The aggregated data from normal saline placebo arms of hyaluronic acid and other knee injection studies for osteoarthritis can be used as a historical control group for single-armed knee injection studies: Results of a systematic review

ABSTRACT

Purpose - The treatment of osteoarthritis (OA) by injection avoids surgery when successful. Platelet-rich plasma (PRP) and stem cell treatments are commonly performed for this purpose. Studies of these treatments are often criticized due to lack of a control group. However, numerous studies of hyaluronic acid and other injectates report detailed characteristics of their placebo arms in which saline was injected. Any benefit seen thus represents either a placebo effect or a saline treatment effect. Here, the magnitude and duration of this placebo/saline effect is characterized so that the accumulated data can serve as a historical control group against which the effects of treatment arms of knee injection studies can be measured

Methods - We performed a comprehensive search of the MEDLINE database for randomized clinical trials in adult humans of an injective therapy for osteoarthritis of the knee which included injection of ‘normal’ or physiological saline (0.9% NaCl) as a placebo cohort. Studies were excluded if the injective therapy was paired with any other intervention including physical therapy programs and surgical procedures, and if scoring instruments, either visual analog scale for pain or WOMAC total score (the Western Ontario and McMaster Universities Osteoarthritis Index), were not reported at least out to 3 months post-injection. Where WOMAC total scores were not reported, they were calculated from pain, stiffness, and function subscores. Mean scores were calculated for pre treatment and at 3 months and 6 months post treatment. Reported scores at other intervals were noted for secondary review.

Results - 32 studies met the criteria, 33 study arms met the criteria of which 24 reported WOMAC total scores and 19 reported VAS scores. The mean change in WOMAC scores peaked at 1-3 weeks, then declined below or near the minimal clinically important difference (MCID) by 12 weeks. The mean VAS scores similarly peaked at 1-3 weeks but never exceeded MCID at any time point.

Conclusions - The placebo, or therapeutic effect, of normal saline for knee injection for OA is small, peaks early, is short-lived and relatively consistent among studies. It can provide a useful, valid control group against which to measure the therapeutic effects of single armed knee injection studies of PRP, stem cell or other injection treatments for osteoarthritis.

INTRODUCTION:

The treatment of arthritis by injection decreases suffering and avoids surgery when successful. This is a significant benefit; surgical treatment of arthritis results in roughly 15,000 deaths annually in the United States [25, 33] and pharmacologic treatment with non-steroidal anti-inflammatory drugs (NSAIDs) has been estimated to result in 16,000 deaths annually in the USA. [43] Platelet-rich plasma and stem cell treatments are common biologic injective treatments performed for osteoarthritis with good results. [26] These autologous biologic injection treatments are completely safe, associated with zero mortality and morbidity, and are obviously much less expensive than surgery. Validation and adoption of these treatments would save lives, reduce suffering and drastically reduce costs. However, research on these injective treatments is hindered, and interpretation of efficacy data made difficult, when the trials that are conducted lack a control group. Controlled studies can be both prohibitively expensive and resisted by patients because of the placebo arm. However, there are a number of studies of hyaluronic acid (HA) and other injectates that report detailed characteristics of the results of saline injections used as placebo arms in these studies. Moreover, these studies often are highly similar in design, with standard intra-articular injection procedures, in most cases one to four injections at short intervals of time that are commensurate across studies, and using standard, validated scoring instruments to measure the effect on osteoarthritis symptoms. Here, studies whose control cohorts were injected with normal or physiological saline are considered, which is the standard in trials of injectate osteoarthritis treatments, although some trials use oral placebos or other injections, such as phosphate buffered saline. This is because it is disputed in the literature whether the improvements regularly seen in these symptoms in patient cohorts injected with normal saline is due to a placebo effect or due to some therapeutic effect of saline. [35] Whatever the cause of these improvements, the accumulated data of these comparable cohorts can serve as a historical control group, against which the effects of

platelet-rich plasma, stem cell injection, or other biologic treatment can be measured, thus obviating the need for a contemporaneous control group. The aim of this review is to characterize the magnitude and duration of the response to saline injection.

MATERIALS AND METHODS

A comprehensive search of the databases index by PubMed for randomized clinical trials in adult humans of an injective therapy for osteoarthritis of the knee which included saline inection as a placebo cohort was performed. The search was conducted in August 2021 using the terms: (knee AND (saline OR placebo OR controlled OR randomized) AND (arthritis OR osteoarthritis OR OA)) AND (adant OR arthrease OR arthrum OR artz OR artzal OR biohy OR clodronate OR cortisone OR durolane OR euflexxa OR fermathron OR gel-200 OR gel-one OR gelsyn-3 OR genvisc OR go-on OR hya-ject OR hya-joint OR hyalgan OR hyaluronate OR hyaluronic acid OR hylan g-f 20 OR hymovis OR interleukin-1 receptor antagonist OR lmwf-5a OR monovisc OR msc OR nasha OR nrd-101 OR nuflexxa OR orthovisc OR ostenil OR platelet-rich plasma OR replasyn OR slm-10 OR sodium hyaluronate OR steroid OR steroidal OR structovial OR sunevyl OR supartz OR suplasyn OR svf OR synject OR synovial OR synvisc OR synvisc-one OR tgf-ß1-expressing chondrocytes OR triamcinolone acetonide OR variofill OR zeel compositum). Studies were excluded if they used more than four injections of placebo, if the placebo contained anything other than ‘normal’ or physiological saline (0.9% NaCl), if the follow up interval was less than 3 months, if the injective therapy was paired with any other intervention including physical therapy programs and surgical procedures, or if they were not written in English. Outcome scores had to include either a visual analog scale for pain (VAS) and/or a total Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score. Outcome scores had to include either pre and post treatment scores or a change from pre to post treatment scores and had to report a score at either 3 months or at 6 months. VAS scores were included if they were global, at rest, or spontaneous. VAS scores after walking or other activity were not included. WOMAC scores were included if either a total WOMAC score was reported or if all three WOMAC subscores were reported and could be combined. WOMAC scores, which can be reported in a number of different scales, were all converted to a 0-96 point scale for analysis.

All selected papers were evaluated and WOMAC and VAS scores pre and post treatment were noted along with study duration. Mean scores were calculated for pre treatment and at 3 months and 6 months post treatment. Reported scores at other intervals were noted for secondary review.

RESULTS:

The search produced 1807 articles. Initial review of the papers resulted in 115 potential papers for more in depth review. In depth reading of these papers eliminated an additional 83 papers resulting in 32 studies that met the inclusion criteria and were reviewed for this paper. (Fig 1) One of the studies [4] had two placebo arms, corresponding to two different volumes of saline injected, resulting in 33 cohorts and a total of 2142 patients whose results were included.

Table 1: Included studies, VAS & WOMAC scores and change in scores at peak effect, 3 months and 6 months

	WOMAC Peak Effect			VAS Peak Effect				WOMAC Scores					VAS Scores				
Author/Year/ Cohort	Time (Wks)	Δ Score	Exceeds MCID?	Time (Wks)	Δ Score	Exceeds MCID?	# of Joints	Pre Treatment	3 MO	Δ 3 MO	6 MO	Δ 6 Mo	Pre Treatment	3 Mo	Δ 3 MO	6 MO	Δ 6 Mo
Altman 2004 [1]	12	13.2	Y	NA	NA	NA	174	46.9	33.7	13.2	35.8	11.1	NA	NA	NA	NA	NA
Altman 2009 [2]	*	*	NA	NA	NA	NA	259	NA	NA	NA	NA	14.4	NA	NA	NA	NA	NA
Baltzer 2009 [3]	7	13.0	Y	7	19.6	N	99	49.6	38.2	11.3	37.8	11.8	66.3	48.8	17.5	48.2	18.1
Bar-Or 2014 - 10ml [4]	*	*	Y	NA	NA	NA	81	42.6	29.0	13.6	NA	NA	NA	NA	NA	NA	NA
Bar-Or 2014 - 4ml [4]	*	*	Y	NA	NA	NA	83	44.3	30.4	13.9	NA	NA	NA	NA	NA	NA	NA
Brandt 2001 [6]	12	13.5	Y	NA	NA	NA	69	61.4	47.9	13.5	49.9	11.5	NA	NA	NA	NA	NA
Bunyaratavej 2001[7]	NA	NA	NA	16	28.0	Y	25	NA	NA	NA	NA	NA	45.0	18.0	27.0	20.0	25.0
Chao 2010 [8]	4	1.0	N	NA	NA	NA	29	45.3	45.9	-0.6	NA	NA	NA	NA	NA	NA	NA
Chevalier 2010 [9]	*	*	Y	NA	NA	NA	129	54.6	NA	NA	42.4	12.2	NA	NA	NA	NA	NA
Cole 2018 [10]	*	*	Y	NA	NA	NA	223	45.8	33.2	12.6	NA	NA	NA	NA	NA	NA	NA

Gomoll 2021 [12]	NA	NA	NA	12	19.9	Y	66	NA	NA	NA	NA	NA	81.0	61.1	19.9	62.5	18.5
Henrotin 2017 [13]	NA	NA	NA	26	35.6	Y	41	NA	NA	NA	NA	NA	66.4	36.2	30.2	30.8	35.6
Karlsson 2002 [16]	12	18.2	Y	3	21.0	Y	57	48.9	30.7	18.2	32.1	16.8	65.0	46.0	19.0	44.0	21.0
Khalifeh 2019 [17]	NA	NA	NA	24	36.0	Y	10	NA	NA	NA	NA	NA	69.0	NA	NA	33.0‡	36.0‡
Kotevoglu 2006 [18]	3	25.3	Y	NA	NA	NA	18	68.8	53.6	15.2	53.6	15.2	NA	NA	NA	NA	NA
Kul-Panza 2010 [19]	5	7.9	N	14	23.0	Y	22	70.6	63.6	7.0	NA	NA	65.0	42.0	23.0	NA	NA
Langworthy 2019 [20]	16	14.1	Y	8	17.0	N	60	51.2	38.9	12.3	38.5‡	12.7‡	63.0	46.0	17.0	47.0	16.0
Lee 2015 [21]	12	7.0	N	12	14.0	N	27	37.0	30.0	7.0	30.0	7.0	64.0	50.0	14.0	52.0	12.0
Lee 2019 [22]	26	11.4	Y	12	3.0	N	12	56.4	52.0	4.4	45.0	11.4	58.0	55.0	3.0	55.0	3.0
Lin 2019 [23]	26	1.5	N	NA	NA	NA	27	46.6	47.1	-1.1	45.1	1.5	NA	NA	NA	NA	NA
McCormack 2017 [25]	6	31.4	Y	NA	NA	NA	69	54.0	25.4	28.7	23.8	30.2	NA	NA	NA	NA	NA
Mendes 2019 [27]	12	13.8	Y	12	23.0	Y	35	47.1	33.3	13.8	NA	NA	45.0	22.0	23.0	NA	NA
Patel 2013 [28]	6	-1.2	N	*	*	N	46	45.5	50.7	-5.2	53.1	-7.6	45.7	NA	NA	46.1	-0.4
Ravaud 1999 [32]	NA	NA	NA	1	10.7	N	28	NA	NA	NA	NA	NA	63.7	61.2	2.5	58.2	5.5
Rossini 2015 [34]	NA	NA	NA	16	38.2	Y	35	NA	NA	NA	NA	NA	55.4	21.1	34.3	NA	NA
Shapiro 2016 [36]	NA	NA	NA	26	21.0	Y	25	NA	NA	NA	NA	NA	29.0	10.0	19.0	8.0	21.0
Shrestha 2018 [37]	6	14.8	Y	2	10.3	N	58	56.5	56.1	0.4	NA	NA	67.3	69.0	-1.7	NA	NA
Smith 2016 [38]	8	15.0	Y	NA	NA	NA	15	46.0	37.0	9.0	44.0	2.0	NA	NA	NA	NA	NA
Strand 2012 [39]	*	*	N	NA	NA	NA	119	65.1	59.0	6.1	NA	NA	NA	NA	NA	NA	NA
VanderWeegen 2015 [41]	12	16.5	Y	12	9.8	N	97	40.8	22.5	16.5	28.8	12.0	24.6	14.8	9.8	21.5	3.1
Wobig 1998 [42]	NA	NA	NA	3	22.0	Y	54	NA	NA	NA	NA	NA	75.0	62.0	13.0	NA	NA
Wu 2018 [44]	26	16.6	Y	NA	NA	NA	20	28.8	13.4	15.4	12.2	16.6	NA	NA	NA	NA	NA
Yavuz 2012 [45]	NA	NA	NA	1	15.0	N	30	NA	NA	NA	NA	NA	76.0	74.0	2.0	NA	NA
Mean Scores	12.6	12.4		13.0	21.1			50.2	39.6	10.2	38.1	11.2	59.2	43.4	16.0	40.5	16.5
Total # Studies 32/Arms 33						# of Patients	2142										

* Only one endpoint reported, ‡ 24 weeks reported

All included studies are shown in Table 1 along with their WOMAC and VAS scores, if reported, for both 3 months and 6 months. Only two studies had follow up of the placebo arm beyond 6 months [38] [12] . The change in score was calculated for both 3 months and 6 months. For all studies that reported at least two post treatment scores, the peak change in score and week post-treatment that the peak score occurred were calculated.

There were 24 study arms that reported WOMAC scores. Twenty-two reported 3 months scores and 16 reported 6 month scores. Mean WOMAC declined from 50.2 pre-treatment, 39.6 at three months post-treatment and 38.1 at 6 months (scale 0-96 with 0 best). The mean change in scores was 10.2 at 3 months and 11.2 at 6 months. An AOSSM Outcome Task Force lead by Irrgang [14] reported that the minimal clinically important difference (MCID) for the WOMAC total score for knee osteoarthritis was 11.5 on a 100 point scale, which is the equivalent of 11.0 on a 96 point scale. The mean change in WOMAC scores were just above this number at the peak time, below it at 3 months and equal to the MCID at 6 months. Of the 24 study arms that included WOMAC scores, 18 of the studies reported a peak change or single score above the MCID. Six of the studies never had a score that exceeded the MCID.

Follow up scores at all additional points of time were extracted and the change in WOMAC scores calculated. Scores were aggregated in four groups; follow up at 1-3 weeks, 4-8 weeks, 12-16 weeks, and 24 to 26 weeks. If more than one score was reported in a time range, the highest reported scores were used. There were only 3 scores reported between 16 and 24 weeks, so this interval was not included. The mean outcomes are shown in Figure 2 along with the MCID. Improvement from treatment with placebo was strongest in the first couple weeks after treatment and rapidly fell so that by 3 months improvement levels were below MCID and remained below or near the MCID level after that point.

There were 19 study arms that included VAS scores. Seventeen reported 3 months scores and 13 reported 6 month scores. Mean VAS declined from 59.2 pre-treatment, 43.4 at three months post-treatment and 40.5 at 6 months (scale 0-100, 0 best). The mean change in scores

was 16.0 at 3 months and 16.5 at 6 months. Tubach [40] reported the MCID for knee osteoarthritis for a VAS pain score was 19.9. The mean change in VAS scores was below this for all reported points. Ten of the studies reported a peak change above the MCID and 9 reported scores that were below the MCID at all times.

Follow up scores at all additional points of time were extracted and the change in VAS scores calculated. Scores were aggregated in four groups; follow up at 1-3 weeks, 4-8 weeks, 12-16 weeks, and 24 to 26 weeks. If more than one score was reported in a time range, the highest reported scores were used. There were only 3 scores reported between 16 and 24 weeks, so this interval was not included. The mean outcomes are shown in Figure 3 along with the MCID. Improvement from treatment with placebo, although always below the MCID, was strongest at 1 to 3 weeks after treatment and fell after that point.

DISCUSSION:

The majority of placebo arms of these studies showed improvement from baseline to 12 weeks and 26 weeks. However, these improvement levels were small and peaked fairly quickly after treatment. The mean change in both WOMAC and VAS peaked in the 1 to three week period after treatment and dropped off after that. While the initial improvement in WOMAC scores was above the MCID, they quickly fell below that level at 12 weeks and just at the MCID at 26 weeks. VAS scores never reached the level of MCID. These changes demonstrate that there is a definite effect, placebo or therapeutic, after injection of saline into the knee joint but that the effect is neither strong or of long duration. If the placebo is being used to compare to a short term treatment such as cortisone, then the placebo effect may make efficacy harder to determine. However, for treatment of injections of longer expected effectiveness, the placebo effect becomes less relevant. For HA injections, whose effect can be expected to last 26 weeks, the placebo effect can be expected to have further attenuated, and for PRP and stem cell treatments whose effects may last a year or more, the placebo effects will have attenuated further still. While more studies with similar placebo cohorts and longer follow up are needed to fully characterize this attenuation, an upper bound for the placebo effect at these later follow up times can be determined by its attenuation already by six months.

While placebo controlled studies remain the gold standard, such studies are extremely expensive and complicated to carry out and poorly received by patients who want clinical improvement, not the chance of extending their pain by receiving a placebo. They recognize that biologic treatments have shown efficacy and do not want to suffer by getting placebo treatment. Indeed, it is ethically wrong to provide a placebo as an alternative when it is clear that the treatment arm is efficacious. The only justification for doing so is that insurance and other payers insist on these studies to authorize treatment. However treatment should be indicated based on medical data, not because of the habits and biases of insurance companies who are much more comfortable with pharmaceutical drugs and their evidence standards and so far have lacked the flexibility to evaluate biologic, non-pharmaceutical treatments appropriately.

This is especially true for treatment modalities such as PRP (platelet-rich plasma) and autologous mesenchymal stem cells, where clinical efficacy has already been shown in dozens of studies. [5, 11, 15, 46, 31] For treatments such as these, which have unquestionably proven to be safe [30] and also have definite evidence of efficacy, the requirement that only placebo-controlled studies be considered as legitimate has a chilling effect on beneficial research. This requirement also introduces bias against autologous treatment and in favor of either pharmaceutical treatments or allogeneic biologic treatments. Because randomized placebo-controlled studies engender massive costs, the costs will only be incurred if a sufficient payoff exists later to warrant them. Realistically, only pharmaceutical companies have the funds to carry out these types of clinical trials. Since autologous tissue treatments cannot be patented and will not create large returns like a patented drug or allogeneic cell line, they are understandably not funded by pharmaceutical companies. This is unfortunate, because in all areas of medicine, autologous tissues have been shown to be safe, as or more effective than allogeneic tissues and significantly less expensive. Thus a requirement that studies be placebo-controlled to be believed exerts a chilling effect on the most effective regenerative medicine treatments – autologous tissue.

Fortunately however, the numerous billion dollar studies paid for by pharmaceutical companies have produced a large literature of placebo treated patients which are perfectly suited to serve as historical controls for single arm treatment studies of PRP, stem cell and other biologic treatments. The “placebo” in all of the studies is saline. It has been argued that saline is not actually a placebo but rather has a therapeutic

effect. [35] Even if this is true it is a suitable historical control group against which to compare other injection treatments. Furthermore it allows comparison both by magnitude of effect and duration of effect to other proposed treatments.

A review of the literature found two other studies that looked at the results of saline injections into the knee. [29, 35] Both of these studies concluded that saline injections provided relief of symptoms and out to at least six months. The mean VAS scores reported in these papers are very similar to the numbers found here, however the improvements are interpreted as significant because the MCID used was 13.7 instead of 19.9 so all the scores were above the MCID. The MCID of 13.7 used was initially calculated based on rotator cuff pain, not knee pain. The 19.9 value used here was based on knee pain and therefore is more likely to be accurate for this situation. If this value is used, all of the VAS scores fall below the MCID at all points in time. The WOMAC score MCIDs for both papers are substantially lower than the one used in this paper. Saltzman [35] reported a 6 month WOMAC score (the only time point reported) was 11.34, which is almost identical to the 11.2 reported here. However, this paper used 8.6 for the MCID instead of 11 as used here. Previtali [29] reported both higher scores at all time points and a lower MCID (6.4) than in this paper. Even applying the MCID of 11 used here, all WOMAC scores would be substantially above the MCID. The authors support the use of the higher MCID of 11.0 for the WOMAC scores, which is based on the AOSSM Outcomes Task Force report. [14] There are multiple ways of calculating a minimum clinically important difference, and their interpretation is open to controversy. What is more important is that the results of Previtali et al. in terms of magnitude of effect differ mainly because that review included studies whose placebo cohorts received more than 4 injections, including cohorts receiving up to 20 injections at regular intervals, in studies with correspondingly longer follow up times. This review only included cohorts with receiving four injections, which is standard in the published efficacy trials of hyaluronic acid and other injectates, so that the comparison of the magnitude and duration of the placebo effect can be characterized. If placebo cohort patients are still regularly receiving injections even as the efficacy of these injections is being measured at late follow up dates, these efficacy data cannot be appropriately compared to other cohorts with fewer and earlier injections. The trials considered in this review were selected to have commensurate study designs, allowing a useful comparison of their findings.

In this study, the peak magnitude of effect generally hovered around or below the MCID. The VAS scores were consistently below the MCID, while the WOMAC scores peaked early then dropped quickly and were attenuated substantially by six months. Thus any injection treatment which shows a substantially larger magnitude of effect within the corresponding time frame can reasonably claim to show significant efficacy over placebo without having to overcome the ethical and financial challenges of creating a placebo arm. An aggregated control group such as this one provides a more robust point of reference than a single historical control group. The authors have used the above results to study the efficacy of their own treatments and report for publication. It is hoped that the medical community will recognize the utility and validity of this approach for the benefit of patients.

CONCLUSION:

The accumulated body of placebo arms of pharmaceutical studies of hyaluronic acid so-called viscosupplementation treatments and other injectates can be usefully aggregated to provide a valid historical control treatment arm against which to compare and validate other injection treatments for arthritis – especially autologous PRP and stem cell treatments.

The authors declare no conflicts of interest.

REFERENCES

[1] Altman RD, Akermark C, Beaulieu AD, Schnitzer T (2004) Efficacy and safety of a single intra-articular injection of non-animal stabilized hyaluronic acid (NASHA) in patients with osteoarthritis of the knee. Osteoarthritis Cartilage. 12(8):642-9.

[2] Altman RD, Rosen JE, Bloch DA, Hatoum HT, Korner P (2009) A double-blind, randomized, saline-controlled study of the efficacy and safety of EUFLEXXA for treatment of painful osteoarthritis of the knee, with an open-label safety extension (the FLEXX trial). Semin Arthritis Rheum. 39(1):1-9.

[3] Baltzer AW, Moser C, Jansen SA, Krauspe R (2009) Autologous conditioned serum (Orthokine) is an effective treatment for knee osteoarthritis. Osteoarthritis Cartilage. 17(2):152-60.

[4] Bar-Or D, Salottolo KM, Loose H, Phillips MJ, McGrath B, Wei N, Borders JL, Ervin JE, Kivitz A, Hermann M, Shlotzhauer T, Churchill M, Slappey D, Clift V (2014) A randomized clinical trial to evaluate two doses of an intra-articular injection of LMWF-5A in adults with pain due to osteoarthritis of the knee. PLoS One. 9(2):e87910.
[5] Belk JW, Kraeutler MJ, Houck DA, Goodrich JA, Dragoo JL, McCarty EC (2021) Platelet-Rich Plasma Versus Hyaluronic Acid for Knee Osteoarthritis: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Am J Sports Med. 49(1):249-260.
[6] Brandt KD, Block JA, Michalski JP, Moreland LW, Caldwell JR, Lavin PT (2001) Efficacy and safety of intraarticular sodium hyaluronate in knee osteoarthritis. ORTHOVISC Study Group. Clin Orthop Relat Res. (385):130-43.
[7] Bunyaratavej N, Chan KM, Subramanian N (2001) Treatment of painful osteoarthritis of the knee with hyaluronic acid. Results of a multicenter Asian study. J Med Assoc Thai. 84 Suppl 2:S576-81.
[8] Chao J, Wu C, Sun B, Hose MK, Quan A, Hughes TH, Boyle D, Kalunian KC (2010) Inflammatory characteristics on ultrasound predict poorer longterm response to intraarticular corticosteroid injections in knee osteoarthritis. J Rheumatol. 37(3):650-5.
[9] Chevalier X, Jerosch J, Goupille P, van Dijk N, Luyten FP, Scott DL, Bailleul F, Pavelka K (2010) Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomised, multicentre, double-blind, placebo controlled trial. Ann Rheum Dis. 69(1):113-9.
[10] Cole B, McGrath B, Salottolo K, Bar-Or D (2018) LMWF-5A for the Treatment of Severe Osteoarthritis of the Knee: Integrated Analysis of Safety and Efficacy. Orthopedics. 41(1):e77-e83.
[11] Dai WL, Zhou AG, Zhang H, Zhang J (2017) Efficacy of Platelet-Rich Plasma in the Treatment of Knee Osteoarthritis: A Meta-analysis of Randomized Controlled Trials. Arthroscopy. 33(3):659-670.e1.
[12] Gomoll AH, Farr J, Cole BJ, Flanigan DC, Lattermann C, Mandelbaum BR, Strickland SM, Zaslav KR, Kimmerling KA, Mowry KC (2021) Safety and Efficacy of an Amniotic Suspension Allograft Injection Over 12 Months in a Single-Blinded, Randomized Controlled Trial for Symptomatic Osteoarthritis of the Knee. Arthroscopy. 37(7):2246-2257.
[13] Henrotin Y, Berenbaum F, Chevalier X, Marty M, Richette P, Rannou F (2017) Reduction of the Serum Levels of a Specific Biomarker of Cartilage Degradation (Coll2-1) by Hyaluronic Acid (KARTILAGE® CROSS) Compared to Placebo in Painful Knee Osteoarthritis Patients: the EPIKART Study, a Pilot Prospective Comparative Randomized Double Blind Trial. BMC Musculoskelet Disord. 18(1):222.
[14] Irrgang J, Anderson A, Dunn W (2012) Summary of clinical outcome measures for sports-related knee injuries, Baltimore, MD: AOSSM Outcomes Task Force.
[15] Jevotovsky DS, Alfonso AR, Einhorn TA, Chiu ES (2018) Osteoarthritis and stem cell therapy in humans: a systematic review. Osteoarthritis Cartilage. 26(6):711-729.
[16] Karlsson J, Sjögren LS, Lohmander LS (2002) Comparison of two hyaluronan drugs and placebo in patients with knee osteoarthritis. A controlled, randomized, double-blind, parallel-design multicentre study. Rheumatology (Oxford). 41(11):1240-8.
[17] Khalifeh Soltani S, Forogh B, Ahmadbeigi N, Hadizadeh Kharazi H, Fallahzadeh K, Kashani L, Karami M, Kheyrollah Y, Vasei M (2019) Safety and efficacy of allogenic placental mesenchymal stem cells for treating knee osteoarthritis: a pilot study. Cytotherapy. 21(1):54-63.

[18] Kotevoglu N, Iyibozkurt PC, Hiz O, Toktas H, Kuran B (2006) A prospective randomised controlled clinical trial comparing the efficacy of different molecular weight hyaluronan solutions in the treatment of knee osteoarthritis. Rheumatol Int. 26(4):325-30.
[19] Kul-Panza E, Berker N (2010) Is hyaluronate sodium effective in the management of knee osteoarthritis? A placebo-controlled double-blind study. Minerva Med. 101(2):63-72.
[20] Langworthy MJ, Conaghan PG, Ruane JJ, Kivitz AJ, Lufkin J, Cinar A, Kelley SD (2019) Efficacy of Triamcinolone Acetonide Extended-Release in Participants with Unilateral Knee Osteoarthritis: A Post Hoc Analysis. Adv Ther. 36(6):1398-1411.
[21] Lee MC, Ha CW, Elmallah RK, Cherian JJ, Cho JJ, Kim TW, Bin SI, Mont MA (2015) A placebo-controlled randomised trial to assess the effect of TGF-ß1-expressing chondrocytes in patients with arthritis of the knee. Bone Joint J. 97-B(7):924-32. Erratum in: Bone Joint J. (2015) 97-B(12):1732.
[22] Lee WS, Kim HJ, Kim KI, Kim GB, Jin W (2019) Intra-Articular Injection of Autologous Adipose Tissue-Derived Mesenchymal Stem Cells for the Treatment of Knee Osteoarthritis: A Phase IIb, Randomized, Placebo-Controlled Clinical Trial. Stem Cells Transl Med. 8(6):504-511.
[23] Lin KY, Yang CC, Hsu CJ, Yeh ML, Renn JH (2019) Intra-articular Injection of Platelet-Rich Plasma Is Superior to Hyaluronic Acid or Saline Solution in the Treatment of Mild to Moderate Knee Osteoarthritis: A Randomized, Double-Blind, Triple-Parallel, Placebo-Controlled Clinical Trial. Arthroscopy. 35(1):106-117.
[24] Maradit Kremers H, Larson DR, Crowson CS, Kremers WK, Washington RE, Steiner CA, Jiranek WA, Berry DJ (20150 Prevalence of Total Hip and Knee Replacement in the United States. J Bone Joint Surg Am. 97(17):1386-97.
[25] McCormack R, Lamontagne M, Vannabouathong C, Deakon RT, Belzile EL (2017) Comparison of the 3 Different Injection Techniques Used in a Randomized Controlled Study Evaluating a Cross-Linked Sodium Hyaluronate Combined With Triamcinolone Hexacetonide (Cingal) for Osteoarthritis of the Knee: A Subgroup Analysis. Clin Med Insights Arthritis Musculoskelet Disord. 10:1179544117725026.
[26] Mehranfar S, Abdi Rad I, Mostafav E, Akbarzadeh A (2019) The use of stromal vascular fraction (SVF), platelet-rich plasma (PRP) and stem cells in the treatment of osteoarthritis: an overview of clinical trials. Artif Cells Nanomed Biotechnol. 47(1):882-890.
[27] Mendes JG, Natour J, Nunes-Tamashiro JC, Toffolo SR, Rosenfeld A, Furtado RNV (2019) Comparison between intra-articular Botulinum toxin type A, corticosteroid, and saline in knee osteoarthritis: a randomized controlled trial. Clin Rehabil. 33(6):1015-1026.
[28] Patel S, Dhillon MS, Aggarwal S, Marwaha N, Jain A (2013) Treatment with platelet-rich plasma is more effective than placebo for knee osteoarthritis: a prospective, double-blind, randomized trial. Am J Sports Med. 41(2):356-64.
[29] Previtali D, Merli G, Di Laura Frattura G, Candrian C, Zaffagnini S, Filardo G (2021) The Long-Lasting Effects of "Placebo Injections" in Knee Osteoarthritis: A Meta-Analysis. Cartilage. 13(1_suppl):185S-196S.
[30] Prodromos C, Rumschlag T (2021) Injection of Autologous Mesenchymal Cells for the Treatment of Arthritis Has So Far Been Found to Be Completely Safe, Current Stem Cell Research and Therapy, Accepted for Publication.
[31] Prodromos C, Finkle S, Rumschlag T, Lotus J (2020) Autologous Mesenchymal Stem Cell Treatment is Consistently Effective for the Treatment of Knee Osteoarthritis: The Results of a Systematic Review of Treatment and Comparison to a Placebo Group. Medicines (Basel). 7(8):42.

[32] Ravaud P, Moulinier L, Giraudeau B, Ayral X, Guerin C, Noel E, Thomas P, Fautrel B, Mazieres B, Dougados M (1999) Effects of joint lavage and steroid injection in patients with osteoarthritis of the knee: results of a multicenter, randomized, controlled trial. Arthritis Rheum. 42(3):475-82.
[33] Ritter MA, Harty LD, Davis KE, Meding JB, Berend M (2003) Simultaneous bilateral, staged bilateral, and unilateral total knee arthroplasty. A survival analysis. J Bone Joint Surg Am. 85(8):1532-7.
[34] Rossini M, Adami S, Fracassi E, Viapiana O, Orsolini G, Povino MR, Idolazzi L, Gatti D (2015) Effects of intra-articular clodronate in the treatment of knee osteoarthritis: results of a double-blind, randomized placebo-controlled trial. Rheumatol Int. 35(2):255-63.
[35] Saltzman BM, Leroux T, Meyer MA, Basques BA, Chahal J, Bach BR Jr, Yanke AB, Cole BJ (2017) The Therapeutic Effect of Intra-articular Normal Saline Injections for Knee Osteoarthritis: A Meta-analysis of Evidence Level 1 Studies. Am J Sports Med. 45(11):2647-2653.
[36] Shapiro SA, Kazmerchak SE, Heckman MG, Zubair AC, O'Connor MI (2017) A Prospective, Single-Blind, Placebo-Controlled Trial of Bone Marrow Aspirate Concentrate for Knee Osteoarthritis. Am J Sports Med. 45(1):82-90.
[37] Shrestha R , Shrestha R , Thapa S , Khadka SK , Shrestha D (2018) Clinical Outcome following Intra-articular Triamcinolone Injection in Osteoarthritic Knee at the Community: A Randomized Double Blind Placebo Controlled Trial. Kathmandu Univ Med J (KUMJ). 16(62):175-180.
[38] Smith PA (2016) Intra-articular Autologous Conditioned Plasma Injections Provide Safe and Efficacious Treatment for Knee Osteoarthritis: An FDA-Sanctioned, Randomized, Double-blind, Placebo-controlled Clinical Trial. Am J Sports Med. 44(4):884-91.
[39] Strand V, Baraf HSB, Lavin PT, Lim S, Hosokawa H (2012) A multicenter, randomized controlled trial comparing a single intra-articular injection of Gel-200, a new cross-linked formulation of hyaluronic acid, to phosphate buffered saline for treatment of osteoarthritis of the knee. Osteoarthritis Cartilage. 20(5):350-356.
[40] Tubach F, Ravaud P, Baron G, Falissard B, Logeart I, Bellamy N, Bombardier C, Felson D, Hochberg M, van der Heijde D, Dougados M (2005) Evaluation of clinically relevant changes in patient reported outcomes in knee and hip osteoarthritis: the minimal clinically important improvement. Ann Rheum Dis. 64(1):29-33.
[41] van der Weegen W, Wullems JA, Bos E, Noten H, van Drumpt RA (2015) No difference between intra-articular injection of hyaluronic acid and placebo for mild to moderate knee osteoarthritis: a randomized, controlled, double-blind trial. J Arthroplasty. 30(5):754-7.
[42] Wobig M, Dickhut A, Maier R, Vetter G (1998) Viscosupplementation with hylan G-F 20: a 26-week controlled trial of efficacy and safety in the osteoarthritic knee. Clin Ther. 20(3):410-23.
[43] Wolfe MM, Lichtenstein DR, Singh G (1999) Gastrointestinal toxicity of nonsteroidal antiinflammatory drugs. N Engl J Med. 340(24):1888-99. Erratum in: N Engl J Med (1999) 341(7):548.
[44] Wu YT, Hsu KC, Li TY, Chang CK, Chen LC (2018) Effects of Platelet-Rich Plasma on Pain and Muscle Strength in Patients With Knee Osteoarthritis. Am J Phys Med Rehabil. 97(4):248-254.
[45] Yavuz U, Sökücü S, Albayrak A, Oztürk K (2012) Efficacy comparisons of the intraarticular steroidal agents in the patients with knee osteoarthritis. Rheumatol Int. 32(11):3391-6.

[46] Yubo M, Yanyan L, Li L, Tao S, Bo L, Lin C (2017) Clinical efficacy and safety of mesenchymal stem cell transplantation for osteoarthritis treatment: A meta-analysis. PLoS One. 12(4):e0175449.

Figure 1: Study Selection

Figure 2: Mean Change in WOMAC Scores

Figure 3: Mean Change in VAS Scores