ROUNDUP360

Research

Platelet-rich plasma – first nail in final coffin or beginning of a trend?

Platelet-rich plasma continues to be discussed widely at meetings around the globe, as well as appearing regularly in a large number of publications. At *360* we feel that the jury is still out on its efficacy, so a meta-analysis from **Hamilton (Canada)** is most welcome. The authors undertook this work in order to determine the efficacy of autologous blood concentrates in decreasing pain and improving healing and function in patients with orthopaedic bone and soft-tissue injuries. They searched MEDLINE and Embase for randomised controlled trials or prospective cohort studies that compared autologous blood concentrates with a control therapy in patients with an orthopaedic injury. They also identified additional studies by searching through the bibliographies of eligible publications as well as the archives of orthopaedic conferences and meetings. They found 23 randomised trials and ten prospective cohort studies although there was a lack of consistency in outcome measures across all studies. In six randomised controlled trials (n = 358) and three prospective cohort studies (n = 88), the authors reported visual analogue scale scores when comparing platelet-rich plasma with a control therapy across injuries to the acromion, rotator cuff, lateral humeral epicondyle, anterior cruciate ligament, patella, tibia, and spine. Looking at all of these studies, the authors concluded that platelet-rich plasma provided no significant benefit up to (and including) 24 months either for the randomised trials or the prospective cohort studies. There was perhaps a small trend in favour of platelet-rich plasma, but the associated wide confidence intervals meant this was likely to be insignificant.[1] The overall conclusion? Here we go again, we think at *360*. There is uncertainty about the evidence to support the increasing clinical use of platelet-rich plasma and autologous blood concentrates as a treatment modality for orthopaedic bone and soft-tissue injuries.

Ageing, bone and mesenchymal stem cells

The ageing process does all manner of horrid things, one of which is to decrease the number of mesenchymal stem cells (MSCs) in bone marrow, which may in turn lead to reduced osteogenesis and bone formation. Both autologous and allogeneic stem cells have been successfully infused for the treatment of degenerative heart and neuronal diseases, or for injury repair. However, systemic infusions of MSCs *in vivo* do not promote an osteogenic response in bone because of the inability of MSCs to home to bone unless they have been genetically modified or are infused after certain conditions, such as injuries. So write authors from **Sacramento (USA)**. However, if MSCs could be directed towards osteogenic differentiation, they could be a viable therapeutic option for bone regeneration. The authors have developed a method to direct MSCs to the bone surface by attaching a synthetic high-affinity and specific peptidomimetic ligand (LLP2A) against integrin $\alpha4\beta1$ on the MSC surface to a bisphosphonate (alendronate, Ale) that has a high affinity for bone. LLP2A-Ale induced MSC migration and osteogenic differentiation *in vitro*. A single intravenous injection of LLP2A-Ale increased trabecular bone formation and bone mass in both xenotransplantation studies and in immunocompetent mice. Additionally, LLP2A-Ale prevented trabecular bone loss after peak bone acquisition was achieved or as a result of oestrogen deficiency. These results provide proof of the principle that LLP2A-Ale can direct MSCs to the bone to form new bone and increase bone strength.[2] It is clear, suggest the authors, and *360* agrees, that it is now time for this concept to be examined in both preclinical and clinical studies for the treatment of osteoporosis and fracture repair.

Cytokines and the herniated intervertebral disc

The herniation of an intervertebral disc can be excruciatingly painful, the associated radicular pain being related to mechanical and chemical factors. However, in both animals and humans, pure compression of a non-inflamed nerve produces sensory and motor changes without pain, whereas pain can be created by manipulation of an inflamed nerve. During the inflammatory process, nociceptive neurones become sensitised and begin to respond to stimuli that were not able to elicit a response previously. This is called hyperalgesia; a process in which cytokines and chemokines are said to be integrally involved. Some interesting work in this field has appeared from **São Paulo (Brazil)** where the authors undertook a rat study for several reasons: 1) to detect in the normal intervertebral disc whether or not there were cytokines known to be involved in the mechanisms of inflammatory hyperalgesia; 2) to see if previous exposure of the disc to specific antibodies might affect the pain behaviour induced by the nucleus pulposus; and 3) to establish the influence of time of contact of the nucleus pulposus with the fifth lumbar dorsal root ganglion in mechanical and thermal hyperalgesia. The cytokines present at highest concentrations in the rat nucleus pulposus were TNF-α, IL-1β and CINC-1. Rats submitted to the disc herniation experimental model, in which a nucleus pulposus from the sacrococcygeal region was deposited over the right fifth lumbar dorsal root ganglion, showed increased mechanical and thermal hyperalgesia that lasted at least seven weeks. When the autologous nucleus pulposus was treated with antibodies against the three cytokines found at highest concentrations within it, there was a decrease in both mechanical and thermal hyperalgesia at different time points, suggesting that each cytokine may be involved in hyperalgesia at different steps in the inflammatory process. The

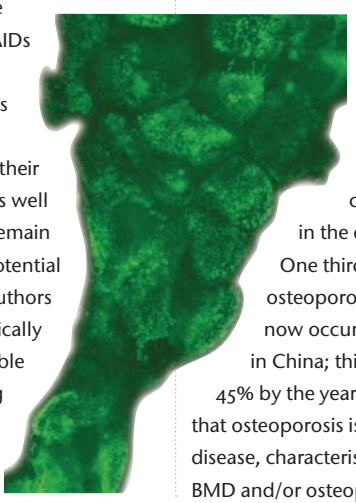
experimental model comprised the surgical removal of the coccygeal intervertebral disc, followed by its implantation over the right fifth lumbar dorsal root ganglion. The surgical removal of the nucleus pulposus from herniated rats one week after the implantation reduced the hyperalgesia to a level similar to that seen in controls. This reduction in the hyperalgesia was also observed in the group that had the nucleus pulposus removed three weeks after the implantation, although the intensity of the hyperalgesia did not decrease completely. The removal of the nucleus pulposus after five weeks did not change the hyperalgesia, which suggests that the longer the contact of the nucleus pulposus with the dorsal root ganglion, the greater the possibility of development of chronic pain. Taken together, these results suggest that specific cytokines released during the inflammatory process induced by the herniated intervertebral disc play a fundamental role in the development of hyperalgesia.[3] It is the maintenance of this inflammation that may result in pain becoming chronic and so the downward spiral begins. Somehow, we think at *360*, if this can be transposed to the human situation, we might be well on our way to helping the many millions of patients with chronic back discomfort.

Ulcerative colitis, Crohn's and anti-inflammatories

Aspirin and NSAIDs are very widely taken by patients all over the world. There seem to be plenty of upsides, but downsides too? A paper from **Boston (USA)** has looked at the association between these medications and both ulcerative colitis and Crohn's disease. This was a prospective cohort study of 76 795 women who provided biennially updated data about their aspirin and NSAID use. The authors identified 123 incident cases of Crohn's disease and 117 of ulcerative colitis over 18 years and 1,295,317 person-years of follow-up. Compared with nonusers, women who used NSAIDs at least 15 days per month seemed to have increased risk for both Crohn's disease and ulcerative colitis. Less frequent NSAID use was not clearly associated with an increased risk for either condition, and there was no clear relationship between aspirin use and disease.[4] So there we are. Frequent use of NSAIDs, but not aspirin, appears to be associated with an increased incidence of Crohn's disease and ulcerative colitis. That said, these findings have more mechanistic than clinical implications, as the absolute incidence of these two conditions when associated with NSAIDs was low. This is therefore unlikely to alter the balance of more common and clinically significant risks and benefits associated with these medications. Keep going with the aspirin seems a reasonable conclusion for those of us of a certain age at *360*.

NSAIDs may compromise bone healing

The healing of bone requires a complex cascade of events in which several cell types participate along with signal pathways and alterations in the biochemical profile of the local area. Bone healing can be primary (direct) or secondary (indirect), the majority of fractures employing the latter process to heal. However, do NSAIDs influence this process? They are, after all, commonly taken to relieve the discomfort associated with bony injuries. A good review of this issue has come out of **Leeds (UK)**, as, over the last decades several studies have suggested that NSAIDs interfere with bone healing while others contradict these findings. Although their analgesic potency is well proven, clinicians remain puzzled over the potential safety issues. The authors have thus systematically reviewed the available literature, analysing and presenting the available *in vitro* animal and clinical studies in this field. This comprehensive review reveals the great diversity of data in all groups of studies. Animal and *in vitro* studies present such conflicting data that even studies with identical parameters have opposing results. Basic science research defining the exact mechanism with which NSAIDs could interfere with bone cells, as well as properly randomised, prospective clinical trials, is warranted.[5] The authors' conclusion is both sensible and logical, we feel at *360*. In the absence of robust clinical or scientific evidence, clinicians should treat NSAIDs as a risk factor for the impairment of bone healing. Their administration should certainly be avoided in high-risk patients.



Osteoporosis is not everything for the fractured hip

In the last issue of *360* we reported a paper that suggested the Chinese suffer fewer fractured hips than the rest of us. Consequently, to find a paper from **Xi'an (China)** on genetic associations with bone mineral density (BMD), and which clearly disagrees with us, was both well timed and interesting. Manifestly, osteoporosis is a serious public health problem, which is characterised by reduced BMD and increased risk of low-trauma osteoporotic fractures. Hip fractures are directly associated with high morbidity and mortality, as well as tremendous healthcare costs. Because of an ageing population, the incidence of hip fractures is increasing greatly, not only in developed countries, but also in the developing world. One third of the world's osteoporotic hip fractures now occur in Asia, mostly in China; this rate will rise to 45% by the year 2050. It is known that osteoporosis is a heritable disease, characterised mainly by low BMD and/or osteoporotic fractures. Most genome-wide association studies on osteoporosis have focused on BMD, whereas little effort has been made to identify genetic variants directly linked to osteoporotic fractures. In order to determine whether BMD-loci are also associated with the risk of an osteoporotic fracture, the authors undertook a validation study to examine 23 BMD-loci reported by recent genome-wide association studies for association with the risk of an osteoporotic hip fracture. Their sample comprised 700 elderly Chinese Han subjects, 350 with osteoporotic hip fractures and 350 healthy matched controls. They identified four BMD-loci that were significantly associated with osteoporotic hip fractures in this Chinese population, including 7q21, 6p21, 13q14, and 18q21. These results further highlight the importance of these loci in the pathogenesis of osteoporosis, and demonstrate that it is feasible and useful to use osteoporotic fractures as the direct phenotype to conduct genetic studies, in order to enhance the understanding of the genetic architecture of osteoporosis.[6] Thank Heaven, we think at *360*, there appears to be more to hip fractures than simply becoming old.

Herbal medicine and recovery after acute muscle injury

Astragaloside is a valued Chinese herbal medicine that comes from the root of *Astragalus membranaceus* (Huangqi). It has been prescribed for centuries as a tonic and is regarded by many as immunostimulatory, anti-inflammatory, antibacterial, antiviral and antioxidant in nature. Astragaloside is seen as an anti-ageing supplement. Meanwhile, tanshinone IIA can be extracted from the root of *Salvia miltiorrhiza*, frequently called Chinese red sage (Danshen), and a native perennial plant to China and Japan. Tanshinone IIA has been widely used for various cardiovascular and cerebrovascular disorders in Asian countries, can improve renal dysfunction and can certainly attenuate cerebral oedema in rats. Consequently, a paper from **Shanghai (China)**

on the effects of astragaloside and tanshinone IIA on the repair of skeletal muscle after acute contusion is most helpful. The authors sought to investigate the effect of these two substances on the expression of embryonic Myosin Heavy Chain (MHC-emb) and vimentin in rat skeletal muscles after acute contusion. They took 80 male Wistar rats and randomly divided them into group A (Astragaloside), group B (Tanshinone IIA), group C (Astragaloside and Tanshinone IIA), group D (Huangqi-Danshen) and group E (physiological saline control). There were 16 rats in each group. Right gastrocnemii were contused in all groups and the damaged locations were then injected with the corresponding drug. The samples were collected from injured muscles four, seven, 14 and 28 days after injury. Western Blot analysis was used to measure the expression of MHC-emb and vimentin in each group at different time points. The results were fascinating. Compared with the group of physiological saline controls, the expression of MHC-emb in each intervention group increased significantly after injury and continued until 28 days after injury. The expression of MHC-emb increased most obviously in groups C and D. Compared with the group of physiological saline controls, the expression of vimentin in each intervention group decreased significantly after injury and continued until 28 days; the expression of vimentin decreased most obviously in groups C and D. The conclusions were thus clear. During the repairing process of an acute contusion of skeletal muscle, astragaloside and tanshinone IIA promoted the expression of MHC-emb and inhibited the expression of vimentin. The effect of a mixed injection of astragaloside and tanshinone IIA was similar to the Huangqi-Danshen injection.[7] We find this very exciting at *360*, as a paper like this exemplifies the very reason for our existence. Herbal preparations may be widely used in some parts of the world within the musculoskeletal specialism but are not used at all in others. It is certainly time for us all to share our experiences.

Ultrasound and time to fracture union

There has been a fair amount of published work on the use of ultrasound in reducing the time to bony union after fracture, so *360* was interested to read the Cochrane review on the topic from a team in **Warwick (UK)**. They highlight that the morbidity and socioeconomic costs of fractures are considerable, that the length of time to healing is an important factor in determining a patient's recovery and that ultrasound may have a therapeutic role in this process. They wished to assess the effects of low intensity ultrasound (LIPUS), high intensity focused ultrasound (HIFUS) and extracorporeal shockwave therapies (ECSW) as part of the treatment for acute fractures in adults. To do this, they searched the Cochrane Bone, Joint and Muscle Trauma Group Specialised Register, the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE, trial registers and reference lists of articles. The selection criteria were randomised controlled trials evaluating ultrasound treatment in the management of acute fractures in adults. Studies that included participants over 18 years of age with acute fractures were used, while two authors independently extracted data from the studies. The researchers found 12 studies, involving 622 participants (648 fractures). There were 11 that tested LIPUS and one that tested ECSW. There were four trials that included participants with conservatively treated upper limb complete fractures and six that included participants with lower limb complete fractures; these were surgically fixed in four trials. The remaining two trials reported results for conservatively treated tibial stress fractures. Very limited data from two complete fracture studies showed no difference between ultrasound and placebo control in functional outcome. Pooled estimates from two studies found LIPUS did not significantly affect the time to return to training or duty in soldiers or midshipmen with stress fractures. A 'worst case' analysis, which, adjusted for incomplete data, pooled results from eight heterogeneous studies, showed no statistically significant reduction in time to union of complete fractures treated with LIPUS. An additional subgroup analysis comparing conservatively and operatively treated fractures raised the possibility that LIPUS may be effective in reducing healing time in conservatively managed fractures, but the test for subgroup differences did not confirm a significant difference between the subgroups. Pooled results from eight trials reporting proportions of delayed union or nonunion showed no significant difference between LIPUS and controls. Adverse effects directly associated with LIPUS were found to be few and minor, and compliance with treatment was generally good. One study reporting on pain scores found no difference between groups at eight weeks. Meanwhile, one quasi-randomised study (59 fractures) found no significant difference between ECSW and no-placebo control groups in nonunion at 12 months. The only reported complication was infection, with no significant difference between the two groups.[8] So *360* finds the authors' conclusions totally reasonable. That is, while a potential benefit of ultrasound for the treatment of acute fractures in adults cannot be ruled out, the currently available evidence is insufficient to support its routine use in clinical practice. Future trials are clearly needed. We do have one query, however. One of the objectives of this study was to look at HIFUS, yet that does not seem to appear in the final report. Next time, perhaps?

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