Several concepts like the race for the surface, biofilm formation, the need for bony reconstruction after debridement and local application of antibiotics are explained for understanding the challenges involved in treatment of bone infection. In the second part of the chapter , we performed a systematic review of the literature on several commonly used biomaterials in the field of bone infections, namely Osteoset-T®, Perossal®, Herafill® beads, Stimulan®, Cerament-G® and BonAlive® bioactive glass. Although results of the included studies (15 in total) imply that treatment of osteomyelitis with antibacterial bone graft substitutes could be a good option, available evidence on any of these biomaterials is not sufficiently robust to determine the effectiveness of antibiotic drug delivery (BonAlive® excluded as it does not act as an antibiotic carrier). Major limitations of the available literature are low levels of evidence and poor quality. We therefore advocate more research of high methodological quality.

In ***Chapter 3*** we presented the results of the first 15 consecutive patients operated for chronic osteomyelitis with bioactive glass S53P4. This was also the first series described in the Netherlands. Infection was eradicated in all patients with a mean follow-up of 21,6 months. The favourable results led to the change in our institutional protocol from a two stage treatment to a one stage treatment for chronic osteomyelitis. Our results were also part of a multinational study, initiated by Nina Lindfors from the Helsinki University Central Hospital, who has been involved in the implementation of bioactive glass for the treatment of bone infection from the very beginning. 116 patients from eleven dedicated infection centres around Europe were included with a minimum follow-up of one year. Despite slightly different treatment protocols in each of these centres, the cure rate was 104/116, which resulted in a total success rate of 90%, concluding that S53P4 can be used as bone substitute without local antibiotics in the

treatment of chronic osteomyelitis with excellent results. Interestingly, this study also showed that bioactive glass used in a one stage setting significantly outperforms the use in a two stage setting.

As there was limited data available on the biomechanical properties of bioactive glass S53P4, we conducted an in vitro study at the TU/e in order to assess the applicability of bioactive glass in load-bearing defects. These results are presented in ***Chapter 4*** and compare stand-alone bioactive glass granule layers with morcelized cancellous bone allograft and different volume mixtures of both under clinically relevant conditions. Both BAG granules and allograft morsels as stand-alone materials exhibit suboptimal mechanical behaviour for load-bearing purpose. BAG granules are difficult to handle and less porous, whereas allograft subsides and creeps. A 1:1 volume mixture of BAG and allograft is therefore proposed as the best graft material in load-bearing defects.

Being a very capable and promising biomaterial for void filling in infected bone, bioactive glass S53P4 is also still expensive (890€ per 10cc). This raised the question of the bioactive glass being cost-effective as this is a growing concern in contemporary settings of budget cuts and financial strain on the healthcare system in general. In ***Chapter 5***, total cost of treatment of chronic osteomyelitis with bioactive glass S53P4 in a one-stage protocol (n=17 patients) was compared to our historical institutional protocol of two-stage treatment with PMMA beads (n=25 patients). Also, a cost-effectiveness analysis was performed together with the evaluation of clinical outcome. This study showed for the first time that one-stage treatment of chronic osteomyelitis with bioactive glass S53P4 is cost-effective (lower total cost, in combination with better clinical outcome).

Because the burden of chronic osteomyelitis is much higher in low and middle income countries and our institutional connection to the St. John of God Hospital in Ghana, we wanted to identify the standard of care of chronic osteomyelitis in these circumstances. This was the preliminary step in order to try and introduce contemporary treatment options like bioactive glass to less supported heath care systems in order to eventually improve treatment outcomes. ***Chapter 6*** reports the systematic review of available literature on treatment of chronic osteomyelitis in low and middle income countries. Nine studies were included and qualitatively analysed, involving 1173 patients from Africa and Asia. No better judgement than moderate risk of selection bias could be made due to the study designs. The evidence is not sufficiently robust to identify the most effective treatment, or to even allow a recommendation of the best suitable treatment of chronic osteomyelitis in low-income countries.

Finally, in ***Chapter 7***, we report the implementation of a one-stage treatment protocol for chronic osteomyelitis with the use of bioactive glass S53P4 in a rural hospital in

Ghana. 18 patients were enrolled (8 type III CM, 10 type IV) and treated in a one-stage procedure with radical debridement and dead space management using bioactive glass S53P4 granules together with adjuvant antibiotic therapy. Specific challenges were encountered and commented on, notably the necessity for adequate imaging, as inferior imaging can compromise the identification of sequestrae, thereby increasing the risk of recurrence. Also, severity of the osteomyelitis and average size of the bony defect are significantly higher than what is commonly encountered in developed countries. Thirdly, the lack of access to microbiologic diagnosis prevents adequate antibiotic treatment and thus outcome. Finally, follow-up is cumbersome and often lacking, resulting in suboptimal postoperative treatment. In conclusion, due to specific challenges treating chronic osteomyelitis in low and middle income countries, contemporary treatment options cannot be “copy-pasted” with the same results in these settings, however, we are convinced that over time treatment of chronic osteomyelitis in low and middle income countries can be significantly improved.