ORIGINAL ARTICLE

Allogenic platelet concentrates from umbilical cord blood for knee osteoarthritis: preliminary results

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ABSTRACT

Aim To investigate the role of cordonal blood platelet-rich plasma (PRP) intra-articular injections for treating the patients with knee osteoarthritis in terms of procedure safety and clinical outcomes.

Methods Twenty-five patients affected by knee osteoarthritis were enrolled and received one single intra-articular knee injection of umbilical cord PRP in a volume of 10 mL. A follow-up was investigated at time 0, 4, 8, 12 weeks and 6 months, evaluating clinical parameters and functional performances.

Results No serious adverse events were identified. The paired t-test analysis showed a significant difference between baseline and each follow-up times for all clinical scales ($p<0.05$), with a significant improvement of clinical outcomes.

Conclusion 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.

Key words: allogenic, cordonal, osteoarthritis, platelet rich plasma

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INTRODUCTION

Osteoarthritis (OA) of the knee is a common problem characterized by joint pain, swelling, stiffness and disability (1,2). The main problem associated with OA is articular cartilage defect which has limited capacity for repair. This imposes a major social burden due to elevated healthcare cost and absence from work (3,4). Despite decades of research, no true disease-modifying OA drugs are described, and clinical effects of pharmacological interventions remain of short duration.

Cells, scaffolds, and growth factors have conventionally been considered as the "three elements" of regenerative medicine (5). Both growth factors and mesenchymal stem cells (MSCs) were identified as a new option in the field of cartilage regeneration, and some authors have reported that patients with knee OA treated with implantation and injection showed clinical improvement (6-9).

Growing attention has been paid to growth factors because of their critical role in cytogenesis and histogenesis. In recent years, platelet-rich plasma (PRP) containing growth factors has attracted attention as a biomaterial useful for regenerative medicine. The PRP, which is a physiological biomaterial (10) and contains various types of platelet-derived growth factors, can be expected to exert the actions of multiple growth factors that are required for histogenesis (11) without the artificial enhancement of a single growth factor (12).

The therapeutic use of platelet concentrates was first described by Whitman in 1997 (13), although blood-derived fibrin glues were already used 30 years earlier to seal wounds and stimulate their healing (14). In 1998, platelet concentrates started to be known as platelet-rich plasma (PRP), generally defined as a volume of autologous plasma containing a higher platelet count than peripheral blood (150,000–350,000 platelets/μL) (15). Thereafter, multiple systems have been developed to concentrate platelets and remove erythrocytes (red blood cells) (RBCs) and, in some cases, also leukocytes (white blood cells) (WBCs) (16).

Application of autologous PRP for cartilage regeneration and OA treatment, our field of interest, has been getting more and more attention over the last decade.

In knee OA, autologous PRP injections aim to stimulate cartilage repair and offer relief to other osteoarthritic symptoms, potentially delaying the need for joint replacement surgery. PRP injections have shown to influence the entire joint environment, leading to a short-term clinical improvement (17) with PRP injections being considered a safe procedure with more favourable outcomes when compared to alternative treatments (18).

However, autologous platelet-rich plasma (PRP) application is harassed by controversial outcome, due to highly variable PRP quality among patients, being influenced by age, comorbidities, modality of preparation. Allogeneic PRP from well-characterized donors can either generate more consistent and reliable therapeutic effect and avoid harvesting large quantities of blood, an additional health burdens to patients. However, the use of allogeneic PRP is generally less investigated, especially for its immunogenicity in such application. Allogenic PRP consist of a new aim in regenerative medicine; novel results are encouraging (19).

The high content of tissue regenerative factors in cord blood platelets makes cordonal blood the ideal source of allogenic PRP. A recent study proposed a standardized production of allogenic cryopreserved cord blood platelet concentrates (CBPC) suitable for later preparation of clinical-grade cord blood platelet gel (20).

The availability of the CBPC units previously prepared and cryopreserved allowed us to conduct a prospective study to investigate the role of umbilical cord (UC) - PRP injections for treating patients with knee osteoarthritis, in terms of procedure safety and clinical outcomes.

PATIENTS AND METHODS

Patients and study design

For the realization of the project, we had the collaboration of the Transfusion Medicine Unit-Di Venere Regional Hospital and Puglia Cord Blood Bank.

On the benealth of the 2011 public Cordonal Blood (CB) banks research project standardized production of cryopreserved CBPC from CB units not fulfilling the criteria for banking for haematopoietic transplant purposes, but otherwise potentially usable for other therapeutic applications, was started on November 1st, 2013. Meanwhile, the Italian National Institute of Health (Istitu-

to Superiore di Sanità) and the Italian National Health Council (Consiglio Superiore di Sanità), determined that allogeneic cordonal blood platlet concentrates (CBPC) and cordonal blood platlet gel (CBPG), in analogy to similar products obtained from adult peripheral blood, belong to the category of blood component.

The CB units were collected after the mothers' informed consent and processed within 48 hours. Standard parameters regarding platelets concentration and centrifugation cycles were applied. The CBPC units were finally transferred into a storage bag and cryopreserved without cryoprotectant in a mechanical freezer at a temperature below −40 °C in view of future clinical use of the CBPG, which requires thawing at 37 °C in a water-bath before activation.

The target population included individuals of 43-79 years of age recruited between December 2019 and April 2020. All patients signed an informed consent for the treatment.

Patients meet the following criteria: symptomatic knee OA (daily pain for at least 3 months not responding to pain medication), grade I-III Kellgren Lawrence radiographic changes (21) without acute meniscal rupture: describe grades. One radiologist independently staged knee OA according to Kellgren-Lawrence system (21) using standard knee X-ray imaging of standing anteroposterior and horizontal lateral projection. Patients were excluded in case of condylar or tibial plateau bone marrow oedema on MRI, major axial deviation defined by valgus (>10°) or varus (>5°) deformity of the involved leg, recent use of intra-articular hyaluronic acid/steroids in the past 6 months, ipsilateral hip or ankle arthritis, previous malignancy.

All patients underwent blood type definition and compatibility (ABO-Rh).

Twenty-five patients were enrolled and received one single intra-articular knee injection of CBPG containing a volume of 10 mL.

All injections were performed by two orthopaedic surgeons with more than five-year experience in knee intra-articular injections in syringes of 10 mL using an anterolateral approach at the medial joint line with 90° of knee flexion.

Patients were asked to avoid physical activity for 72 hours after the procedure. Acetaminophen was allowed in case of pain (3 g/day).

Methods

Cord blood units collected at public banks with total nucleated cell counts $<1.5\times10^9$, platelet count $>150\times10^9$/L and volume >50 mL, at first, underwent soft centrifugation within 48 hours of collection. Then, platelet-rich plasma was centrifuged at high speed to obtain a CBPC with target platelet concentration of $800–1{,}200\times10^9$/L, which was cryopreserved without cryoprotectant below −40 °C. The cost of preparation was estimated at € 160.92/CBPC. About 2 hours were needed for one technician to prepare four CBPCs (20).

One independent orthopaedic surgeon performed a clinical evaluation as assessed by validate clinical outcome scales: Visual Analogue scale (VAS) (22)**,** Western Ontario and McMaster Universities Arthritis Index (WOMAC) (23), Knee Injury and Osteoarthritis Outcome Score (KOOS) (24), and International Knee Documentation Committee (IKDC) (25).

This clinical analysis was performed at baseline (T0), 4 weeks (T1), 8 weeks (T2), 12 weeks (T3) and 24 weeks follow-up (T4).

The primary endpoint of our trial was the safety of UC-PRP treatment, evaluating the number of treatment related adverse events. The secondary endpoint of the trial was the efficacy of the treatment validated by clinical scales.

The visual analogue scale (VAS) (22) is a validated, subjective measure for acute and chronic pain. Scores are recorded by making a handwritten mark on a 10-cm line that represents a continuum between "no pain" and "worst pain." The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (23) is a widely used, proprietary set of standardized questionnaires to evaluate the condition of patients with osteoarthritis of the knee and hip, including pain, stiffness, and physical functioning of the joints. The Knee Injury and Osteoarthritis Outcome Score (KOOS) (24) is self-administered and assesses five outcomes: pain, symptoms, activities of daily living, sport and recreation function, and knee-related quality of life.

The International Knee Documentation Committee (IKDC Questionnaire) (25) is a knee-specific patient-reported outcome measure. It is considered to be one of the most reliable outcome reporting tools in its category.

Statistical analysis

Statistical analysis was performed using paired-t test to investigate a statistical difference in terms of painful symptoms and functional outcomes between preoperative and postoperative times. The test was performed with a confidence level of 5%; a $p<0.05$ was considered statistically significant.

RESULTS

The sample consisted of 25 patients, 10 males (40%) and 15 females (60%). The average age was 62.68±8.76 (range 43-79) years. In 10 (40%) cases the right limb was involved. In 14 (56%) cases there was radiographic evidence of joint change based on Kellgren–Lawrence grade II and in 11 (44%) cases grade III (Table 1).

Table 1. Demographic characteristics of 25 patients

Variable	
Gender (No; %)	
Males	10 (40)
Females	15 (60)
Average age (±SD) (years)	62.68 (±8.76)
Average BMI (±SD)	27.84 (±3.04)
Kellgren-Lawrence grade (No; %)	
I	0
II	14 (56)
III	11 (44)
Kellgren-Lawrence grade (average; SD)	2.44 (±0.51)

BMI, body mass index;

No serious adverse events were identified. The most common adverse event was acute and painful synovitis during for a mean of 4 days. Local oedema and difficulties in walking were observed in two patients and completely resolved in 7 days. No one required hospitalization or arthrocentesis. Thirteen patients assumed acetaminophen with partial complete regression of pain.

The average values at baseline (T0) were: VAS score 7.36 (range 3-10), WOMAC score 53.96 (range 28-65), KOOS score 46.39 (range 32-64), IKDC score 39.79 (range 25-51.33).

At T1 (4 weeks) the mean values were: VAS score 3.24 (range 1-7), WOMAC score 30.6 (range 12-40), KOOS score 61.77 (range 46-74.2), IKDC score 60.93 (range 46-72).

The average values at 8-week follow-ups (T2) were: VAS score 3.16 (range 2-5), WOMAC score 29.84 (range 20-37), KOOS score 60.56 (range 48-78), IKDC score 60.88 (range 47-73).

At 12-week follow-ups (T3) the mean values were: VAS score 3.64 (range 1-6), WOMAC score 31.8 (range 13-40), KOOS score 59 (range 45-80), IKDC score 59.32 (range 44-78).

At the final 6-month follow-up (T4), the mean values were: VAS score 6.72 (range 4-8), WOMAC score 37.24 (range 20-45), KOOS score 53.64 (range 41-75), IKDC score 54.4 (range 41-74) (Table 2).

Table 2. Clinical outcomes at baseline (T0), 4 (T1), 8 (T2), 12 weeks (T3) and 6 months (T4) follow-up

scale (mean ±SD)	Follow-up period				
	T0	**T1**	**T2**	**T3**	**T4**
VAS	7.36±1.73	3.24±1.42	3.16±1.07	3.64±1,11	6.72±1.1
womac	53.96±9.55	30.6±6.43	29.84±5.44	31.8±6.55	37.24±6.18
koos	46.39±6.79	61.77±7.06	60.56±6.87	59±7.61	53.64±7.15
ikdc	39.79±6.94	60.93±7.85	60.88±7.24	59.32±8.26	54.4±8.00

VAS, Visual Analogue Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; KOOS, Knee Injury and Osteoarthritis Outcome Score; IKDC, International Knee Documentation Committee

The paired t-test analysis showed a significant difference between baseline and each follow-up times for all clinical scales ($p<0.05$), with a significant improvement of these clinical outcomes (Table 3).

Table 3. Statistical analysis of clinical outcome at baseline (T0), 4 (T1), 8 (T2) 12 weeks (T3) and 6 months (T4) follow-up

Scale	Paired t test between two time points*			
	T0-T1	**T0-T2**	**T0-T3**	**T0-T4**
vas	3,65948E-13	2,9892E-11	3,12881E-11	0.029
womac	4,84524E-16	1,65277E-15	1,70372E-16	1,03557E-12
koos	6,12018E-12	9,79963E-12	3,42026E-10	2,05478E-06
IKDC	1,09353E-10	4,09279E-11	5,17389E-10	9,66833E-08

*The paired t test was used to test the statistical differences between two time points; Number E-n, in which E (exponent) multiplies the preceding number by 10 to the nth power.
VAS, Visual Analogue Scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index; KOOS, Knee Injury and Osteoarthritis Outcome Score; IKDC, International Knee Documentation Committee;

DISCUSSION

One of the most interesting therapeutic choices in regenerative medicine for the gonarthrosis treatment is the use of Platelet Rich Plasma (PRP). The PRP is a concentrate of platelets and growth factors (GFs) obtained by the centrifugation of venous blood. It may be autologous or allogenic. Preparation methods are not standardized yet and regenerative mechanisms related to the biomolecular pathway are still the object of study. In the last fifteen years, the PRP application has expanded to a wide range of clinical fields, including plastic surgery, dermatology, maxillofacial surgery, orthopaedics and others (26-30).

PRP in vitro studies actually available state almost consistently that PRP stimulates the proliferation

of the human cell. This observation is also the case regarding cell motility and exocytosis of several important regenerative extracellular ground substances, for example, collagen type I and III, HA and so forth. Regarding the optimal platelet concentration for cell proliferation, the studies diverge severely. An overall trait is seen - when the PRP concentration increases, the volume of culture media (nutrition) decreases and a lower optimal concentration for cell proliferation is observed (31).

In vivo studies are actually still limited and results are not of unique interpretation. Variables such as type of PRP, proper timing, treatment periodicity, location and technique for injection would need to be selected to establish efficacy in each treatment and to compare different studies. However autologous PRP is generally considered microbiologically safe with regard to the risk of acquiring microbial and viral transmissible infections. Moreover, autologous PRP has significant practical limitations which may prevent its clinical use in different categories of patients, for example elderly hypo-mobile patients, chronic inflammatory diseases; repeated blood collections for multiple PRP applications may be difficult or clinically inappropriate. These limitations prompted several groups to standardize platelet gel as an allogeneic blood component obtained from healthy adult blood donors, to be routinely offered to clinicians for the treatment of patients suffering from different conditions, thus avoiding the inconvenience of autologous blood collection (32-34). This approach also reduces potential negative effects of pathological biological effectors possibly present in the patient's blood in relation to his or her morbid conditions (35).

At least three recent works have described the use of allogenic PRP clinically. Smrke et al. performed a case study in which a 50-year-old male with type 2 diabetes suffering from a comminuted fracture of the tibia and delayed union was treated with a graft composed of allogenic platelet gel mixed with autologous cancellous bone. After 6 months the graft was incorporated, the bone defect was fully bridged and full weight-bearing capacity was achieved. No side effects were observed and no platelet or HLA class I antibodies were detected (35). As a follow-up, a prospective clinical study was conducted by the same group to treat long bone non-unions using the same type of allogenic product (allogenic platelet gel and autologous cancellous bone) in nine patients (36). They used random single-donor allogenic PCs (ABO and RhD matched, serologically HIV, hepatitis B virus, hepatitis C virus and lues-negative, leukocyte depleted, and irradiated) from standard blood bank stocks. As in the case study, screening for HLA antibodies class I, and human platelet antibodies was performed before implantation and after 3 months, also without detecting any sign of immunologic reactions. At 1 year after surgery, seven out of nine patients treated achieved complete healing.

More recently, Bottegoni and colleagues (37) performed a prospective open-label, uncontrolled, single-centre, pilot study with 60 patients. Participating patients (aged 65–86 years) suffered symptomatic early or moderate knee OA (Ahlbäck grade I–III) and were affected by hematologic disorders, preventing autologous PRP treatment. Effectiveness, as measured with the International Knee Documentation Committee (IKDC), knee injury and osteoarthritis outcome score (KOOS) and EuroQol-visual analogue scales (EQ-VAS), was varied. As noted in other trials, younger patients with lower degree of degeneration showed a better response. In addition, they did not report any severe complications related to the allogenic nature of the PRP.

The high content of tissue regenerative factors in cord blood platelets makes this a great source of allogenic PRP. Moreover the widespread availability of allogeneic cord blood units generously donated for hematopoietic transplant but unsuitable for this use solely because of low hematopoietic stem cell content prompted different Italian cordonal Bank to develop a national programme to standardise the production of allogeneic cryopreserved cord blood platlet concentrates (CBPC) suitable for later preparation of clinical-grade cord blood platelet gel (38-43), which can be used in different fields including osteoarthritis.

Our study can be considered a clinical application of a multicentric Italian study performed to standardize a clinical grade procedure for the preparation of allogeneic PCs from umbilical cord blood (20).

Our results were encouraging. No adverse events were observed. Transitory pain resulted responder to acetaminophen. VAS reduction at first follow-up promoted quality of life and function

improvement, maintaining good clinical outcomes all six months long.

The limitation of our study was the short follow-up. Additionally, a cohort study with a control group (for example, hyaluronic injection) could provide more information regarding the real efficacy of the procedure.

In conclusion, we strongly believe that PRP is effective for tissue regeneration through a composite of actions exerted by types of growth factors that are released from concentrated platelets. Autologous PB-PRP injection is actually considered a safe procedure. Allogenic PRP still needs to be evaluated throughout more high-quality trials. In both cases PRP formulations need to be standardized to allow comparison across studies.

OA remains a heterogenous and multifactorial pathology. It is now known that in OA patients who present the same symptoms, the underlying mechanisms causing them might be different. Different OA phenotypes are emerging that will most likely require different treatment approaches. Therefore, PRP might be effective in a selected group of patients, and those need to be identified to obtain a target effective treatment.

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TRANSPARENCY DECLARATION

Conflict of interest: None to declare.

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