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POST-PROCEDURAL REHABILITATION: NICE TO DO OR NEED TO DO?

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Abstract

Patients with musculoskeletal disorders who are recalcitrant to formal rehabilitation may seek non-surgical interventions such as orthobiologics. The care pathway following an orthobiologic procedure may include but is not limited to ancillary modalities, supplements, booster injections, and formal rehabilitation. In some cases, the decision to pursue post-procedural rehabilitation may be questioned due to a paucity of evidence supporting efficacy and safety following orthobiologic procedures. Moreover, patients and physicians may possess a level of uncertainty in pursuing an intervention that may have been previously unsuccessful. Although higher-level evidence does not exist to support routine post-procedural rehabilitation, a body of evidence supports enhanced physical functioning as well as cellular and molecular effects synergistic to orthobiologics. Given the potential benefits of post-procedural rehabilitation, there would seem to be little downside to participation, provided that the physician and rehabilitation specialist consider individual patient characteristics such as the current pathoanatomical diagnosis, stage of acuity, and pre-morbid activity levels.

Globally, an estimated 1.71 billion people are living with a musculoskeletal disorder, and well over two-thirds of these individuals will seek conservative care such as rehabilitation or pharmacotherapy as a first-line treatment.[1] Unfortunately, many individuals with musculoskeletal disorders are recalcitrant to routine conservative care, and it is plausible that a sub-group of individuals receiving orthobiologic interventions have been minimally or non-responsive to prior rehabilitation efforts. Thus, the need for formal post-procedural rehabilitation may not be apparent.

In the authors' experience, formal rehabilitation following orthobiologic procedures may be pursued to mitigate impairments and accelerate recovery. Additionally, when performed properly, many rehabilitation interventions offer cellular and molecular benefits synergistic to orthobiologics.[2] While the benefits of appropriate physical activity following an orthobiologic procedure are inarguably positive, a paucity of research exists to support the safety and efficacy of formal post-procedural rehabilitation as a best practice in the specialty area of regenerative medicine. Thus, an appraisal of post-procedural rehabilitation's overarching safety and efficacy is presented in the context of published outcomes and biological plausibility. The authors' experiences and perspectives on post-procedural rehabilitation are integrated into the discussion to bridge the gap between research and clinical practice.

Concerning safety and adverse events, a lack of literature exists to determine "help versus harm" from post-procedural rehabilitation conclusively. However, the outcomes of previously published research can be used to understand better the effects of incorporating post-procedural rehabilitation into standard practice. For example, a recent meta-analysis[3] conducted on studies evaluating the efficacy of mesenchymal stem cells for treating patients with knee osteoarthritis (N = 2385) reported significant improvements in pain and physical function with a wide-ranging (2–60%) prevalence of minor adverse events such as swelling and pain. The analysis concluded that performing post-procedural rehabilitation was associated with greater improvements in physical function and no differences in pain compared to groups not receiving rehabilitation. Although the analysis did not compare adverse events in the rehabilitation versus no rehabilitation groups, the impact of rehabilitation was clear in terms of superior physical function. Furthermore, it can be postulated that the absence of differences in pain suggests, at minimum, that rehabilitation did not harm or worsen.

Further evidence on post-procedural rehabilitation's relative efficacy and safety can be gleaned from published case series and case reports. In one study, a case series of four patients (7 knees) with knee osteoarthritis who received platelet-rich plasma (PRP), stromal vascular fraction cell therapy, and rehabilitation reported that all knees achieved improved pain, function, and quality of life with post-procedural pain that was minimal, only requiring paracetamol.[4] Two additional case series studies on patients with knee and shoulder osteoarthritis support the immediate integration of post-procedural rehabilitation based on outcomes; however, minor reports of swelling and pain in the first few days were reported at a rate of 20 and 30% of the patients, which does appear to exceed a previously reported multi-center study average of 12.1%.[5–7] Although the minor reports of pain and swelling appeared to resolve in a few days, it should be noted that patients all had severe osteoarthritis grade ≥ 3 and were advised to stay active immediately after the procedures. In another case series, the effects of PRP and rehabilitation (stretching and strengthening) were assessed on six patients with shoulder pain and spinal cord injury.[8] In the aforementioned case series, all participants were previously recalcitrant to prior efforts, and following care demonstrated improvements in shoulder pain and function with no adverse events reported, which may be of considerable value as wheelchair users are known to have shoulder pain at a much higher prevalence than the general population.[8,9] Furthermore, two case reports support the positive benefits of post-procedural rehabilitation following PRP injections[10,11] for rotator cuff tendinopathy and a partial tear of the distal triceps. Although the evidence is limited, one can conclude that formal post-procedural rehabilitation, at minimum, will lead to enhanced functional outcomes. Despite the absence of studies evaluating the safety of post-procedural rehabilitation, it can be reasonably assumed that improved functional outcomes are unlikely to occur in the presence of harm or heightened adverse events.

Arguably, the most interesting benefit of formal post-procedural rehabilitation is the synergistic cellular and molecular benefits to orthobiologic interventions. Generally speaking, the efficacy of regenerative medicine is likely to be enhanced when coupled with mechanical input and overload. Specifically, mechanotherapy or mechanotransduction describes the process whereby a physical overload or unaccustomed load (mechanical input) produces a signaling mechanism that travels from the extracellular to the intracellular region to initiate a cellular response (e.g., protein/collagen synthesis).[12] Mechanotransduction is the biological model underpinning many positive reactions to exercise at the cellular and molecular levels. For example, a body of evidence has indicated that resistance training focused on primarily loading the eccentric phase has been shown to improve the pathoanatomical appearance of tendinosis (decreased thickness and improved heterogeneity), increase muscle mechano-growth factor mRNA, decreased tumor necrosis factor alpha, and increased interleukin-10.[13-15] Other interesting outcome-based studies have shown increases in serum growth hormone and testosterone from high volume isometric contractions as

well as increases in Insulin-like growth factor from both isometric and eccentric overload exercises.[16,17] Further to this point, it appears that higher intensity (increased load and volume) resistance training decreases myostatin levels, which may be a solution to mitigate atrophy.[17] Lastly, evidence suggests that acute exercise mobilizes both stem and progenitor cells into peripheral blood as soon as 15 minutes after exercise and for up to 1 hour; however, it appears that the effects are intensity-dependent and do not occur with habitual or low-intensity exercise.[18–20] In summary, evidence strongly supports the cellular and molecular benefits of unaccustomed physical activity and overload. Readers who desire a more detailed approach to post-procedural care are encouraged to review the following articles for additional recommendations.[2,10,21]

In conclusion, post-procedural rehabilitation may be an effect modifier to patient outcomes. Although a lack of research exists to support post-procedural rehabilitation, the potential benefits can be gleaned from existing studies supporting the efficacy of exercise. Further to this point, the efficacy of regenerative medicine should be enhanced when coupled with mechanical input (e.g., loading and movement) based on the synergistic cellular and molecular benefits and physical functioning outcomes. There is currently no evidence to support harm when considering safety and the potential for an increase in adverse events. However, an absence of evidence does not imply evidence of absence, and overzealous or premature exercises most certainly increase the potential for mild adverse events such as pain and soreness. In the authors' experience, several measures can mitigate untoward responses to post-procedural rehabilitation. Specifically, the individual patient's needs at various stages of the recovery process may dictate the decision to begin, delay, or avoid formal rehabilitation. The patient's needs may include their pathoanatomical diagnosis (*still present at the time of initiating rehabilitation)*, patient response to adverse events from the orthobiologic procedure, physical demands of the patient's lifestyle, and willingness to participate in rehabilitation. When combined with an evidence-informed approach that considers biologic plausibility, these considerations should serve as the primary basis for answering the question of "nice to do or need to do."

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