Systematic Review

Placenta-Derived Products Demonstrate Good Safety Profile and Overall Satisfactory Outcomes for Treating Knee Osteoarthritis: A Systematic Review of Clinical Evidence

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Purpose: To summarize the available evidence regarding the clinical application of placenta-derived products to treat knee osteoarthritis (OA), underlining the differences existing among products, their preparation methods, and the clinical results reported so far. **Methods:** A research on PubMed, Cochrane, and Google Scholar databases was performed. The following inclusion criteria for relevant articles were used: (1) randomized controlled trials (RCTs), prospective and retrospective studies, on humans; (2) written in English; (3) published in indexed journals in the last 10 years (2011-2022); and (4) dealing with the use of placenta-derived products for the treatment of knee OA. Exclusion criteria were articles written in other languages; animals or in vitro trials; reviews; and trials analyzing other applications of placenta-derived products not related to knee OA. **Results:** In total, 16 studies were included in the present systematic review. Five studies investigated placenta-derived products as an augmentation during surgical procedures, whereas 11 studies were focused on the injective approach only. Of these, only 4 were RCTs and were all from the injective approach group. Potential risk of bias was carried out using Cochrane Risk of Bias 2 tool for RCTs and a modified Coleman approach for nonrandomized studies, revealing for both an overall insufficient quality. Clinical outcomes reveal excellent safety profile and notable efficacy, despite the different types of products used and different administration methods adopted. **Conclusions:** Placental products showed a good safety profile and overall satisfactory outcomes for the treatment of knee OA. **Level of Evidence:** Level IV, systematic review of Level II, III and IV studies.

Knee osteoarthritis (OA) is one of the most prevalent causes of disability worldwide,[1] representing more than 80% of the total burden of OA,[2] and affecting 15% of people aged 85 years and older.[3] The conservative approaches[4] to the disease address relieving symptoms and postponing metal resurfacing.[5] However, given the questions that have arisen regarding the long-term safety of corticosteroid injections or the mixed evidence of hyaluronic acid (HA), injective treatments are moving forward to new products.[2,6-9] Therefore, in the last few years, attention has shifted toward the use of the so-called "ortho-biologics,"[10] defined as biological products, both autologous and homologous, that could promote tissue anabolism[11] and counteract pro-inflammatory stimuli, thus modulating the joint homeostasis toward tissue repair and healing.[12,13] Ortho-biologics include (1) platelet-rich plasma (PRP), a blood derivative containing a high concentration of platelets and a variety of growth factors[14-16]; and (2) mesenchymal stem cells (MSCs), harvested from different sources, such as bone marrow,[17] adipose tissue,[18] synovium, amniotic fluid, umbilical cord,[19] and placental tissue.[20,21]

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The authors report that they have no conflicts of interest in the authorship and publication of this article. Full ICMJE author disclosure forms are available for this article online, as supplementary material.

Received January 7, 2023; accepted March 21, 2023.

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0749-8063/238/$36.00

https://doi.org/10.1016/j.arthro.2023.03.033

Both in vitro and in vivo studies have shown PRP and MSCs to have immunomodulatory and anti-inflammatory effects, decreasing the secretion of pro-inflammatory cytokines like tumor necrosis factor-α and interferon-γ and increasing the secretion of the anti-inflammatory cytokine, such as interleukin-10.[20,22] In the everyday clinical practice, PRP has found an extensive application,[23] since it requires a simple blood harvesting and preparation kits that can be easily used in an outpatient setting. Regarding MSCs, bone marrow and adipose tissue are by far the most common harvest sources and, in most cases, their application involves the use of minimal manipulation strategies (e.g., filtration, centrifugation, and mechanical processing), since cell expansion is logistically more complex, extremely expensive, and burdened by strict regulations.[24-26]

In addition, the need of a harvesting procedure and the risks of donor site's complications led to the introduction of homologous products (including those derived from placenta), which might be considered as a valid alternative to autograft, allowing multiple injections while avoiding the concerns related to the harvesting.[27]

The rationale behind the use of cells derived from the placenta in the treatment of knee OA lies in the presence of growth factors and stem cells in these tissues which, in animal models, have shown to be chondroprotective.[28] For example, the presence of epidermal growth factor, transforming growth factor-α, keratinocyte growth factor, hepatocyte growth factor, and basic fibroblast growth factor could shift the intra-articular environment from a state of low-grade inflammation (which is present in OA) to a regenerative environment slowing the progression of OA itself.[29,30] Furthermore, the MSC present in these tissues interact with the synovium, downgrading the expression of matrix metalloproteinases and thereby reducing the expression of matrix-degrading enzymes, which are key contributors to the progression of OA.[31,32]

Early results have been encouraging, with studies showing pain reduction and improvement in patient-reported scores.[33-35] However, some concerns might rise on their safety profile and middle-term outcomes and, to date, there are no comprehensive reviews evaluating the safety and efficacy of these homologous products.

The aim of the present systematic review is to summarize the available evidence regarding the clinical application of placenta-derived products to treat knee OA, underlining the differences existing among products, their preparation methods, and the clinical results reported so far. Our hypothesis was that the use of placenta-derived products would result in satisfactory clinical outcomes (including excellent safety profile and good functional outcomes), with minimal adverse events.

Methods

Extensive research on the PubMed, Cochrane, and Google Scholar databases was performed on November 30, 2022, using the following words: ((placental) OR (umbilical) OR (Amniotic fluid) OR (Wharton's jelly) OR (wharton) OR (amniotic) OR (umbilical cord) OR (fetal) OR (cord blood) OR (cord cells) OR (placenta-derived) OR (placenta) OR (placenta-derived stem cells)) AND ((osteoarthritis) OR (knee cartilage) OR (chondral defects)). The screening process and analysis was conducted separately by 2 independent observers (A.G. and G.M.M.C.G.). First, the articles were screened by title and abstract. The following inclusion criteria for relevant articles were used during the screening: (1) randomized controlled trials (RCTs), prospective and retrospective studies, on humans; (2) written in English; (3) published in indexed journals in the last 10 years (2011-2022); and (4) dealing with the use of placenta-derived products for the treatment of knee OA. Exclusion criteria were articles written in other languages; animals or in vitro trials; reviews; and trials analyzing other applications of placenta-derived products not related to knee OA.

In the second step, the full texts of the selected articles were screened, with further exclusions according to the previously described criteria. The reference list of all the retrieved articles was further screened for identification of potentially relevant studies. A flowchart of the systematic review is provided in Figure 1. Discrepancies between the 2 reviewers were resolved by discussion and consensus and the results were reviewed by senior investigators (B.D.M. and E.K.). Relevant data were then extracted and collected in a unique database to be analyzed for the purposes of the present manuscript.

In case of RCTs, the risk of bias was assessed using the Cochrane Risk of Bias tool for Randomized Controlled Trials, which evaluates 7 different types of bias. Each of them, based on specific criteria, was classified "low risk," "high risk," or "unclear risk." Subsequently, the results of this assessment were converted to Agency for Healthcare Research and Quality standards, which ultimately rank the RCTs in "good quality," "fair quality," and "poor quality." For non-randomized controlled trials, quality assessment was performed following the Coleman methodology score modified by Kon et al.[36]

Results

A total of 16 studies were ultimately included in the present systematic review. Five studies investigated placenta-derived products as an augmentation during surgical procedures, whereas 11 studies were focused on the injective approach only. A synopsis of the features of the included studies is reported in Table 1 (surgical studies)[33,34,37-39] and Table 2 (injective studies).[35,40-49] Details on the preparation methods and

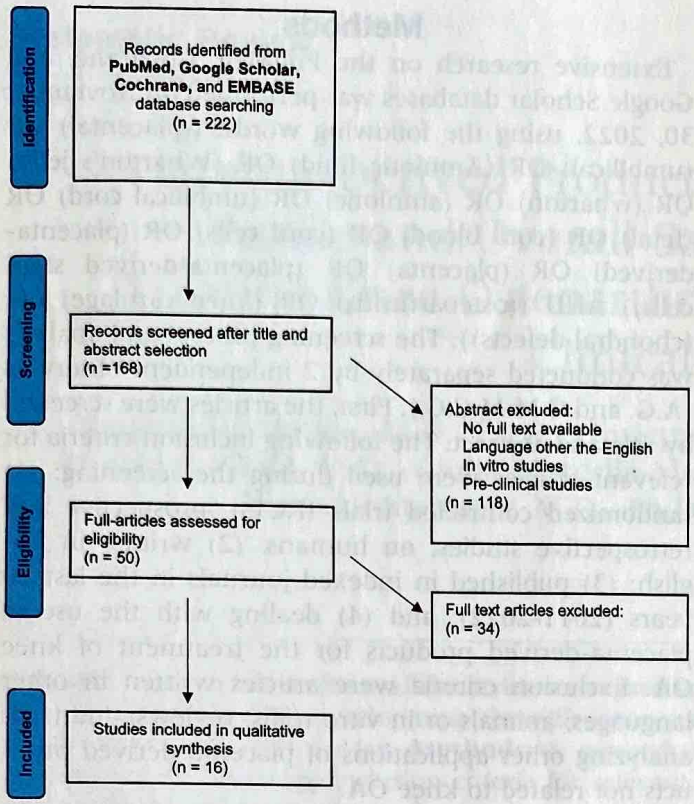

Fig 1. PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flowchart of the systematic literature review.

the biological features of the placenta-derived products are described in Table 3.[33-35,37-39,40-42,44-49]

Quality Assessment

Randomized Controlled Trials

A total of 4studies presented a randomized design.[35,40-42] Notably, among these, the trials by Farr et al.[35] and Gomoll et al.[42] investigated the same population of patients evaluated at 6- and 12-month follow-up, respectively. Furthermore, Gomoll et al.[43] later published a "cross-over study" reporting the results of patients previously randomized to saline who failed and were then retreated by placental product injection: although this follow-up study does not present a randomized design, it is strictly related to the original RCT and therefore it will be discussed jointly.

The Quality Assessment for the RCTs included in the present systematic review has been carried out using the Cochrane Risk of Bias 2 tool[50] and detailed in Table 4. According to the Agency for Healthcare Research and Quality standard, we found that none of the studies selected for this systematic review reached a standard of "good quality," and all the RCTs reached a standard of "fair quality." Regarding the process of generation of the random sequence, it was specified in all papers. It was based on block randomization in 3 studies,[35,40,42] and by the use of a random table in 1 study.[41] The allocation concealment method was not described in sufficient detail in 2 studies[40,41]; in the remaining 2 studies, the authors used the sealed envelope method.[35,42] One article reported outcomes in full[41]; one article excluded from the analysis patients who discontinued the treatment[40]; and the remaining 2 articles addressed the missing data using the last observation carried forward[35,42] and the mixed effects model for repeated measures.[42] Regarding the sample size calculation, only 2 studies clarified their power analysis method,[35,42] while in the remaining 2 studies, there was no mention of the power analysis methods.[40,41] Regarding the blinding methods, 2 studies used unmarked syringes and vials for patients blinding,[35,42] one study used syringes of equal volume and external aspect,[40] and one study covered the barrel of all injectable syringes.[41] Three studies used the CONSORT flow chart to describe grouping and flow of patients throughout the studies.[35,40,42] All studies were registered in a public registry of clinical trials, 3 in ClinicalTrials.gov[35,40,42] and 1 in the Iranian Registry of Clinical Trials.[41]

Nonrandomized Clinical Studies

The mean Coleman Methodology Score (CMS) modified by Kon et al.[36] of the 11 nonrandomized studies was 45.4 of 100 (Table 5), showing that the methodology represented in the available literature is still insufficient to consider it as "strong." The 11 studies investigating nonrandomized trials involved 501 knees from 455 patients. There was not strong uniformity in the selection of the population: 5 studies[33,34,37-39] that took into account more than 1 criteria (such as K-L, International Cartilage Regeneration and Joint Preservation Society grade, or thickness of the lesion) and 6 studies[44-49] that considered just 1 criteria (mainly K-L or the presence of OA). In almost all of those studies the criteria of inclusion and exclusion were reported, and the recruitment rate of the population was described in 3 studies[34,37,49] The population size of the studies was heterogenous, with a mean of CMS in this field of 5.7 of 10.3 studies. Three authors had a population size greater than 60.[34,38,47] The mean follow-up was overall mid-to-low, with just one study having a mean follow-up longer than 60 months.[33] Regarding the surgical procedures, more than one half of the studies performed one single procedure,[33,45-47] using a variety of placental stem cell–derived products such as human umbilical cord blood-derived mesenchymal stem cells (hUCB-MSC) combined with hyaluronic acid (HA) hydrogel,[33] cordonal blood PRP,[45] amniotic suspension allografts (ASA),[46] micronized dehydrated human amnion/chorion membrane,[47] and amniotic membrane/umbilical cord particulate.[48,49] One author[48] repeated the injection of amniotic membrane/umbilical cord in patients who did not show more than 30% of reduction in pain after 6 weeks. Some authors

Table 1. Clinical Studies Regarding the Use of Placental Derived Products in Combination With Surgical Procedures for the Treatment of Knee OA

Publication	Study Design	Level of Evidence	Disease	Therapeutic Protocol	Outcome	Patient Characteristics	Follow-up	Main Findings
Park et al.[33]	Prospective	III	OA K-L 3 + ICRS grade 4 cartilage lesions	Composite of culture-expanded allogeneic hUCB-MSCs and hyaluronic acid hydrogel ([CARTISTEM]) was applied to the lesion site.	VAS, IKDC, MRI	7 hUCB-MSCs Age: 29-77 y Sex: M-F = 5:2	6 months + 7 years safety and efficacy assessment	VAS and IKDC scores improved at 24 weeks. Outcomes were stable over 7 years of follow-up.
Song et al.[37]	Retrospective	IV	OA K-L IV, a full-thickness chondral defect ≥4 cm^2 of the medial femoral condyle (MFC), and a varus deformity ≥ 3°	A mixture of sodium hyaluronate and hUCB-MSC was implanted into the chondral defect and a high tibial osteotomy was performed in all patients.	IKDC, WOMAC, VAS, arthroscopy	25 hUCB-MSCs + osteotomy Sex: M-F = 2-23 Age: 64.9 ± 4.4 y	24 months	Clinical scores improved compared to preoperative scores
Chung et al.[38]	Retrospective	IV	ICRS grade III or IV cartilage defects (>2 cm^2), mechanical femorotibial varus angles >3°, and Kellgren-Lawrence (KL) grade 3 osteoarthritis	hUCB-MSC + osteotomy	IKDC, WOMAC, KSS, HSS	93 hUCB-MSCs + osteotomy Age: mean 56.6 y	Mean 1.7 y (range 1.0-3.5)	Significant improvements with signs of cartilage amelioration at second-look arthroscopy
Ryu et al.[39]	Retrospective	IV	OA K-L I-II; cartilage defects 2- 10 cm^2; ICRS grade IV	BMAC + HA scaffold vs hUCB-MSC	VAS, IKDC, KOOS, MRI	52 patients (BMAC: 25 knees; hUCB-MSCs: 27 knees). Sex: M-F (13:12 for BMAC group) (11:16 for hUCB-MSC group). Age: 39.64 ± 9.83 y for BMAC group, 53.93 ± 8.6 y for hUCB-MSC group	24 months	Clinical outcomes and MRI findings improved in both groups with no differences between groups.

(continued)

Table 1. Continued

Publication	Study Design	Level of Evidence	Disease	Therapeutic Protocol	Outcome	Patient Characteristics	Follow-up	Main Findings
Lee et al.[34]	Retrospective	IV	Medial tibiofemoral OA+ varus deformity	HTO+ MFX combined with BMAC or allogeneic hUCB-MSCs followed by a second-look arthroscopy	HSS score, KSS score, WOMAC	74 patients (42 BMAC, 32hUCB-MSCs) Sex: M-F = (6-36 in BMAC group, 6-26 in hUCB-MSCs) Age: 60.7 ± 4.1 y for BMAC group, 58.1 ± 3.6 y for hUCB-MSCs	Minimum 12 months (20.7 ± 6.1 for BMAC, 15.6 ± 2.8 for hUCB-MSCs)	Both treatments effective but hUCB-MSC procedure was more effective than the BMAC

BMAC, bone marrow aspirate concentrate; F, female; HA, hyaluronic acid; HSS, Hospital for Special Surgery; HTO, high tibial osteotomy; hUCB, human umbilical cord blood; ICRS, International Cartilage Regeneration and Joint Preservation Society; IKDC, International Knee Documentation Committee; K-L, Kellgren-Lawrence; KOOS, Knee Injury and Osteoarthritis Outcome Score; KSS, Knee Society Score; M, male; MFX, microfractures; MRI, magnetic resonance imaging; MSC, mesenchymal stromal cells; OA, osteoarthritis; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

combined different surgical procedures. Two authors performed a high tibial osteotomy combined with the implantation of hUCB-MSC into the chondral defect.[37,38] In one study, authors investigated about the effects of a combination of HTO with either bone marrow aspirate concentrate (BMAC) and microfractures or hUCB-MSC implantation.[34] One author injected intra-articularly hUCB-MSC with HA, followed by 2 more injections of HA 1 week apart each.[44] The difference about clinical outcomes between the implantation of hUCB-MSC and BMAC with HA scaffold was investigated in 1 study.[39] The descriptions of the performed surgical procedures and the rehabilitation postoperative protocols were overall accurate and precise, with a mean CMS of 5 of 5 and 3.09 of 5, respectively. In regards to the outcome analyzed, changes in magnetic resonance imaging (MRI) scans following the therapeutic procedure were taken into account in 4 studies of 11.[33,39,44,48] Histological biopsy during the follow-up was performed in 1 study.[33] The majority of the authors used reliable clinical scores (such as Western Ontario and McMaster Universities Osteoarthritis Index, Knee Injury and Osteoarthritis Outcome Score, visual analog scale score, and Knee Society Score), whereas one author used questionnaires based on the Patient Global Impression of Change and Global Perceived Improvement together with the simplified OMERACT–OARSI responder criteria for the evaluation of treatment response.[49] Concerning the study design, 5 of 11 studies were prospective[33,44,45,46,48]; the others were retrospective.

Clinical Outcomes

Surgical Application

All the studies assessing the efficacy of placental derived products combined to a surgical procedure are prospective or retrospective. The main finding of the retrieved articles was a significant improvement in clinical scores evaluated in all the cohorts. Lee et al.[34] was the only study in which HTO plus microfractures of the chondral lesion site was combined with BMAC or placental product. Clinical results were favorable in both groups, with a clear superiority for placental product treatment, even at the second-look arthroscopy at 12 months, which evidenced better cartilage regeneration. Chung et al.[38] and Song et al.[27] also applied the biological treatment combined to an HTO surgery, without a control group. They both reported improvements of the clinical outcomes and Chung et al.[38] also reported signs of cartilage regeneration during second-look arthroscopy. When analyzing the results coming from the implantation of scaffold of placental product alone, Park et al.[33] proved amelioration both in clinical outcomes and at MRI on the 7 patients treated, which persisted for the seven following years. Conversely, Ryu et al.[39] went further comparing scaffold with BMAC

Table 2. *Clinical Studies Regarding the Use of Injectable Placental-Derived Products for the Treatment of Knee OA*

Publication	Study Design	Level of Evidence	Disease	Therapeutic Protocol	Outcome	Patient Characteristics	Follow-up	Main Findings
Matas et al.[40]	RCT	II	OA K-L I-II-III	UC-MSCs repeated at 6 months vs UC-SCs followed by placebo at 6 months vs HA	WOMAC, VAS, SF-36, Patient Global Assessment, OARSI, Responder Index Criteria, MRI	26 (9 UC-MSCs at baseline and 6 months; 9 UC-MSCs only at baseline followed by placebo at 6 months; 8 HA at baseline and 6 months) Age: Mean 56 y	12 months	No differences in MRI scores were detected. WOMAC and VAS got significant lower scores in UC-MSC-2 group. No changes in function subscale and SF-36 were detected.
Farr et al.[35]	RCT	II	OA K-L II-III	4mL injection of ASA vs HA vs saline	EQ-5D-5L, KOOS, Tegner Activity Scale, VAS, SANE	200 (68 ASA, 64 HA, 68 saline)	6 months	Patients treated with ASA had significantly greater improvements in all scores
Khalifeh Soltani et al.[41]	Double-blind RCT	II	OA K-L II-IV	1 injection of placental MSCs vs 1 injection of saline	VAS, ROM, KOOS, MRI	20 patients	6 months	Statistically significant improvement until 8 weeks; not significant amelioration at 6 months. Chondral thickness was increased in approximately 10% of total knee joint cartilage
Gomoll et al.[42]	Single-Blinded RCT	II	OA K-L II-III	1 injection of ASA vs HA vs saline	EQ-5D-5L KOOS, SANE, VAS, Tegner Activity Scale, radiographs	200 (68 ASA, 64 HA, 68 saline) Sex: M-F = 35-33 for ASA, 33-31 for HA, 37-31 for saline) Age: 55.9 ± 12.3 y for ASA, 55.4 ± 11.0 for HA, 54.9 ± 9.8 for saline)	12 months	Clinical superiority of ASA over HA and saline
Gomoll et al.[43]	Crossover study	III	In the RCT,[34] subjects self-reporting unacceptable pain at 3 months were eligible to participate in a crossover arm.	1 injection of ASA	EQ-5D-5L KOOS, SANE, VAS, Tegner Activity Scale, radiographs	95 from HA and saline groups were crossed to ASA There were no statistically significant differences in baseline demographics and radiographic data between the HA and saline groups	12 months	Treatment with ASA following failed treatment with HA or saline resulted in significant improvements in KOOS and VAS scores compared with crossover baseline.

(continued)

Table 2. Continued

Publication	Study Design	Level of Evidence	Disease	Therapeutic Protocol	Outcome	Patient Characteristics	Follow-up	Main Findings
Dilogo et al.[44]	Single-arm, open-label study	III	OA K-L I-IV	2 mL of hUC-MSC + 2 mL of HA, followed by 2 injections of 2 mL of HA 1 week apart each other	VAS, IKDC, WOMAC, MRI	29 patients—57 knees Sex: M-F = 17-12 Age: 58.3 ± 9.6 y	12 months	Improvement of clinical scores with maximum reached at 6 months. No significant difference at MRI
Caiaffa et al.[45]	Prospective	III	OA K-L I-III	1 cordonal blood PRP injection	VAS, WOMAC, KOOS	25 patients Sex: M-F = 10-15 Mean age: 62.68 y	6 months	Allogeneic PRP can generate reliable therapeutic effect. The high content of tissue regenerative factors in cord blood platelets makes cordonal blood one of the ideal sources of PRP.
Vines et al.[46]	Prospective	III	Tibiofemoral grade III OA	1 ASA injection	KOOS, IKDC, SANE score	6 patients Sex: M-F = 2-4 Age: 55.3 y	12 months	Improvement in all the scores
Alden et al.[47]	Retrospective	IV	OA	1 injection mdHACM	KOOS	82 patients (100 knees)	6 months	All scores improved throughout the observation period.
Castellanos et al.[48]	Prospective	III	OA	1 ultrasound guided AMUC injection. Patients who did not show >30% reduction in pain (11) received a second injection of AMUC at 6 weeks.	WOMAC, Patient Global Assessment, medication usage, MRI	20 patients Sex: M-F = 5-15 Age: 71.0 ± 6.4 y	6 months	Significantly improved pain and function scores. Severity of bone marrow lesions decreased in 7 patients.
Mead and Mead[49]	Retrospective	IV	OA K-L III-IV	1 injection of AMUC	PGIC, GPI, OMERACT-OARSI	42 patients Sex: M-F = 24-18 Age: 74.1 ± 9.0 y	12 months	Effective in alleviating pain and improving function in patients with moderate to severe knee OA, with the potential to delay TKR for up to 12 months

AMUC, amniotic membrane umbilical cord; ASA, amniotic suspension allograft; EQ-5D-5L, European Quality of Life 5 Dimensions, 5-Level Version; F, female; GPI, Global Perceived Improvement; HA, hyaluronic acid; HSS, Hospital for Special Surgery; hUCB, human umbilical cord blood; IKDC, International Knee Documentation Committee; K-L, Kellgren-Lawrence; KOOS, Knee Injury and Osteoarthritis Outcome Score; KSS, Knee Society Score; M, male; mdHACM, micronized dehydrated human amnion/chorion membrane; MFX, microfractures; MRI, magnetic resonance imaging; MSC, mesenchymal stromal cells; OA, osteoarthritis; PGIC, patient global impression of change; PRP, platelet-rich plasma; RCT, randomized controlled trial; ROM, range of motion; SANE, Single Assessment Numeric Evaluation; UCB, umbilical cord blood; VAS, visual analog scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.

Table 3. Preparation Methods and Biological Features of the Placental-Derived Products

Product Name	Product Components	Preparation Details and Biological Features
CARTISTEM[33,34,37-39,44]	hUCB-MSCs and HA	Human umbilical cord blood is collected from umbilical veins at the time of neonatal delivery and stored in a cord blood bank. Mononuclear cells are separated and verified for positive (CD29, CD73, CD90, CD105, CD166) and negative (CD14, CD45) surface markers by flow cytometry, then cultured and mixed with HA
CELLISTEM[40]	UC-MSCs	Full-term human placentas by cesarean section within 3 hours from birth are aseptically stored and then Wharton's jelly is dissected into small fragments (1-2 mm), seeded and expanded
PLMSC[41]	Placental MSCs	Placenta from vaginal delivery is rinsed, minced into minute pieces, then seeded and cultured.
ASA[35,42,46]	Human amniotic membrane (HAM) and human amniotic fluid –derived cells (HAFCs).	Obtained during elective cesarean section. When collected, 2 mL of the ASA are thawed, and volume expanded with sterile 0.9% saline in order to be injected
AMUC[48,49]	Cryopreserved amniotic membrane and human umbilical cord MSCs.	A cryopreservation process at low temperatures is adopted: it devitalizes the living cells but retains the natural biological characteristics relevant to this tissue
mdHACM[47]	Micronized dehydrated human amnion/chorion membrane	Human amnion chorion membrane dehydrated and then micronized for suspension in saline
Cordonal blood PRP[45]	Form of cordonal PRP	Obtained from cord blood stored in public banks and cryopreserved without cryoprotectant below −40°C

ASA, amniotic suspension allograft; AMUC, amniotic membrane umbilical cord; HA, hyaluronic acid; hUCB, human umbilical cord blood; mdHACM, micronized dehydrated human amnion/chorion membrane; MSC, mesenchymal stromal cells; PRP, platelet-rich plasma.

and scaffold with placental products. Clinical results and MRI parameters improved in both groups, with no significant differences between groups.

Injective Application

Most of the clinical evidence concerning the use of placental products arises from injective application. Reviewing the results obtained, we can highlight some important findings: first, none of the patients treated reported any serious adverse event after the injection, conferring to injected placental products an excellent safety profile. Second, all the studies demonstrated improvement among the outcomes analyzed (Western Ontario and McMaster Universities Osteoarthritis Index, visual analog scale score, SF-36, European Quality of Life 5 Dimensions 5-Level Version, Knee Injury and Osteoarthritis Outcome Score, International Knee Documentation Committee, Tegner Activity Scale, Single Assessment Numeric Evaluation). Lastly, it seems that the favorable results achieved do not correlate to the type of preparation used, since most of the studies differ by the placental product adopted.

Starting from results coming from RCTs, only 2 studies evaluated the MRI response to placental products injection, when compared to control. In particular, Khalifeh Soltani et al.[41] observed increased chondral thickness at 6 months follow-up suggesting some form of cartilage regeneration, whereas the study by Matas et al.[40] did not report any significant variation. However, both the 2 aforementioned trials reported improvements in the clinical scores compared with placebo, up to 8 weeks in the study by Khalifeh Soltani et al.[41] and up to 12 months in the study by Matas et al.[40] The latter study has also shown superior clinical benefit in patients who received a second injection of UC-MSCs at 6 months compared with the group treated by a single administration. The other 2 RCTs available represent the largest studies carried out to date and were conducted on the same cohort of patients, evaluated at 6 months[35] and 12 months.[42] When comparing ASA with HA or saline, patients treated with a single 4-mL ASA injection achieved significant improvements in all the scores analyzed up to the latest follow-up. Significant superiority was demonstrated

Table 4. Quality Assessment of RCTs Using Cochrane RoB 2 Tool

	Randomization Process	Deviation From Intended Intervention	Missing Outcome Data	Measurement of the Outcome	Selection of the Reported Results	Overall
Matas et al.[40]	Some concerns	Low risk	Some concerns	Low risk	Some concerns	Some concerns
Farr et al.[35]	Low risk	Low risk	Some concerns	Low risk	Some concerns	Some concerns
Gomoll et al.[42]	Low risk	Low risk	Some concerns	Low risk	Some concerns	Some concerns
Soltani et al.[41]	Some concerns	Low risk	Low risk	Low risk	Some concerns	Some concerns

RoB 2, Risk of Bias 2.

Table 5. Study Quality Assessment With the Coleman Methodology Modified by Kon et al.

Study	Total	Study Size	Mean Follow-up	Different Surgical Procedure	Type of Study	Surgical Procedure Description	Postoperative Rehabilitation	MRI Outcome	Histologic Outcome	Outcome Criteria	Outcome Assessment	Selection Process
Park et al.[33]	75	0	10	10	10	5	5	10	10	5	7	3
Song et al.[37]	37	4	5	4	0	5	5	0	0	5	3	6
Dilogo et al.[44]	49	7	2	4	10	5	0	10	0	5	3	3
Chung et al.[38]	37	10	2	4	0	5	5	0	0	5	3	3
Ryu et al.[39]	47	7	5	4	0	5	5	10	0	5	3	3
Caiaffa et al.[45]	46	4	0	10	10	5	2	0	0	5	7	3
Lee et al.[34]	44	10	2	4	0	5	5	0	0	5	7	6
Vines et al.[46]	40	0	4	10	10	5	0	0	0	5	3	3
Alden et al.[47]	33	10	0	10	0	5	0	0	0	5	3	0
Castellanos et al.[48]	55	4	0	10	10	5	5	10	0	5	3	3
Mead et al.[49]	37	7	2	10	0	5	2	0	0	2	3	6

MRI, magnetic resonance imaging.

compared with both saline and hyaluronate, without evidence that ASA injections stimulated immune reaction compared with the control groups (evaluated by measuring immunoglobulin and class I anti-HLA antibodies). The same research group published a further follow-up study[43] on the same cohort of patients, focusing on those who failed to respond to placebo or HA: 95 unblinded patients crossed-over to ASA injection, achieving a significant clinical improvement up to 12 months evaluation, comparable with that of the original, blinded ASA group. Regarding nonrandomized studies, only Castellanos and Tighe[48] and Dilogo et al.[44] considered the MRI among the study outcomes, demonstrating no significant variation in cartilage thickness over time. Nonetheless, Castellanos and Tighe[48] described 7 cases of amelioration of bone marrow lesions, and it was the only study in which a second injection was performed at 6 weeks in patients not showing a reduction in pain of at least 30%. All the other studies included,[45,46,47,49] even if lacking of a control group, report significant improvements in the clinical scores assessed after a single injection of placental products. Lastly, therapeutic protocols did not differ significantly among the nonrandomized studies, apart from the placental product used. Administration method was different only in one study[45] which combined the placental product with HA, repeating 2 HA injection alone 1 week apart, therefore certainly masking the effect of the placental product alone.

Discussion

The main findings of our present systematic review are (1) no standardization in the preparation process of these products; (2) overall clinical safety in their application; (3) encouraging clinical outcomes up to short-middle term evaluation; and (4) overall lack of high-quality evidence, with only a few RCTs available. Injective approaches for the treatment of knee OA have taken a "biological" path in the last 2 decades: first, it was the advent of PRP products that shifted the attention of clinicians and basic researchers toward the possibility of applying autologous product to modulate the intra-articular environment[51] and provide anti-inflammatory and anabolic stimuli to osteoarthritic joints.[15,52] Although the claim of a "regenerative medicine" treatment seemed more an advertisement than a tangible achievement,[53] a new research field had been opened, which is currently still growing. Soon after the introduction of PRP products, it was the time of MSCs,[24] which reached clinical application in many countries thanks to the development of "minimal manipulation" strategies, allowing to prepare MSCs concentrate (from bone marrow aspirate or lipoaspirate) directly in the operating room, without the need of laboratory expansion.[54,55] This was a crucial issue to promote the spread of these biologic

treatments, since cell cultures are extremely expensive and strictly regulated: although many trials have described the outcomes following the application of expanded MSCs, the current regulatory scenario in United States and Europe restricts the routinary use of cell expansion, thus explaining the development of single-use kit to harvest and concentrate MSCs for immediate use as an injective product or as an augmentation for more invasive procedures (i.e., cartilage defect repair or during osteotomies).[56] To this regard, recent trials have shown promising outcomes both in terms of clinical response and imaging improvement, but without any clear evidence on the best source (bone marrow or adipose tissue) and the optimal preparation methods.[57,58] It is likely that answering these questions will still require many years of research but, in the meantime, further and more "practical" problems needs to be addressed. In fact, the most common use of MSCs is through intra-articular injections and, although minimal manipulation procedures have helped in spreading MSCs application, their harvesting is an invasive procedure requiring in most cases anesthesiologic surveillance and, consequently, postprocedure monitoring.[59] We clearly know that no injective treatment is able to produce permanent beneficial results and, therefore, in comparison with other approaches, such as viscosupplementation and PRP, which can be repeated over time with minimal effort for the patients, MSCs injections are burdened by more invasivity and morbidity. Therefore, in case of relapse of symptoms, it is not easy to propose a new MSCs application, also considering that, in most cases, patients have high expectations from this treatment and have tried other injectables in the past, thus being aware of the effectiveness of other "traditional" approaches.

A potential solution might be the banking of bone marrow or adipose tissue for delayed use in orthopaedic patients, but this approach is not customary in many countries, especially those where stringent limitations exist on the use of allograft, whose use is limited to "salvage" procedures.[60] Based on these premises, the use of allogeneic tissues, such as placental-derived products, might represents a valid alternative to autograft, allowing multiple injections while avoiding the need of any harvesting procedure and donor site morbidity. Placenta is a significant source of bioactive agents, from growth factors to different cell lineages, including MSCs, and preclinical experiments have found their ability in counteracting inflammation and catabolic distress.[19,61,62] The downregulation of inflammatory response provided by amniotic cells has been exploited in several preclinical models of inflammatory diseases, such as lung fibrosis, colitis, autoimmune encephalomyelitis and even arthritis.[2] Handling and storage of placental tissues are well established and therefore, as proven by the present review, several methods exist to obtain placenta-derived products ready to be used in OA joints. Seven different preparations have been applied in vivo, including morcelized tissues (amnion, chorion, or both), cells extracted and expanded from the amniotic fluid, amniotic fluid itself, or combinations of the aforementioned components. Safety of these products has been proved in all the trials considered: it is noteworthy to underline that, although being homologous products, there is no evidence either of immune reaction or graft-versus-host disease, and there is no need to perform any compatibility tests between donor and host before application.[63] In fact, clinical studies have proven that allogeneic transplantation of morcelized amniotic membrane or amniotic cells is not able induce acute immune rejection in the absence of immunosuppressive treatment.The poor immunogenicity is due to the low or limited expression of HLA class II (HLA-DR) and other costimulatory molecules responsible for T-cell activation.[64]

Beyond the safety profile, the evidence regarding efficacy is still limited and only a few RCTs are available[35,40-42]: in all cases, different placental products provided superior outcomes compared with either saline or HA, up to 12 months' evaluation. Interestingly, one trial showed that 2 placental injections provided better results than a single shot, thus further supporting the assumption that multiple biologic injections over time may contribute to increase clinical response. Furthermore, one study found also an increase of cartilage thickness after the injection of placental stem cells. These products have also been tested in more challenging conditions, i.e., as an augmentation during surgery: despite the lack of RCTs, results of high tibial osteotomy seemed to be improved by the concurrent use of placental products, which contributed to a better cartilage repair than BMAC.[34]

As for previous studies on autologous MSCs, the interproduct variability emerged from the literature represents a confounding factor in the analysis of outcomes. Anyway, despite different preparation methods and the lack of clear data on the biological content of the products available, they have shown promising clinical potential with the advantage of being ready to use and always available for multiple re-treatments over time, without the need of a surgical room and anesthesiologic surveillance. Further trials are still needed to confirm the superiority of placenta-derived products over "traditional" injective approaches: only one study against hyaluronate is currently available and it is necessary to gain more data, especially in terms of cost–benefit ratio since placental products are significantly more expensive than on-the-shelf injectable or even PRP, and therefore their use can be endorsed only if a clear superiority will be demonstrated.

Limitations

Some limitations of the present study must be acknowledged: first of all, the lack of a meta-analysis, which was not possible because of the very low number of RCTs, which did not offer comparable data to be pooled together. Furthermore, looking at surgical application, the paucity of trials and their low methodologic quality must be underlined again as a significant flaw. Lastly, as previously mentioned, the absence of any cost–benefit analysis, which was not considered in any trial but represents a crucial point for an eventual consolidation in the use of placenta-derived products.

Conclusions

Placental products showed a good safety profile and overall satisfactory outcomes for the treatment of knee OA.

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