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Minimally Invasive Therapies in the Treatment of Arthropathy

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Abstract

This literature review explores the efficacy of minimally invasive therapies that precede and delay surgical intervention in adult patients experiencing functional limitations and pain in major joints. The effectiveness of physical therapy and injections such as corticosteroids, hyaluronic acid, platelet-rich plasma, and mesenchymal stem cells (MSC) was evaluated. A comprehensive search of PubMed utilizing MeSH terms yielded 114 relevant studies, which were screened based on inclusion criteria of human studies published within the past five years. Keywords included mesenchymal stem cells, stem cells, mesenchymal, arthroplasty, and joints. Producing few results, inclusion criteria were later expanded to include studies within the past ten years, their references, articles citing results, and articles similar to results. Of note, the chondrotoxic nature of corticosteroid (CS) injections suggests alternative first-line therapies in hyaluronic acid (HA) and platelet-rich plasma (PRP), particularly in earlier stages of disease. Regarding MSC findings, low side-effect profiles with evidence of induced regeneration are encouraging, but studies that evaluate their effectiveness compared to other treatments are lacking. Although MSC therapies lack a robust evidence base, their potential warrants further investigation.

Introduction

- An estimated 27% of adults >45 years of age suffer osteoarthritis of the hip, surging to 42% those >75.
- Joint pain diminishes capacity and quality of life; worsens progression of life-style diseases such as obesity, non-insulin dependent diabetes, and cardiovascular disease.
- Arthropathy treatments vary in efficacy and reliability.
- This review evaluates common minimally invasive interventions and novel biologics such as MSC therapy.

Statement of the Problem

- Arthropathies are generally progressive in nature, ultimately requiring definitive treatment/arthroplasty.
- These treatments are highly invasive and come with substantial risks. Access in rural settings is limited.
- Physical therapies, while effective, require direct supervision and repeat treatment. Access may be limited.
- Other minimally invasive therapies have variable duration and effect, with minimal delay in surgical intervention.

Research Question

Does the use of mesenchymal stem cell therapies restore tissue integrity, functional utility, or significantly delay surgical intervention of major joints compared to conservative and minimally invasive alternatives in adult patients with functional deficit or pain in any major joint that involves damage to tendon, ligament, cartilage, or arthritic changes?

Literature Review – Convention

- Conservative physical therapies have a durable effect (Hando, 2012) in reducing pain, increasing range of motion, and improving physical function in injured or diseased joints (Abbot, 2013; Beselga, 2016).
- High-force manual therapies are more effective than low- or moderate-force treatments (Estébanez-de-Miguel, 2018), and patient education absent manual therapy is insufficient for symptom improvement (Poulson, 2013).
- Arthropathies are progressive via inflammation-proteolysis positive feedback (Matthiessen, 2017).
- Corticosteroid (CS) injections have wildly variable degrees and duration of effect (McCabe, 2016), with only 32.9% of patients showing symptom improvement greater than two weeks (Lai, 2018). >40% progress to surgical intervention within one year (Walter, 2019).
- CS injection accelerates degeneration, hastening the need for total joint replacement (10.2 months with versus 24.9 months without) (Hess, 2018). Risks of infection increase, worsened by repeat injections (Chambers, 2017)
- Hyaluronic acid (HA) injections are similarly reliable and effective compared to corticosteroids, but there is a several-week delay in symptom improvement (Tammachote, 2016; Brander, 2019; Wu, 2017).
- HA is most effective in mild to moderate disease states (Pagliocomi, 2018; Piccarilli, 2016), with improvements enhanced by concomitant physical therapy (Mauro, 2017).
- Platelet rich plasma (PRP) injections are effective adjuncts to physical therapy in the treatment of acute injury (Koch, 2018).
- Similar to HA, PRP is more reliably effective in mild to moderate disease states (Kraeutler, 2016). Compared to HA, PRP demonstrates greater degree of improvement (Dallari, 2016; Nouri, 2022).

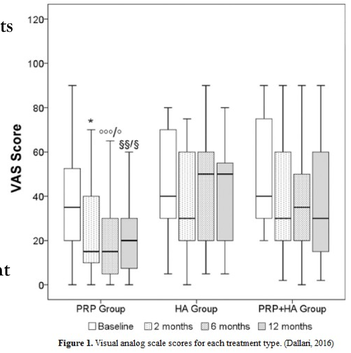

Figure 1. Visual analog scale scores for each treatment type. (Dallari, 2016)

Literature Review – MSC Therapy

- Commonly harvested from bone marrow or adipose tissue, MSCs are thought to differentiate into numerous cell lines, contribute to and coordinate tissue remodeling, modulate inflammation, and stimulate angiogenesis (Pak, 2018).
- Single-dose treatment of expanded bone marrow-derived MSC demonstrated significant, durable improvement of symptoms in 18 patients with hip, knee, or ankle arthropathy. There were no serious adverse events (Emadedin, 2015).
- MRI analysis demonstrated significant articular cartilage regeneration following treatment (Emadedin, 2015).

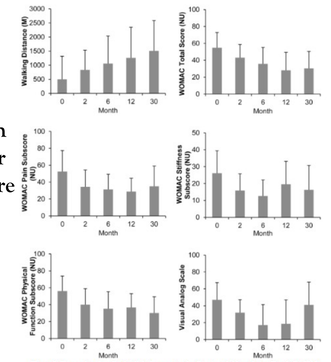

Figure 2. Change from baseline in clinical parameters in all osteoarthritis patients. (Emadedin, 2015)
WOMAC - Western Ontario and McMaster Universities Osteoarthritis Index
Visual Analog Scale - subjective pain measure

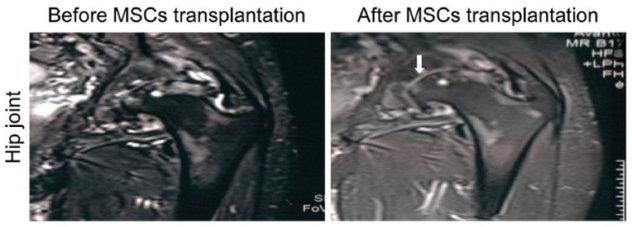

Figure 3. MRI analysis. (A) Sagittal T2 weighted MR image of patient with hip OA shows cartilage surface before MSC transplantation (arrow). (B) Note the predominant increase in cartilage thickness after MSC transplantation (arrow). (Emadedin, 2015)

- Substantial reductions in 15-year total knee arthroplasty rates in MSC transplantation to subchondral bone (20%) relative to intra-articular transplantation (70%) (Heringou, 2021)
- Single-dose treatment of adipose-derived MSC (ad-MSC) demonstrated significant improvements in pain, stiffness, and function in mild-to-moderate knee OA. Little or no benefit was demonstrated in patients with advanced OA (Bąkowski, 2021).
- Advanced knee OA responsive to single-dose treatment of expanded ad-MSC following arthroscopic abrasion with significant hyaline cartilage regeneration. (Freiteg, 2020)

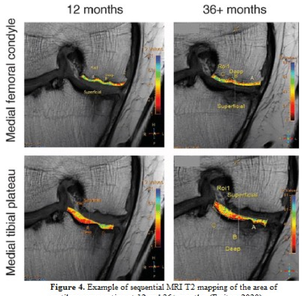

Figure 4. Example of sequential MRI T2 mapping of the area of cartilage regeneration at 12 and 36+ months. (Freiteg, 2020)

Discussion

Single dose responses in MSC therapies are dramatic and durable, both in symptom reduction and hyaline cartilage regeneration. Unfortunately, techniques and materials required to perform MSC transplantation preclude their use in clinical settings. Conventional treatments review reveals unreliable and chondrotoxic effect with CS use, with PRP and HA serving as safer alternatives. It is apparent throughout that each treatment is most effective when used earlier in the course of arthropathy.

Applicability to Clinical Practice

Corticosteroids, while a powerful and inexpensive tool in the treatment of arthralgia, come with consequences that patients pay in accelerated degeneration and symptom progression over the months and years that follow. Proving equally reliable and effective, alternative therapies such as hyaluronic acid and platelet-rich plasma treatments should be considered. Contrasting platelet-rich plasma, hyaluronic acid injections are shelf-stable and involve no harvest requirements or lengthy centrifugation process. As such, providers in the clinical setting may consider hyaluronic acid a lower-risk alternative to corticosteroids for persistent joint pain and dysfunction refractory to conservative measures. A review of the therapies above demonstrates a needed shift in first-line intra-articular injections for the treatment of arthropathy, and while the treatments above help to delay surgical intervention, definitive treatment is unlikely to be found through the use of mesenchymal stem cells given their equipment, laboratory, and imaging requirements.

References

Abbott, J. H., Robertson, M. C., Chapple, C., Pinto, D., Wright, A. A., Leon de la Barra, S., Baxter, G. D., Theis, J.-C., & Campbell, A. J. (2013). Manual therapy, exercise therapy, or both, in addition to usual care, for osteoarthritis of the hip or knee: A randomized controlled trial. 1: Clinical effectiveness. Osteoarthritis and Cartilage, 21(4), 525–534. https://doi.org/10.1016/j.joca.2012.12.014

Bąkowski, P., Kaszyński, J., Baka, C., Kaczmarek, T., Ciemniewska-Gorzela, K., Bąkowska-Żywicka, K., & Piontek, T. (2021) Patients with stage II of the knee osteoarthritis most likely benefit from the intra-articular injections of autologous adipose tissue—from 2 years of follow-up studies. Archives of Orthopaedic and Trauma Surgery, 143, 55–62. https://doi-org.ezproxylr.med.und.edu/10.1007/s00402-021-03979-w

Brander, V., Skerpnik, N., Petrella, R. J., Jiang, G. L., Accomando, B., & Vardanyan, A. (2019). Evaluating the use of intra-articular injections as a treatment for painful hip osteoarthritis: A randomized, double-blind, multicenter, parallel-group study comparing a single 6-mL injection of hylan G-F 20 with saline. Osteoarthritis and Cartilage, 27, 59–70. https://doi.org/10.1016/j.joca.2018.08.018

Chambers, A. W., Lacy, K. W., Liow, M. H. L., Manalo, J. P. M., Freiberg, A. A., & Kwon, Y.-M. (2017). Multiple hip intra-articular steroid injections increase risk of periprosthetic joint infection compared with single injections. Journal of Arthroplasty, 32(6), 1980–1983. https://doi.org/10.1016/j.arth.2017.01.030

Dallari, D., Stagni, C., Rani, N., Sabbioni, G., Pelotti, P., Torricelli, P., Tschon, M., & Giavaresi, G. (2016). Ultrasound-guided injection of platelet-rich plasma and hyaluronic acid, separately and in combination, for hip osteoarthritis. American Journal of Sports Medicine, 44(3), 664–671. https://doi.org/10.1177/0363546515620383

Emadedin, M., Ghorbani Liastani, M., Fazeli, R., Mohseni, F., Moghadasali, R., Mardpour, S., Hosseini, S. E., Niknejadi, M., Moeininia, F., Fanni, A. A., Eslaminejhad, R. B., Dizaji, A. V., Labibzadeh, N., Bahghi, A. M., Baharvand, H., & Aghdami, N. (2015). Long-term follow-up of intra-articular injection of autologous mesenchymal stem cells in patients with knee, ankle, or hip osteoarthritis. Archives of Iranian Medicine, 18(6), 336–344.

Estébanez-de-Miguel, E., Fortún-Agud, M., Jimenez-del-Barrio, S., Caudevilla-Polo, S., Bueno-Gracia, E., & Tricás-Moreno, J. M. (2018). Comparison of high, medium and low mobilization forces for increasing range of motion in patients with hip osteoarthritis: A randomized controlled trial. Musculoskeletal Science and Practice, 36, 81–86. https://doi.org/10.1016/j.msksp.2018.05.004

Freitag, J., Wickham, J., Shah, K., Li, D., Norsworthy, C., & Tenen, A. (2020). Mesenchymal stem cell therapy combined with arthroscopic abrasion arthroplasty regenerates cartilage in patients with severe knee osteoarthritis: a case series. In Regenerative Medicine,15, 1957–1977. Future Medicine Ltd. https://doi.org/10.2217/rme-2020-0128

Hando, B. R., Gill, N. W., Walker, M. J., & Garber, M. (2012). Short- and long-term clinical outcomes following a standardized protocol of orthopedic manual physical therapy and exercise in individuals with osteoarthritis of the hip: A case series. Journal of Manual & Manipulative Therapy, 20(4), 192–200. https://doi.org/10.1179/2042618612Y.0000000013

Heringou, P., Bouthors, C., Bastard, C., Flouzat Lachaniette, C. H., Rouard, H., & Dubory, A. (2021). Subchondral bone or intra-articular injection of bone marrow concentrate mesenchymal stem cells in bilateral knee osteoarthritis what better postpone knee arthroplasty at fifteen years? A randomized study. International Orthopaedics, 45(2), 391–399. https://doi-org.ezproxylr.med.und.edu/10.1007/s00264-020-04687-7

Hess, S. R., O'Connell, R. S., Bednarz, C. P., Waligora, A. C., Golladay, G. J., Jiranek, W. A., et al. (2018). Association of rapidly destructive osteoarthritis of the hip with intra-articular steroid injections. Arthroplasty Today, 4(2), 205–209. https://doi.org/10.1016/j.artd.2017.12.002

Kraeutler, M. J., Garabekyan, T., & Mei-Dan, O. (2016). The use of platelet-rich plasma to augment conservative and surgical treatment of hip and pelvic disorders. Muscles, Ligaments and Tendons Journal, 6(3), 410–419. https://doi.org/10.11138/mltj/2016.6.3.410

Koch, M., Mayr, F., Achenbach, L., Krutsch, W., Lang, S., Hilber, F., Weber, J., Pfeifer C.G., Woehl, R., Eichhorn, J., Zellner, J., Nerlich, M., Angele, P. (2018) Partial anterior cruciate ligament ruptures: advantages by intraligament autologous conditioned plasma injection and healing response technique—midterm outcome evaluation. BioMed Research International, 2018. https://doi.org/10.1155/2018/3204869

Phen, H. M., & Schenker, M. L. (2019). Minimizing posttraumatic osteoarthritis after high-energy intra-articular fracture. The Orthopedic Clinics of North America, 50(4), 433-443. https://doi-org.ezproxylr.med.und.edu/10.1016/j.ocl.2019.05.002

Lai, W. C., Arshi, A., Wang, D., Seeger, L. L., Motamedi, K., Levine, B. D., et al. (2018). Efficacy of intraarticular corticosteroid hip injections for osteoarthritis and subsequent surgery. Skeletal Radiology, 47(12), 1635–1640. https://doi.org/10.1007/s00256-018-3052-z

Mauro, G. L., Sanfilippo, A., & Scaturro, D. (2017). The effectiveness of intra-articular injections of Hyalubrix® combined with exercise therapy in the treatment of hip osteoarthritis. Clinical Cases in Mineral and Bone Metabolism, 14, 146–152. https://doi.org/10.11138/ccmbm/2017.14.1.146

Matthiessen, A., & Conaghan, P. G. (2017). Synovitis in osteoarthritis Current understanding with therapeutic implications. Arthritis Research & Therapy, 19(1), 18. https://doi.org/10.1186/s13075-017-1229-9

Nouri, F., Babaee, M., Peydayesh, P., Esmaily, H., & Raeissadat, S. A. (2022). Comparison between the effects of ultrasound-guided intra-articular injections of platelet-rich plasma (PRP), high molecular weight hyaluronic acid, and their combination in hip osteoarthritis A randomized clinical trial. BMC Musculoskeletal Disorders, 23, 856. https://doi.org/10.1186/s12891-022-05787-8

Pak, J., Lee, J. H., Pak, N., Pak, Y., Park, K. S., Jeon, J. H., et al. (2018). Cartilage regeneration in humans with adipose tissue-derived stem cells and adipose stromal vascular fraction cells: Updated status. International Journal of Molecular Sciences, 19(7). https://doi.org/10.3390/ijms19072146

Piccirilli, E., Oliva, F., Murè, M. A., Mahmoud, A., Foti, C., Tarantino, U., & Maffulli, N. (2016). Viscosupplementation with intra-articular hyaluronic acid for hip disorders: A systematic review and meta-analysis. Muscles, Ligaments and Tendons Journal, 6(3), 293–299. https://doi.org/10.11138/mltj/2016.6.3.293

Pogliacomi, F., Schiavi, P., Paraskevopulos, A., Leigheb, M., Pedrazzini, A., Ceccarelli, F., & Vaienti, E. (2018). When is indicated viscosupplementation in hip osteoarthritis? Acta Biomedica, 90(1-S), 67–74. https://doi.org/10.23750/abm.v90i1-S.8000

Poulsen, E., Hartvigsen, J., Christensen, H. W., Roos, E. M., Vach, W., & Overgaard, S. (2013). Patient education with or without manual therapy compared to a control group in patients with osteoarthritis of the hip: A proof-of-principle three-arm parallel group randomized clinical trial. Osteoarthritis and Cartilage, 21(10), 1494–1503. https://doi.org/10.1016/j.joca.2013.06.009

Tammachote, N., Kanitnate, S., Yakumpor, T., & Panichkul, P. (2016). Intra-articular, single-shot hylan G-F 20 hyaluronic acid injection compared with corticosteroid in knee osteoarthritis: A double-blind, randomized controlled trial. Journal of Bone and Joint Surgery - American Volume, 98, 885–892. https://doi.org/10.2106/JBJS.15.00544

Urits, I., Orhurhu, V., Powell, J., Murthy, A., Kiely, B., Shipon, S., Kaye, R. J., Kaye, A. D., Arron, B. L., Cornett, E. M., & Viswanath, O. (2020). Minimally invasive therapies for osteoarthritic hip pain: A comprehensive review. Current Pain and Headache Reports, 24(37). Springer Science+Business Media. https://doi.org/10.1007/s11916-020-00874-8

Walter, W. R., Bearison, C., Slover, J. D., Gold, H. T., & Gyftopoulos, S. (2019). Clinical and patient-reported outcomes after image-guided intra-articular therapeutic hip injections for osteoarthritis-related hip pain: A retrospective study. Skeletal Radiology, 48(5), 713–719. https://doi.org/10.1007/s00256-018-3113-3

Wu, B., Li, Y. M., & Liu, Y. C. (2017). Efficacy of intra-articular hyaluronic acid injections in hip osteoarthritis A meta-analysis of randomized controlled trials. Oncotarget, 8(49), 86865–86876. https://doi.org/10.18632/oncotarget.20995

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