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Review Article

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Interventional Regenerative Medicine for Pain Control and Quality of Life Improvement as an Alternative Therapy: Review Article

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Abstract

Osteoarthritis (OA) and injuries are common presentations to orthopaedic and pain specialists. OA is related to ageing joints, but it could develop prematurely secondary to trauma (s), as in athletes and manual workers. Injuries could happen in the form of sprain or tear in the tissues; it might affect joint, tendon, ligament, bursa or other connective tissues like the meniscus and labrum. The standard management of orthopaedic conditions involves non-steroidal anti-inflammatory drugs (NSAIDs), steroid injections, and physical therapy. If the above measures fail, then surgical intervention is implemented using repair or reconstruction of the injured structure (s) like meniscus, labrum, tendon, or ligament. Furthermore, symptomatic OA would eventuate in joint replacement. As the science progresses, we are emerging promising non-invasive interventional regenerative medicine as a step to be considered before surgery. We need to adapt to the new era of giving options to the patients to choose the preferred approach following an algorithm from the conservative approach to the regenerative medicine trial therapy before proceeding to surgical intervention; the latter stays as the last resort.

We are trying several regenerative therapies for symptoms control, including; pain, stiffness, swelling and reduced range of motion, and improving patients' quality of life. In OA, labral and meniscus tears, we try intra-articular injections of non-soluble long-acting hyaluronic acid injections like durolane or platelet-rich plasma (PRP) alone or in combination with soluble hyaluronic acid. Additionally, we found a significant positive outcome using expanded mesenchymal stem cell (MSC) therapy combined with PRP; we sometimes add soluble hyaluronic acid or exosome therapy as a scaffolding technique. MSC therapy was shown in multiple studies to slow or stop the degenerative process with an excellent anabolic effect. Tendon tear has been treated successfully with PRP alone or combined with MSC therapy to heal the tendon entirely or partially.

Our article addresses the use of regenerative medicine as an alternative to the long-term use of analgesics, NSAIDs, and neural blockade agents. Those treatments have potential body toxicity, such as NSAIDs induced gastrointestinal bleeding, renal failure, and liver damage. Narcotics have a problem with addiction, and neural blockade agents can cause dizziness, drowsiness, impair work function, driving and other unwanted side effects. Furthermore, we try to avoid surgical intervention by using non-invasive harmless regenerative therapy like hyaluronic acid or autologous treatment using PRP alone or in combination with expanded MSC therapies.

Keywords: Osteoarthritis, Pain, Tendon, Ligament, Meniscus, Labrum, Tear, Platelet-Rich Plasma, PRP, Hyaluronic Acid, Mesenchymal Stem Cell, MSC

Background

Musculoskeletal (MSK) pain is one of the most common presentations to health professionals. It can be acute or chronic; the acute one is usually transient and does not require long term intervention. Our topic in this article is chronic persistent pain resulting from either sport or non-sport injury or the degenerative process of the joint or tendon.

Osteoarthritis (OA) is a degenerative joint disease, and it is the most common type of arthritis; the knee joint is typically involved. Pathological processes are seen in OA joint, including; osteophytes formation, subchondral bone thickening, variable degrees of synovial inflammation, degeneration of menisci and ligaments of the Knee joint, capsule hypertrophy, and progressive articular cartilage destruction leading to narrowing of joint space [1]. The aetiology of OA is multifactorial and includes articular injury, ageing, overweight, and heredity [2, 3].

OA is a significant source of morbidity and physical restriction among people over the age of 40 [4, 5]. The clinical presentations include chronic pain, stiffness, swelling, joint instability, and reduced range of motion. Even though OA predominantly affects the elderly, sports-related injuries at all ages can take the lead to post-traumatic OA. Presently, apart from pain management and surgical intervention for the advanced stages, there are no effective therapeutic treatments for OA.

Tendon tear is a common pathology, mainly rotator cuff tears (RCTs); they are prevalent with ageing due to the degenerative process [6]. The main issue with failure in rotator cuff repair is probably biological. It is a fact that the fragile and highly specialised fibro-cartilaginous transition zone between the rotator cuff and the bone is hard to regenerate following repair [7-9]. When a tear is symptomatic, it causes significant pain and functional impairment; medical and physical therapies are suitable to try first. A subacromial steroid injection can potentially help the symptoms, often short-lived [10, 11]. RCTs are unlikely to heal naturally; thus, ongoing pathology requires surgical repair [12].

Meniscus tears occur due to rotational or cropping powers laid across the tibiofemoral joint. Such developments include positions with heightened degrees of closed dynamic flexion like kneeling and squatting, heavy lifting, acceleration/deceleration activities, rapid change of direction, and jumping [13, 14]. Relatively more minor power is required to give rise to tears in degenerative meniscus pathology in association with OA. A conservative approach manages a simple tear, but a complex one needs surgery. Physical therapy will be part of the management plan in both conventional and post-surgical cases [15, 16].

Hip labral tear commonly occurs from two possible processes: a single, acute significant injury, especially involving strenuous hip flexion resistance (running or kicking), or repetitive microtrauma in a hip with chronic, degenerative joint disease [17, 18]. The management for asymptomatic tear is conservative by avoiding injuries and physical therapy; we use surgical repair to treat the symptomatic labral tear.

Ligament tear is usually the result of sports injury. The most frequent pathology presented to the orthopaedic surgeon in the knee area is the collateral and cruciate ligaments or multiple ligament injuries diagnosed by an MRI imaging [19]. The talocrural lateral ligaments in the ankle area are mostly injured; they consist of anterior talofibular, posterior talofibular, and calcaneofibular ligaments [20]. Ligament injury is generally managed conservatively with rest, non-steroidal anti-inflammatory drugs (NSAIDs), and physical therapy. Should all those measures fail with significant joint instability, a surgical repair might be indicated.

Our regenerative clinic initially treats clients with simple measures, including a short course of NSAIDs and physiotherapy. We avoid the long-term use of anti-inflammatory, narcotic analgesics, and nerve blockade medications, as they all have adverse effects and toxicities. If there is any soft tissue inflammation or synovitis, then a trial of local steroid injection in some cases might be worthwhile.

We embraced using the latest technology of harmless regenerative medicine, including PRP, hyaluronic acid or a combination of both, depending on the pathology. We add autologous expanded adipose-derived MSC therapy with various doses adjusted accordingly in more complex persistent cases. We use the ultrasound guidance approach as this is more precise to maximise the benefit of our therapy.

We have treated hundreds of patients for various orthopaedic conditions, and below are brief descriptions of our few published case series.

Case Series

Case 1

A 54-year-old salesperson enjoys active sports. He presented with symptomatic right knee OA. An MRI scan of the Knee showed patellofemoral subchondral bone marrow oedema, multiple subchondral cysts, synovitis and large baker cyst (Fig. 1a and 1b). In addition, there was a medial meniscus tear, medial and patellofemoral cartilage loss.

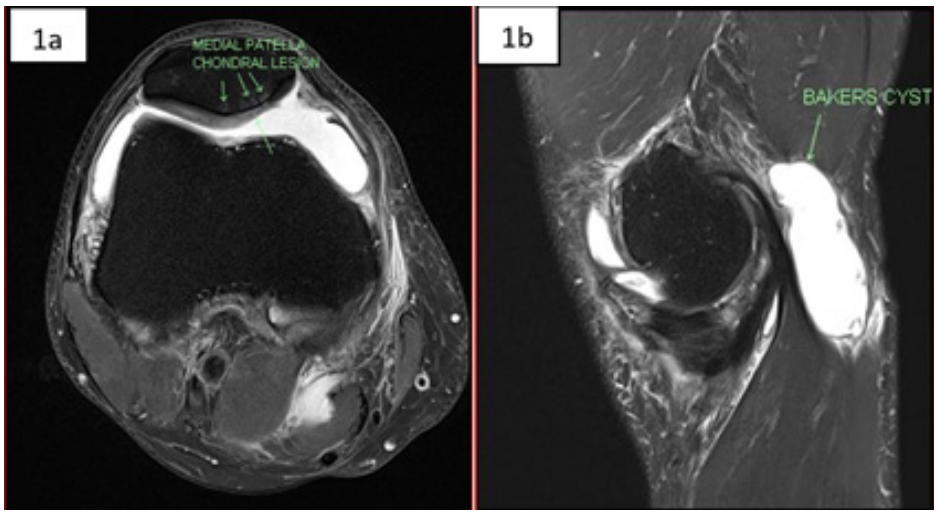

Figure 1a: Pre-treatment MRI shows patellar subchondral bone marrow oedema and cysts, and **1b:** demonstrating large baker's cyst

He failed conservative treatment with NSAIDs and physiotherapy, then ultrasound-guided knee steroid injection. He responded dramatically to a single dose of autologous fat-derived expanded MSCs combined with PRP. He became asymptomatic three months following the therapy, and that persisted. He had a series of follow-up MRI scans; the last one, 36 months post-therapy, revealed full resolution of bone marrow oedema and subchondral bone cysts with the disappearance of the baker's cysts and synovitis (Fig. 2a and 2b). This case showed promising results, which may alter the way we practice medicine in OA management as a step before contemplating surgery.

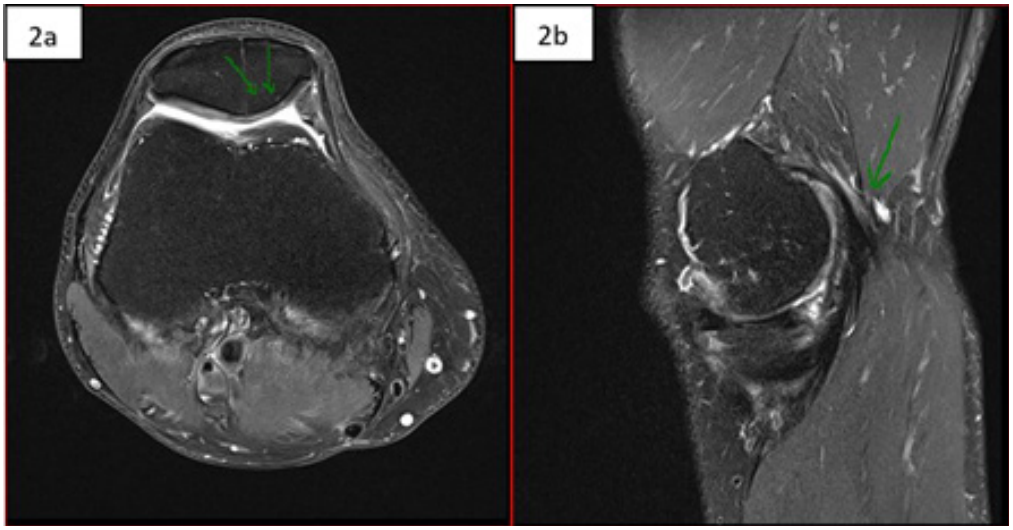

Figure 2: Shows post-MSC therapy complete resolution of bone marrowoedema and cysts, and **2b:** significant diminution of baker's cyst

Case 2

A 66-year-old female bothered by symptomatic hand osteoarthritis (OA) for six years affected her daily activities and job; she works as an aromatherapist. She responded well to adipose-derived autologous expanded MSC therapy; this was performed under ultrasound guidance after digital nerve block for bilateral 2nd - 5th distal interphalangeal (DIP) joints. The improvement began one month after the MSC injections, with the most significant lasting benefit occurring ten months post-therapy. A 14-month follow-up X-ray revealed no radiological progression of OA in the treated joints compared to the baseline X-ray. She continued to enjoy painless activities of daily livings and work. Despite the persistent response, she chose a booster dose of MSC therapy to maintain her hand's function and prevent the progression of OA. This case demonstrated good symptomatic and functional outcomes, with no further OA joint deterioration on X-rays as in Fig 1A and B.

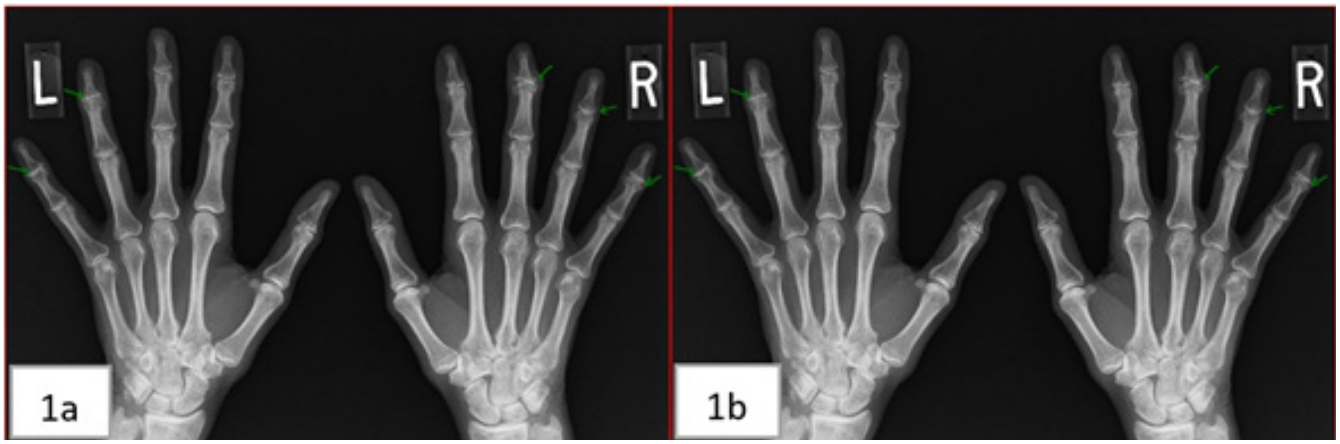

Figure1a: Shows pre-treatment OA on X-ray. **1b:** Shows stable X-ray post-treatment with MSCs

Case 3

A 70-year-old female presented with a painful shoulder following an injury suffered on a flight when a bag fell out of the baggage rack, landing on her right shoulder. Her family doctor treated her with conservative treatment, including analgesia and physiotherapy. USS revealed a small partial tear of the supraspinatus tendon (SST) with subacromial bursa thickened to 2.8 mm. She underwent a subacromial steroid injection with good effect. She had further right shoulder injuries with the progression to full-thickness SST tear in anterior, middle and posterior fibres measuring 9 mm length, 13 mm width, with the overlying bursa was swollen to 2.9 mm without features of capsulitis (Fig.1a). She failed conservative treatment with NSAIDs, subacromial steroid injection, and shoulder rehabilitation. She elected experimental adipose-derived autologous expanded MSC therapy combined with PRP; this resulted gradually in the resolution of

her symptoms three months post the treatment to become completely asymptomatic after eight months with complete regeneration of the SST (Fig. 1b). This case suggests that a non-invasive therapy could replace long-term harmful medicine and eliminate the need for complex surgery.

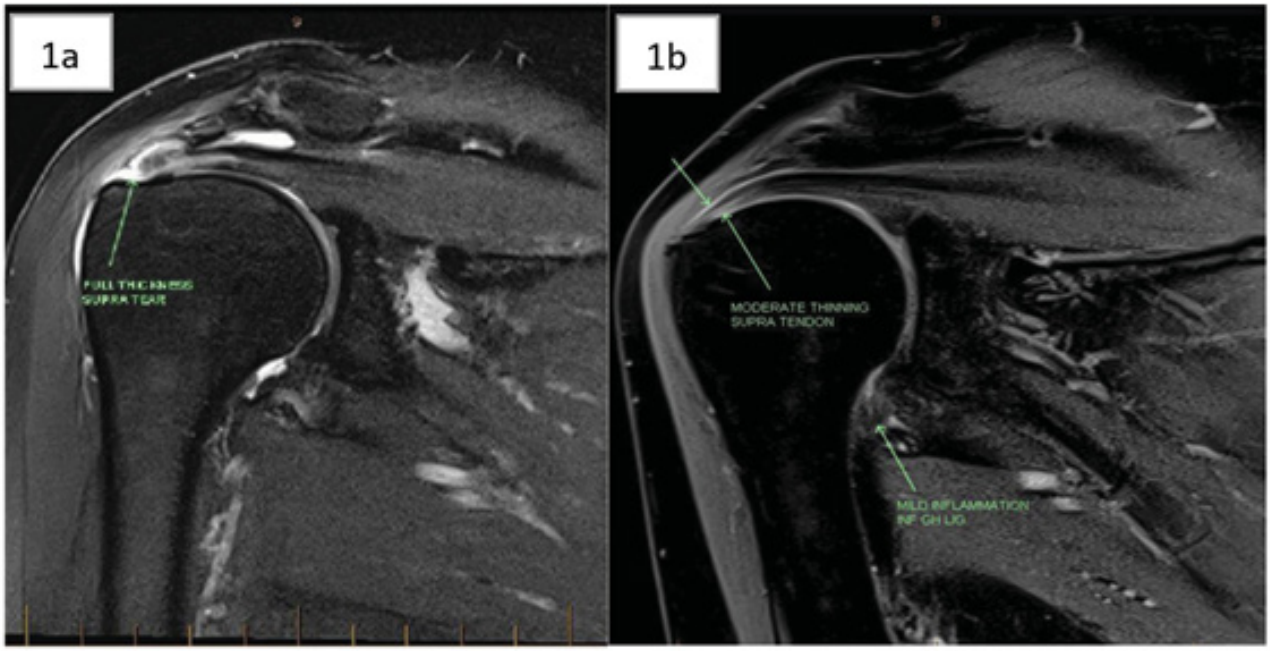

Figure 1a: Pre-treatment MRI shows. **1b:** post-treatment with MSCs shows complete thickness supraspinatus (SST) tear regeneration of SST

Case 4

A 44-year-old female patient suffered a left Achilles tendon (AT) rupture during a netball game. Initially, she was treated conservatively with NSAIDs, moon boot, and rehabilitation with good results, but AT spontaneously ruptured again, leading to reconstruction surgery with flexor hallucis longus tendon (FHLT) transfer. Despite good rehab, she developed calf muscle weakness and atrophy at the grafted musculo-Achilles junction. She had an MRI scan eight years following the repair surgery that revealed remodelling of the left tendo-Achilles and post-surgical changes at the reconstruction site with tendinopathy and partial-thickness tear at the soleus musculotendinous junction (Fig.1a). Her symptoms included the inability to perform a single heel raise, decreased recreational activities, and calf muscle wasting and weakness. The Foot & Ankle Disability Index (FADI) score was 74. Her orthopaedic surgeon suggested no further surgical intervention, given it would not be helpful. She has opted for a trial of autologous adipose-derived expanded MSCs combined with PRP. Six months following the treatment, she had a good outcome evidenced by improved daily activities, heel-raise, and running slowly for the first time after several years post reconstruction surgery. Her FADI score rose to 91.3. Post-treatment MRI revealed an increased signal at the musculo-Achilles junction suggesting a healing process (Fig. 1b).

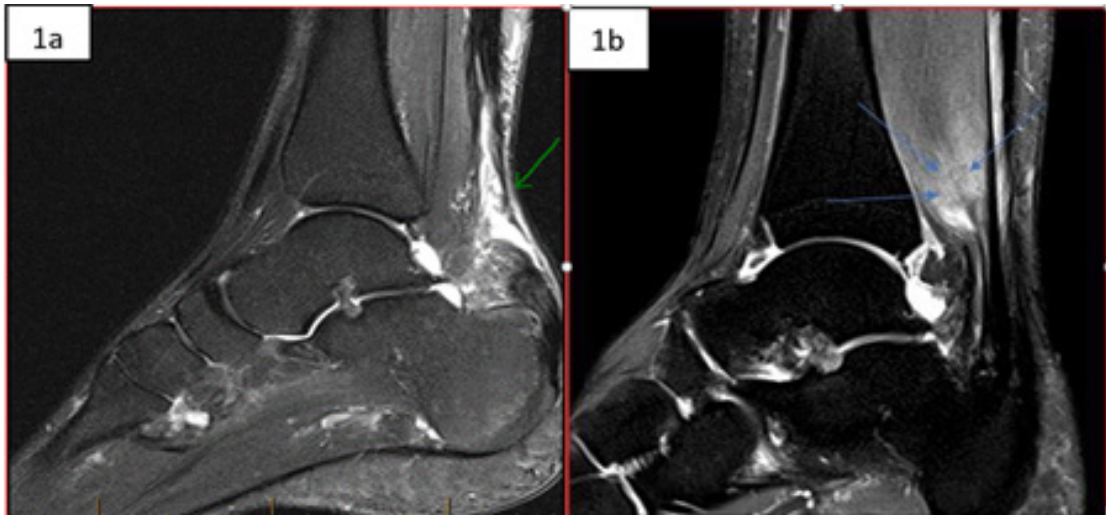

Figure 1a: MRI showed post-surgery muscle atrophy and partial-thickness tear, and **1b:** increase in signal may be due to post - treatment changes (healing response)

We noted improvement of the muscle bulk compared to pre-treatment calf muscle atrophy (Fig. 2a and b). This case presents a successful outcome with a single MSCs and PRP, indicating we can try MSC therapy to repair wasted calf muscle and tendon from previous scars.

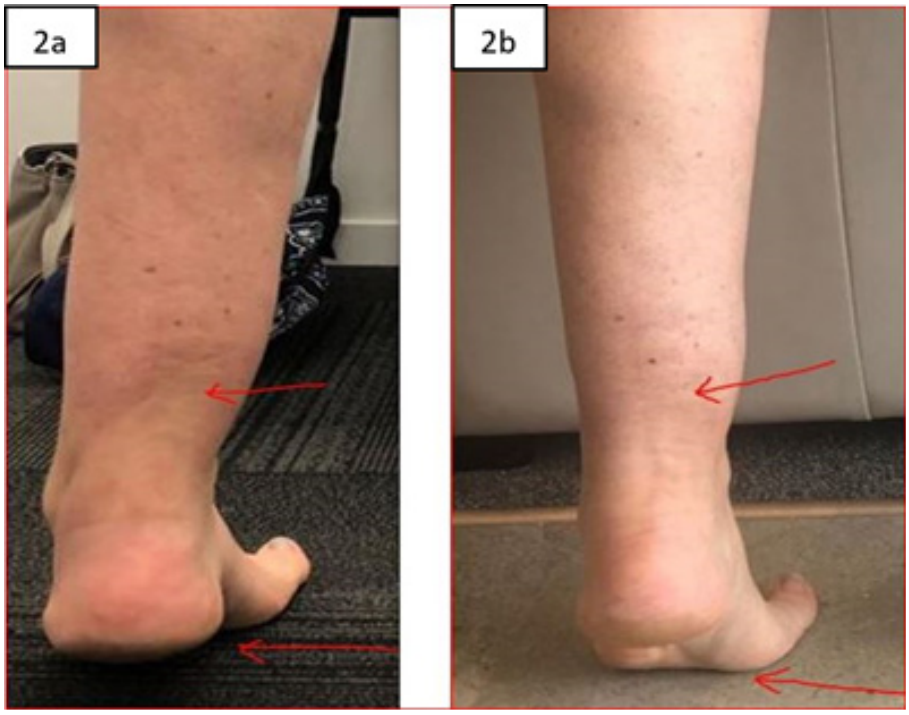

Figure 2a: Before MSC therapy shows left calf muscle atrophy and **2b:** post-treatment revealed improved muscle atrophy and able to do heel-raise (arrows)

Discussion

Management of orthopaedic conditions generally uses a conservative approach with NSAIDs, narcotic analgesics, neuropathic drugs, physical therapy, and sometimes steroid injections for symptomatic relief and restoring function. Those medications are helpful for acute pathology, and we should not use them for long due to the adverse effects and interactions with the patient's regular medicines. In addition, those measures might not alter the outcome of the disease process.

We avoid the long-term use of NSAIDs to prevent gastrointestinal bleeding [21]; they can also cause renal failure, especially in patients with diabetes and hypertension. NSAIDs can interact negatively with angiotensin-converting enzyme inhibitors and diuretics.

Narcotic analgesics such as morphine, codeine phosphate, and tramadol are well known to cause addiction and alter mental status thus, we prefer to avoid their use in chronic MSK conditions[22, 23]. We use neuropathic blockade medicines in some instances, commonly tricyclic anti-depressants (TCA) like amitriptyline and certain anti-epileptics (gabapentin and pregabalin). TCA can cause various side effects, including anticholinergic symptoms, such as tachycardia, dry mouth, constipation, raised intraocular pressure, blurred vision, urinary retention. TCA can also cause dizziness, drowsiness, and confusion/agitation [24]. Anti-epileptics like pregabalin have common side effects, including dizziness, drowsiness, and ataxia [25]. Other side effects include weight gain, blurred vision, tremors, and impaired concentration.

We consider surgery as our last resort when every other measure fails. Surgery has significant complications related to general anaesthesia and surgical procedures; surgery also has a lengthy recovery period. Surgical options sometimes fail, and if that happens, the patients will have no other choice. Most joint replacements have different life spans; thus, patients might go for revision, which could be not feasible on many occasions. We recommend trying every alternative option before deciding the operative path.

We implemented the latest technology of safe regenerative medicine, including PRP, hyaluronic acid or combination therapy, that showed more effectiveness in OA than either therapy alone [26]. In more complex cases, we either use autologous expanded adipose-derived MSC therapy alone or combined with PRP and sometimes we add soluble hyaluronic acid.

MSC therapy is promising science as it can deliver suitable cellular signals to encourage tissue regeneration, anti-inflammatory effect, and local immune modulation. Multiple randomised controlled trials indicated the positive impact of MSCs in OA [27,28, 29]. MSCs are currently being analysed in numerous research resources and clinical practices to establish efficacy and safety [30,31,32]. The speculative proposition of MSCs can restore cartilage and might eliminate the need for knee replacement [33].

There is growing interest in animal and human trials in regenerative medicine, including MSCs and PRP as an experimental therapy to surgical intervention for rotator cuff treatment [34, 35, 36, 37, 38, 39, 40].

We decide our doses based on the affected joint area and the severity of the condition. We do all procedures under ultrasound guidance; our dosage ranges between 10-100 million cells combined with PRP with/without soluble hyaluronic acid for peripheral joints. Except in the finger and toes joints, we use only MSCs as we found concentrated MSCs per se more effective than combination therapy. We avoid using hyaluronic acid for the tendons and ligaments to prevent triggering a remarkable inflammatory response. We have also tried plasma-derived micro-RNA exosome particles in joint and tendon protocols. Exosomes work like biologic garbage bins that hold proteins, lipids, mRNAs, non-coding RNAs, and even DNA out of cells [41]. Exosomes also enhance cell-cell communication [42]. We found that regenerative medicine is effective in about 80 % of cases; success is measured by controlling symptoms and improving activities of daily living, sport, and work. We have also eliminated the need for surgery in most cases; additionally, we noticed radiologic evidence of slowing or stopping the progression of OA or regeneration and healing of partial and full-thickness tears.

Conclusion

Regenerative therapy is a new experimental modality in treating pain for musculoskeletal and orthopaedic conditions. Regenerative therapy is the future medicine and might replace mainstream surgery in most cases if used appropriately; this option is favourable over the use of long-term toxic anti-inflammatory, addictive narcotics, or neuropathic medications with significant adverse reactions. We need a randomised controlled trial to confirm the consistency of those findings in regenerative medicine.

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Competing Interests

The author has declared that no competing interests exist.

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