PM R 7 (2015) S76-S80

www.pmrjournal.org

Regenerative Medicine

The Role of Physiatry in Regenerative Medicine: The Past, The Present, and Future Challenges

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Abstract

Historically, the foundation of physical medicine and rehabilitation training has provided the capabilities to optimize nonoperative treatments of a variety of musculoskeletal conditions, including acute and chronic muscle, tendon, ligament, and cartilage disorders. Such treatments include the use of nonsteroidal anti-inflammatory drugs (NSAIDs), therapeutic modalities (eg, thermal and manual therapies), and corticosteroid injections in conjunction with specific rehabilitation exercises. Although NSAIDs, modalities, and corticosteroids may be helpful for short-term pain reduction and early recovery of function, they do not typically reverse the structural changes associated with degenerative conditions and may contribute to worse long-term outcomes by potentially interfering with tissue healing. Regenerative interventions, including platelet-rich plasma and mesenchymal stem cells, recently have been used to treat refractory painful conditions such as chronic tendinopathies because of the potential of these interventions to facilitate tissue healing. The future development of these regenerative techniques will require a variety of conditions to be met, including determining the most appropriate procedures based on the disease being treated; establishing the optimal preparations of these regenerative techniques; and providing clinicians, patients, and regulatory agencies with high-quality evidence demonstrating the safety, effectiveness, and long-term results of these treatments. Clarification of current regulatory uncertainty, improved access for all patients, proper training for clinicians who incorporate these techniques into their practice, and determination of the most appropriate postinjection protocols will allow physical medicine and rehabilitation specialists to play a unique role in the long-term management of patients with musculoskeletal and sports injuries. This article will also address the role physiatrists *should* have in the inevitable growth of regenerative medicine applications.

Introduction

The incorporation of interventional pain procedures, integration of musculoskeletal ultrasound into clinical practice, and development of regenerative medicine techniques have offered providers of musculoskeletal care additional treatment strategies that feature minimally invasive interventions. These tools have coincided with increased participation in competitive and recreational sports that are performed repetitively beginning at a young age and in the context of longer life spans, leading to an increase in degenerative joint disease and traumatic and overuse injuries. Thus, the concept of regenerative interventions has become very appealing to health care providers. Furthermore, increasing public awareness of elite and professional athletes and media coverage of procedures such as stem cell and platelet-rich plasma (PRP) treatments with reported good outcomes have piqued the curiosity of the general population [1-4]. This situation highlights the need for PM&R and other sports medicine specialists to be fully aware of the scientific evidence for these novel techniques and continue to optimize the efficacy of nonoperative treatment outcomes [5-7].

The "physiatric approach" provides a unique perspective in treating patients with a variety of musculoskeletal conditions, from acute to chronic injuries, throughout the continuum of care. This task first requires identifying an accurate diagnosis of the pain source through an understanding of functional anatomy and unique physical examination skills; then a comprehensive treatment plan that includes the appropriate use of medications, modalities, and rehabilitation treatments can be developed (Figure 1). Corticosteroid injections and nonsteroidal anti-inflammatory drugs (NSAIDs) have also been used to

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http://dx.doi.org/10.1016/j.pmrj.2015.01.004

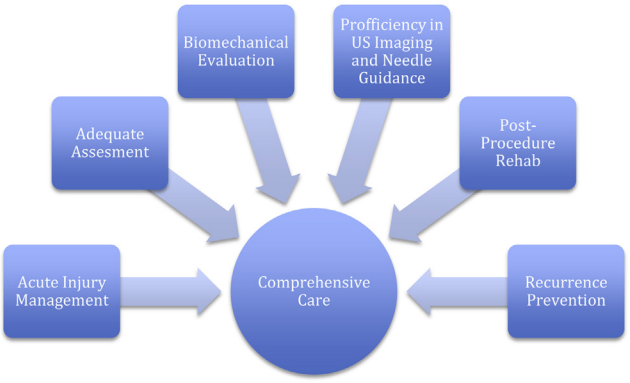

Figure 1. Physiatric approach to regenerative treatments. US = ultrasound.

reduce pain and facilitate the rehabilitation process; this approach reduces acute symptoms by limiting the body's inflammatory response [8-13]. However, these treatments do not facilitate tissue healing and may in fact have negative effects on acutely injured bone, tendon, and other musculoskeletal tissues [14-19]. During the past decade, regenerative techniques such as PRP and stem cell therapies have been used, based on their capabilities to facilitate tissue healing. Although numerous studies have been performed with promising results, many questions persist regarding conflicting scientific evidence, cost of treatments, and regulatory issues pertaining to how these treatments may be used within U.S. Food and Drug Administration (FDA) guidelines.

The Past—What We Have Learned

Therapeutic modalities have been used for many years in the treatment of pain after musculoskeletal injury [20]. Some of the classic modalities such as electrical stimulation and therapeutic ultrasound are beneficial in reducing acute symptoms, specifically pain and associated arthrogenic inhibition, along with local inflammation [21,22]. Their value in the long-term recovery of soft tissue and articular damage is less clear and is not well supported in the medical literature [21]. Some newer techniques such as extracorporeal shock wave therapy and soft tissue laser have gained popularity because proponents believe they provide more benefit for actual tissue healing when compared with the more classic modalities [22-24]. However, evidence supporting their widespread use and their role in the long-term healing response is lacking.

The use of NSAIDs has been a mainstay in the treatment of musculoskeletal injuries, and NSAIDs are the most commonly prescribed medication in sports medicine [11,12]. In persons with acute injuries, including ankle sprains and tendon injuries, these medications can provide effective short-term pain relief that is likely related to both their anti-inflammatory and analgesic properties [11,12]. However, the concern has arisen that inhibiting prostaglandins and reducing the inflammatory response may result in impaired tendon healing by reducing fibroblast proliferation and migration and adversely affect fracture healing by preventing callus formation [8,11-16].

Intra-articular and soft tissue corticosteroid injections are also interventions that are used frequently. These injections also likely provide short-term pain relief, which may facilitate earlier participation in a comprehensive rehabilitation program. However, pain and dysfunction due to chronic tendinopathies are highly recurrent, and increasing evidence suggests that corticosteroids may adversely affect tendon and cartilage structural properties. Therefore, the use of corticosteroids in the clinical setting of recurrent injury, or when evidence of tendon or cartilage degeneration is present, should be avoided unless there is a clear necessity for short-term symptom relief to meet other patient-specific goals [8,9,17-19,25].

These aforementioned treatments must be combined with therapeutic exercise, such as strengthening, stretching, and stability training, to have an impact on long-term recovery, which clearly requires patient compliance for lasting effects [26]. For example, the use of quadriceps strengthening and improved neuromuscular education has been widely reported as effective in reducing pain and improving quality of life in patients who have knee osteoarthritis [27,28]. The effectiveness of incorporating eccentric training and flexibility exercises for Achilles and other tendinopathies has also been documented [29]. However, it must be emphasized that even these reactivation strategies may not result in rejuvenated tissues, and the risk of reinjury remains greater once the degenerative process ensues.

The Present—Uncertain Yet Developing

With the current understanding that a majority of musculoskeletal conditions are related to suboptimal healing responses or tissue degeneration, treatments historically directed at "inflammation" have been challenged [8-10]. This situation has led to the increasing application of regenerative techniques that offer patients minimally invasive treatment alternatives that can potentially facilitate the reversal of degenerative changes in various tissue types.

Prolotherapy, PRP, and mesenchymal stem cells are being used in the treatment of tendinopathies, ligament injuries, and degenerative joint disease, with an increasing number of both animal and clinical studies to support their use. Some evidence indicates that these treatments may be superior to the traditional treatment interventions from the "past" [5-7,20].

However, evidence regarding the efficacy of these treatments (particularly PRP) continues to be conflicting because of the great variability in the preparations and techniques used in the delivery of these treatments. For PRP, these variables include the optimal number of platelets, the role of leukocytes, the need for activation, the time frame before additional interventions, and the optimal post-treatment rehabilitation [30]. Even more complex issues exist with regard to the standardization of treatments using stem cells [5]. These issues include the debate over using bone marrow aspirate or adipose tissue, the exact protocol regarding extraction, and regulatory issues regarding expanding stem cells. In addition to the challenge of deciphering the appropriate treatment protocols for any given disease, the long-term effects (both positive and negative) of these therapies remain unknown.

In addition, although some centers are actively treating patients with autologous stem cells, most payers consider stem cell treatment to be "experimental" and thus not a covered treatment. Considering patient cost and lack of conclusive scientific evidence for the effectiveness of these procedures, clinical application remains limited. In addition, training opportunities in regenerative medicine remain limited, and such training is not standardized.

The Future—Opportunity and Challenges

Attempting to predict future trends and developments in regenerative medicine presents a difficult task because of ongoing scientific, economic, and regulatory uncertainties (Figure 2). However, based on the current state of knowledge, the prospect of tissue regeneration and modulation of the healing response remains promising and enticing for medical specialists treating these various musculoskeletal degenerative conditions. An objective look at the current landscape identifies different challenges that will have to be met and questions that need to be answered in the near and mid-term future.

Economic considerations are inevitable when contemplating the development and implementation of regenerative medicine techniques. Incorporating the equipment necessary for the application of PRP or mesenchymal stem cells to a medical practice requires a sizable investment in training, equipment, and staffing and, likely, an increase in liability coverage. An ongoing issue is who will (should) cover the cost of these procedures: the patient or a third-party payer? In addition, will these payments cover the expense of the procedure and the investment from the practitioner? Further, will these treatments result in a reduction in the overall cost of these various conditions? The cost of these therapies may also result in accessibility issues, with patients being classified as those who can afford these cutting-edge procedures and those who will only receive treatments covered by their insurance companies.

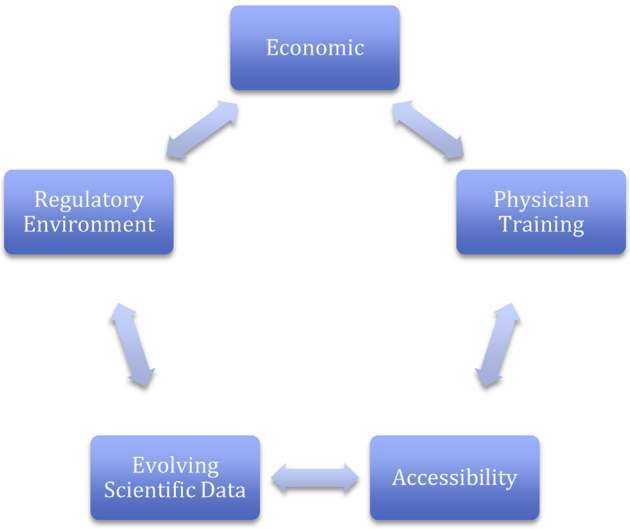

Figure 2. Challenges faced to optimize potential.

Increasing but as of yet insufficient high-level evidence exists that these newer interventions are effective for the treatment of tendinopathy [10] and mild to moderate osteoarthritis [7]. Further high-quality research is necessary to answer questions such as optimal patient selection (eg, age, activity level, weight, and the severity and chronicity of the condition), the type and timing of such procedures, and when to repeat regenerative interventions versus using conventional treatments or surgery. It will also be necessary to document that regenerative techniques are cost-effective when compared with currently available interventions.

Rehabilitation programs that follow regenerative interventions will need to be optimized. Currently no trials have been published that compare different rehabilitation protocols, including their efficacy and effectiveness. Current rehabilitation concepts of progression from early load protection to functional training [30-32] require comparison with alternative (eg, slower or accelerated) protocols to determine the optimal approach to rehabilitation after these regenerative procedures.

The lack of a solid scientific basis begs the question of whether physiatrists should be using these techniques to treat patients before the data are more conclusive. Furthermore, incorporating these techniques into physiatric residency training presents the conundrum of whether residents should receive education and training in these interventions with evolving scientific data, or whether this training should be provided at more advanced levels such as accredited fellowships in pain or sports medicine.

Economic and accessibility issues, the lack of solid scientific data, and the incorporation of regenerative

interventions in residency curriculums and clinical practice will all be affected by how the regulatory landscape overlooking these techniques is shaped in the coming years. The current regulatory framework includes the fact that the FDA is considering limiting same-day procedures involving centrifugation, and that manipulation or cultivation of mesenchymal stem cells will not be permitted in clinical practice [33-34]. It should be expected that more regulatory challenges will arise as novel techniques are introduced.

In the future, we can foresee that the use of NSAIDs and corticosteroid injections will likely be greatly reduced in persons with chronic degenerative conditions; PRP will more commonly be used for chronic refractory tendon disorders, such as lateral epicondylopathy and patellar tendinopathies; and mesenchymal stem cells will be used to treat mild to moderate cartilage injury and knee osteoarthritis. This approach should be followed by evidence-based postinjection treatment protocols, including comprehensive rehabilitation programs. To fulfill the potential of regenerative medicine for these common and debilitating conditions, a greater burden has been placed upon clinicians and researchers to provide a clear rationale and scientific basis for regenerative techniques and to prove that these newer interventions (1) are safe and effective, (2) will benefit patients with degenerative disease, overuse injuries, and traumatic injuries, and (3) will result in a reduction of the long-term costs of musculoskeletal disability. Regenerative techniques can provide exciting new alternatives to improve long-term outcomes in persons with muscle/tendon tears, tendinopathy, cartilage injury, early osteoarthritis, and possibly spine disorders. Evaluating the best combination, timing, and frequency of regenerative interventions is of vital importance. Future research should also be focused on optimizing postintervention protocols and return to activity criteria after these treatments. Although "interventional physiatrists" may seek opportunities to perform these regenerative medicine procedures, the real value from physiatry for patients may be based on the study of how to thoughtfully and appropriately incorporate these treatments into well-established principles of nonoperative treatment and the postprocedural implementation of exercise and training protocols after these regenerative procedures—the opportunity and the challenge.

Summary

Because of a surge in sports participation and physical activity, more patients are presenting to physical medicine and rehabilitation physicians with overuse or degenerative injuries. With increased media coverage of innovative treatment techniques such as PRP and stem cells, the lay public has a greater interest in these procedures. Despite the intrigue accompanying regenerative techniques, the use of these treatments must follow sound medical judgment based on the pathophysiology and contemporary evidence of efficacy and safety. Commonly used treatments such as NSAIDs and corticosteroid injections have a limited role in providing short-term pain relief as an adjunct to comprehensive rehabilitation; however, the current evidence argues against their use in persons who have chronic degenerative conditions without inflammation. It is when other comprehensive rehabilitation treatments have failed in patients with refractory pain that regenerative treatments such as PRP and stem cell therapies may have a role in facilitating tissue healing and functional rehabilitation. Postprocedure rehabilitation should be based on the underlying tissue pathology and an understanding of the tissue healing process specific to the patient's injury. The physiatrist's understanding of functional anatomy, biomechanics, modalities, and rehabilitation methods makes him or her uniquely trained to provide care that optimizes nonoperative treatments to patients with various musculoskeletal conditions, strategically integrating new regenerative treatments when necessary. It is critical that regenerative treatments be viewed as complementary to a broader rehabilitation approach. The potential of regenerative medicine will be determined by how physiatrists and other musculoskeletal specialists meet the scientific, regulatory, and economic challenges related to these interventions.

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Disclosure

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Disclosure: nothing to disclose

Submitted for publication September 4, 2014; accepted January 9, 2015.