Delayed and non-union fractures in small animals...

FOR any given fracture the normal time to healing will vary according to the breed, age, general health, the bone involved, severity of the fracture (especially comminuted fractures), soft tissue damage and type of fixation.

Delayed union can be diagnosed when no or minimal union of the bone is observed in what would be considered a “normal” healing time. “Normal” relates to that of a similar fracture, in the same bone of a patient of similar breed, age and general health, which has been repaired in the same way, and heals without complication.

The causes of delayed union are typically one or more of: inadequate immobilisation, distraction, excessive compression, impaired blood supply, infection, excessive implant quantifies or excessive fracture gap.

Fracture gap may be the prime cause of delayed union because it often leads to other causes such as excessive motion at the site. This may cause soft tissue disruption, affecting vascular supply and ultimately callus formation.

With internal fixation, external fixation and external coaptation, adequate stability is the key to the progress of healing.

Cast immobilisation allows relatively large amounts of movement between fracture ends during the progression through haematoma, fibrin clot, cartilage and finally bone. Each stage will tolerate varying degrees of movement within the limits of each tissue.

This tolerance varies over time and is susceptible to slight changes in treatment such as modification of casts or splints. This means re-examination and regular radiographic assessment is required as it may be necessary to modify support depending on whether the delay in healing is temporary or evolves into non-union.

Following internal fixation, bone ends are fixed relative to each other and the gap between them is maintained. This may delay healing as lack of stimulation may prevent effective ingrowth of granulation tissue.

Non-union fracture

The difference between delayed and non-union is difficult to interpret. The standard definition of non-union fracture is the cessation of all reparative processes of healing without bony union.

Diagnosis of non-union is both subjective and dependent on a range of factors. There may be extrenity non-use which may lead to muscle atrophy, stiffness, reduced range of motion in joints and malignment of the bone.

If fixation is too stiff the patient may bear weight comfortably, effectively “walking on implants”. This can be seen particularly in the radius and ulna of small dogs, where osteoporosis and resorption of bone can occur when there is extended immobilisation with no weight bearing or internal fixation is too rigid. These changes can be difficult to reverse without further intervention, and can result in implant fatigue and failure before healing.

Radiographically, a radiolucent line will remain at the fracture site. The medullary cavity may be sealed with sclerosis at the edge of the bone and resorption of bone or osteoporosis may be present. The fracture fragments may have rounded ends or a hypertrrophic “elephant’s foot” callus may be present.

Once non-union is diagnosed but before treatment, examination is required to identify the presence of associated pathology such as nerve damage or soft tissue injury, as well as limitations in joint function. Even if bone union itself can be achieved through further intervention, it may be that adequate function cannot be restored due to ongoing problems.

Treatment options

Both surgical and non-surgical techniques may be required. In many cases increasing or decreasing the level of fixation will be required. In some, reduction of external coaptation may be sufficient to promote healing if some stability is present.

If revision surgery is required, open reduction with compression plating to increase stability is common. This may be necessary in cases that have initially been managed conservatively, or to revise previous internal or external fixation.

Depending on alignment of the original reduction, this may be achieved with minimal disturbance. It may be necessary to debride fibrous tissue, or resect fragment ends. This may result in limb shortening. This is particularly true if the original reduction is inadequate. Cancellous bone grafts may be applied in isolation or in conjunction with revised fixation, depending on the scenario.

Other methods to address non-union and delayed healing include shockwave, electrical stimulation and low intensity pulsed ultrasound (LIPUS). The use of extracorporeal shockwave therapy is well-established and has been used to treat non-union of long bone fracture.

Bioelectrical stimulation has been used since the 1950s and invasive, semi-invasive and non-invasive devices exist with specific applications to particular bones.

Non-invasive LIPUS is a relatively new therapy in the veterinary world but well-established in the treatment of humans where it has a large clinical evidence base including guidance from NICE supporting use in treating fresh fractures as well as delayed and non-unions.

One of its advantages in delayed or non-union fractures is that it can be used alongside invasive techniques as its effect on healing is not compromised by the presence of wires or other fixations.

Recent reviews from a wide range of human and animal studies concluded that LIPUS accelerated the healing of fresh fractures on average by 38% and had a success rate in delayed and non-unions of 86%.

Case study

One-year-old Labrador Retriever treated after referral to Mark Morton, Davies Veterinary Specialists, Hertfordshire. Condition: fracture to proximal calcaneus 10 weeks prior to referral which had been conservatively managed with a cast.

Radiographs revealed a non-union with further proximal displacement of the tuber calcanei. Treatment: fibrous tissue was debrided and the proximal fragment stabilised with k-wires and tension band wire. A combination of allogeneic cancellous chips and demineralised bone matrix was applied to promote healing. After six weeks, follow-up radiographs showed no evidence of healing and resorption of the proximal fragment, leaving a large gap and looseness of the k-wire. Due to poor bone quality in the proximal fragment, revision surgery to improve fixation and apply further graft was undesirable. LIPUS (using the Sonivet device) was employed to aid healing. A splinted dressing was also applied whilst daily 20-minute treatments were performed at home for three weeks. A small window was left in the dressing so treatment could be applied.

Outcome: three weeks after treatment, radiographs revealed bone density and quantity had increased significantly enabling the supportive dressing to be removed and exercise levels gradually increased. Normal function was achieved. Radiographs performed following an unrelated spinal fracture four months later showed almost complete healing of the calcaneus.

• The author wishes to thank Mark Morton Davies of Veterinary Specialists (www.vetspecialists.co.uk) for his contribution to this article. More information on the Sonivet device is on www.curar.co.uk.
Stem cells in small animal orthopaedics

IN 1909, Alexander Maximow, a Russian academic, introduced the concept of “multipotent” blood stem cells when he addressed the Berlin Haematologic Society.

Decades later, in 1976, another Russian, Alexander, Friedenstein, was investigating haematopoietic stem cells in mice when he discovered a population of cells harvested from bone marrow that were adherent to culture vessels, mesenchymal (fibroblast-like) and colony forming with high replicative capacity (Friedenstein et al, 1976).

These cells became known as “mesenchymal stem cells” (MSCs). As well as their discovery, Friedenstein is credited with foresight into the clinical application of MSCs, particularly in the field of orthopaedics.

He performed detailed studies with Gabriel Ilizarov, who any budding orthopaedist will recognise as a pioneer of external fixation and limb-lengthening methods. MSCs are currently in clinical veterinary use for fracture management, osteoarthritis (OA) and tendon injury.

The defining characteristics of an MSC are those of self-renewal (the ability to go through numerous cycles of cell division whilst maintaining their undifferentiated state), and of multipotency (the ability to generate progeny of several distinct cell types).

MSCs offer potential as they have the property of multipotency, but with fewer ethical considerations than embryo-derived stem cells. In fact, the scientific and public interest has grown exponentially.

Figure 1 illustrates the number of papers published in each of the last 20 years that show up in a PubMed search for “mesenchymal stem cells”: 60 in 1993; 5,118 in 2013.

A surge in interest also followed the discovery, made in 2002, that MSCs could be derived from adipose tissue (Zuk et al, 2002), the harvest of which is easier and associated with less morbidity than that of bone marrow. The extraction of MSCs from fat and their expansion is now commercially available to vets in the UK via The Veterinary Tissue Bank.

Extraction-only services are also advertised for MSC isolation. These services are quicker as they do not require the expansion of MSCs. However, the extraction process yields a heterogeneous population of cells called the stromal vascular fraction (SVF).

Only an estimated 1 to 10% of the SVF are actually MSCs (Mitchell et al, 2006; Oedayrajsingh-Varma et al, 2006; Zhu et al, 2008).

Bone healing

A canine fracture gap model has been used to demonstrate beneficial effects of autogenous (Bruder et al, 1998) and allogeneic (Arinzeh et al, 2003) MSCs on bone healing.

In 2007 Bajada and colleagues, from the Robert Jones and Agnes Hunt Orthopaedic Hospital in Oswestry, reported the successful management of a tibial fracture in a man that had been refractory to six attempts at surgical management over a nine-year period. Calcium sulphate pellets combined with cultured, autogenous, bone marrow-derived MSCs were implanted.

However, as the expansion (culture) of MSCs takes approximately two weeks, MSCs are unlikely to replace autogenous bone graft, or off-the-shelf osteoinductive products such as deminerallised bone matrix (DBM) or recombinant human bone morphogenic proteins (rhBMP), in the management of routine fractures. They might, however, prove useful in planned revision surgeries of non-unions.

The authors are aware of an unpublished case of autogenous MSCs being used to successfully treat a delayed union in the tibia of a cat.

Osteoarthritis

The therapeutic rationale for MSCs is a shifting paradigm. The original hypothesis was that MSCs, or other stem cells, could be injected or implanted, either systemically or locally, into a patient, and that the cells would find their way to the damaged tissue, differentiate into the needed cell-type, and assist repair.

Indeed, a current trend in cartilage defect treatment is the implantation of stem cells, often on a synthetic scaffold, with the aim of tissue regeneration (Emadedin et al, 2012; Haleem et al, 2010; Kasemkijwattana et al, 2011).

However, it is increasingly recognised that MSCs may have modes of action that are paracrine in nature. That is, they may alter the environment of a diseased tissue or organ, such that reparative processes are augmented.

In a caprine model of OA (involving complete excision of the medial meniscus and resection of the cranial cruciate ligament) a single injection of an expanded population of autogenous bone marrow-derived MSCs resulted in reduced cartilage degradation, osteoarthropathy and sub-chondral sclerosis compared to controls.

Yet, there was no evidence of MSC engraftment in the cartilage of the treated joints, engraftment was only high in the synovium, fat pad and lateral meniscus (Murphy et al, 2003).

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Tendon injury

In equine orthopaedics there is considerable interest in the use of MSCs to treat tendon injury.

In a tendon gap model, using rabbit’s Achilles tendons, MSC treated tendons had better mechanical properties than operated controls (Young et al, 1998). Re-injury rate of National Hunt horses with overstrain injuries of the superficial digital flexor tendon treated with intra-articular MSC injections have been reported as 23.7%, which is significantly lower than those treated by other methods (Grobhm et al, 2011).

Summary

Interest in MSCs is set to continue. In small animal orthopaedics at least, perhaps the most promising application is in the treatment of joint disease.

Anecdotal reports of response to intra-articular injections of MSCs for the management of OA are encouraging. It is anticipated that reports concerning the safety and efficacy of MSCs will be forthcoming in the near future.

References

The full list of references is available on request to editor@veterinary-practice.com.

VetsNorth 2014

PROFESSOR John Innes is, once again, one of the lead speakers at VetsNorth – on orthopaedics. In addition to four lectures, including one on stem cells, he will present a workshop entitled, “What can synovial fluid do for me?” Details are on www.vetsnorth.com.