Injury, Int. J. Care Injured 44 (2013) S1, S1–S2

Contents lists available at SciVerse ScienceDirect

Injury

journal homepage: www.elsevier.com/locate/injury

EDITORIAL

Bone regeneration strategies: Current trends but what the future holds?

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Bone tissue constitutes one of the most important units of the loco-motor system. For many years it has been in the center of intense clinical and research activity within the musculoskeletal discipline. However, despite its property to heal without scar formation, its regenerative capacity remains limited. There have been sporadic reports in the literature of spontaneous healing of large bone defects but this phenomenon has been a rare occasion and scientists suggested as a possible explanation a genetic prothiathesis in addition to some local co-factors such as the presence of a remnant periosteum sleeve.[1]

It has been shown that for small bone defects where adequate soft-tissue coverage is present, the bone gap can be treated with conventional cancellous autologous bone grafting or bone substitutes.[2–9] For defects however of more than 5 cm any grafting technique is predisposed to failure, and the necessity for more advanced and specialised treatment is crucial.[10]

With the advances made in miscovascular techniques, vascularized bone grafting became a good option, and in this context fibula has been used to provide restoration of bone defects of up to 25 cm with marginal donor site morbidity.[11] Other donor sites of vascularized bone grafts include the iliac crest and the ribs. This treatment modality however requires special skills and medical comorbidities along with advanced patient age are considered as limitations.

In the middle of 19th century Professor Ilizarov introduced the concept of distraction osteogenesis for the treatment of bone defects. This technique represents the de novo production of bone between divided bone surfaces (corticotomy) undergoing gradual distraction.[12] Treatment involves 3 phases: latency, distraction, and consolidation. The latency period usually lasts up to 7 days and represents the time from osteotomy until distraction begins. During the distraction period, distraction is applied by 1 mm per day at a rhythm of 0.25 mm four times a day. Finally, during the consolidation phase (longest), the newly formed tissue is allowed to bridge and corticalize.

While both the vascularised bone grafting and distraction osteogenesis are considered today as gold standards with good outcomes, other novel techniques have been emerging. Intramedullary lengthening devices utilising the concept of distraction osteogenesis have been used with satisfactory outcomes and very few complications. The availability of osteoinductive substances, such as bone morphogenetic proteins (BMPs) has opened new avenues in the treatment of impaired fracture healing.[13–16] However, the exact volume of bone that can be produced locally by the induction properties of the active substance remains unknown. Based on the available clinical evidence and personal experience, one vial of BMP is thought to promote bone healing in defects of up to 2 cm.

Cellular therapies in the form of implantation of concentrated osteoprogenitor cells (mesenchymal stem cells (MSCs)) harvested by bone marrow aspiration from the pelvis has lately emerged as another strategy. Nonetheless, the clinical experience gathered thus far is related to long bone non-unions rather than the treatment of large bone defects.[17–19]

Bioactive membranes have also appeared as another attractive option guiding bone regeneration with or without the additional implantation of bone graft or osteoinductive agents. However, most of the available evidence is based on experimental studies and the current clinical evidence is sparse.[20] Lately, the “induced membrane technique” has been also popularized for the treatment of large bone defects but such a strategy requires 2 procedures.[21] During the second procedure (removal of the cement spacer after the membrane has been formed), simultaneous grafting of the defect with allograft or autograft or combination of both is needed.

The use of scaffolds loaded with osteoprogenitors cells and/or growth factors has also gained a lot of interest.[22,23] The type of material to be implanted, its porosity, chemical affinity, orientation of fibers, size of the fibers (nanostructure) the type of cells loaded (differentiated or undifferentiated), and the addition of a growth factor amongst others are some of the issues of ongoing debate for optimization of such a strategy. Most of the available evidence has derived from experimental trials and such an approach in the clinical setting for the treatment of bone defects is still at its infancy.

Most recently, the “diamond concept” for the treatment of bone defects has gained great popularity.[24] The diamond concept represents the desirable tissue engineering strategy where all the important constituents of bone repair are implanted during surgical treatment (a growth factor, a scaffold, osteoprogenitor cells) while special attention is given to a successful osteosynthesis, in other words, optimization of the mechanical environment. This

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approach appears very attractive and preliminary clinical data indicate favorable outcomes.

So what does the future hold for the treatment of clinical conditions where bone regeneration is desirable? What should we expect in the treatment of critical size bone defects?

Definitely, distraction osteogenesis will continue to be a reliable option despite the length of time required and its associated technical hitches. The option of vascularised bone grafting despite the induced morbidity at the harvesting site of the graft will also remain another worthy option. Joint replacement will continue to be a good choice particularly in elderly patients and in patients who have suffered bone loss secondary to tumor excision.

Tissue engineering approaches however, will dominate the research portfolio of scientists and clinicians.[25] The conceptual framework of the diamond concept will be applied under different combinations of materials, different doses and innovative techniques. Moreover, the concept of "biological chamber" and of local "bioreactor" representing a well-defined, regulated, molecular environment promoting bone regeneration in a timely fashion will be further developed and tested.[26]

Simultaneous administration of systemic pharmacological agents of anabolic properties with the implantation of local factors would be another avenue to be explored.[27] Overall, combination therapies in the form of polytherapy certainly will dominate the activities of the clinical and scientific community.[28,29]

Certainly, a breakthrough can be envisaged to allow us to treat bone loss and non-union in a more efficient, reliable and hopefully accelerated manner.

Conflict of interest

The authors declare no conflict of interest.

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