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Platelet-rich plasma injections delay the need for knee arthroplasty: a retrospective study and survival analysis

Mikel Sánchez[1,2] · Cristina Jorquera[2] · Pello Sánchez[2] · Maider Beitia[2] · Beatriz García-Cano[1] · Jorge Guadilla[1] · Diego Delgado[1,2]

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Abstract

Purpose The biological action of platelet-rich plasma (PRP) could slow down the osteoarthritis progression, resulting in a delay of joint replacement. This work aims to evaluate the ability of PRP to postpone and even avoid knee replacement in patients with knee osteoarthritis (KOA) analyzing, on the one hand, the time of delay and on the other hand the percentage of patients without undergoing total knee arthroplasty (TKA).

Methods A retrospective analysis and a survival analysis were conducted. KOA patients who underwent knee replacement between 2014 and 2019 and previously received PRP infiltrations were included in the retrospective analysis. Regarding survival analysis, KOA patients who received PRP treatment during 2014 and with follow-up until 2019 were included. The dates of PRP treatment and TKA, KOA severity, age of the patients, number of PRP cycles, and administration route were analyzed.

Results This work included 1084 patients of which 667 met the inclusion criteria. 74.1% of the patients in the retrospective study achieved a delay in the TKA of more than 1.5 years, with a median delay of 5.3 years. The survival analysis showed that 85.7% of the patients did not undergo TKA during the five year follow-up. The severity degree, age, PRP cycles, and administration route had a statistically significant influence on the efficacy of PRP in delaying surgery.

Conclusion These data suggest that the application of PRP in KOA patients is a treatment that could delay TKA, although further studies are needed to understand and improve this therapy.

Keywords Knee osteoarthritis · Platelet-rich plasma · Growth factors · Total knee arthroplasty · Joint replacement

Introduction

Knee osteoarthritis (KOA) is a degenerative pathology that causes pain, stiffness, functional deterioration, and deformation of the affected areas. It presents a high prevalence with 250 million people worldwide, being one of the main causes of disability among the adult and elderly population [1, 2]. Consequently, healthcare processes related to KOA management consume considerable resources of health systems, outstanding total knee arthroplasties (TKA), and their revisions or complications derived from factors such as infections. Factors such as aging, obesity, sedentary lifestyle, and uncontrolled sport will make the figures increase in the coming years, becoming a challenge not only for health professionals and patients but also for the sustainability of public health systems [3, 4].

Conservative treatments should avoid or at least delay KOA-related surgery, minimizing the number of TKA, second interventions for complications, and surgical revisions of operated patients, relieving hospitals and health systems. However, current treatments focus on mitigating the symptoms, reducing pain and inflammation, or improving lubrication. Although this approach may be effective in the symptomatologic aspects, it fails to stop the pathology progression, and the ultimate solution is the TKA [5]. In recent years, biological treatments are emerging within the framework of regenerative medicine, such as platelet-rich plasma (PRP) or cell therapies that aim to modify or interfere with the processes that cause joint degeneration. The use of these therapies alone

✉ Diego Delgado
diego.delgado@ucatrauma.com

[1] Arthroscopic Surgery Unit, Hospital Vithas San José, Beato Tomás de Zumarraga 10, 01008 Vitoria-Gasteiz, Spain

[2] Advanced Biological Therapy Unit, Hospital Vithas San José, Vitoria-Gasteiz, Spain

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or in combination with other conservative treatments may help improve the symptoms and slow down the joint degenerative process.

Among these biologic therapies, PRP is the most widely used, for being easily obtained and applied and more accessible from both a regulatory and operational perspective [6]. This therapy is based on an autologous product from the patient's blood with a series of biological characteristics derived from plasma and platelet biomolecules. The action of these biomolecules and growth factors act on the joint homeostasis, promoting a favourable biological environment by promoting anti-inflammatory effects, analgesia, lubrication, or cell modulation [7].

Although there is a growing body of published work on the use of PRP versus other conservative treatments for KOA with promising results [8], there is no knowledge about PRP and delaying TKA. This work aims to evaluate the ability of PRP to delay knee replacement in patients with KOA.

Methods

This work consists of two different approaches analyzing two different cohorts of patients to address the effectiveness of PRP in delaying joint replacement. On the one hand, a retrospective study of patients who underwent TKA was conducted to know the delay time achieved. On the other hand, a survival analysis was carried out to evaluate the percentage of KOA patients treated with PRP who have not yet undergone TKA.

Data for this work were collected from the Arthroscopic Surgery Unit (Vitoria-Gasteiz, Spain), from patient's records employed for medical and scientific use. A total of 1084 patients were reviewed between 2014 and 2019 to perform the two approaches.

The present study was carried out in accordance with the international standard on clinical studies: Declaration of Helsinki in its latest revised version (Fortaleza, Brazil; 2013) and Good Clinical Practice Regulations (International Conference for Harmonization). Ethical approval for this study (protocol no: EPA2019037) was obtained from the Ethics Committee of the Basque Country.

PRP preparation and application

Thirty-two milliliters or 90 mL of venous blood were extracted from the patient depending on the applied treatment. Blood in 9 mL tubes containing 3.8% (wt/V) sodium citrate was centrifuged at 580*g* for eight minutes at room temperature. The 2 mL plasma fraction located above the sedimented red blood cells, but not including the buffy coat, was collected. This plasma fraction preparation contained 1.5 to 2.5 times the concentration of platelets compared with peripheral blood, without leukocytes or erythrocytes. PRP was activated with $CaCl_2$ before administration, which could be intra-articular or intraosseous. One cycle of intra-articular treatment consisted of three weekly administrations of 8 mL of PRP injected into the joint space. One cycle of intraosseous treatment included a first visit in which two intraosseous injections into femoral condyle and tibial plateau combined with one intra-articular injection were performed according to the protocol described by Sanchez et al., followed by two weekly intra-articular injections. This type of administration is indicated for patients with severe KOA (Ahlbäck III–IV) without response to previous conservative treatments including intra-articular PRP [9]. It aims to act not only in the intra-articular space and synovial membrane but also on the subchondral bone to try to enhance the effectiveness. In these cases, treatment is explained to the patient, and its application is agreed or not, taking into consideration the preferences of the patient. In both treatment protocols, at least 6 months elapsed between each treatment cycle, which were repeated according to the clinical evolution of the patient.

Approach 1: Retrospective study

This retrospective study reviewed the medical records and data of KOA patients who underwent TKA between 2014 and 2019. The selected patients met the following inclusion criteria: (1) patients who, before undergoing unilateral TKA, accepted to receive PRP to treat KOA. (2) At the time of initiating PRP treatment, these patients were candidates for TKA. This decision was based on imaging studies using severity scales, namely, Ahlbäck (grades III–V) and Kellgren-Lawrence (grades 3 and 4) scales, as well as clinical examination considering pain and functional limitation according to the images and the failure of previously applied conservative treatments. The patients chose the PRP treatment option after explaining both TKA and PRP treatment. (3) Six months before and during PRP treatment, they did not undergo surgery or conservative treatment that could also contribute to delay of the joint replacement.

The time delay was considered from the time the patient began PRP treatment until the patient signed the acceptance agreement for the surgical procedure. These dates, age of the patients, and the number of PRP cycles were analyzed. Patients were divided into responders and nonresponders, depending on whether they experienced a delay in TKA of more than 1.5 years or less, respectively.

Approach 2: Survival analysis

All patients treated with PRP for KOA throughout 2014 were identified, with the endpoint for this study in 2019. Patients

who underwent surgery or other conservative treatments six months before and during PRP treatment that could also contribute to the delay in TKA were excluded as well as other knee-associated conditions requiring treatment. Survival was defined as the percentage of patients who did not undergo TKA at different follow-up times. Some of these patients began PRP treatment before 2014, obtaining survival data from more than five years. Those who began PRR treatment in 2014 were analyzed in greater detail due to the higher number of patients, evaluating the following variables: the date on which the TKA occurred, age at which PRP treatment was initiated, the presence of severe KOA according to the above criteria, and the inclusion of intraosseous PRP [9]. Patients who dropped out as well as their withdrawal dates were also included in the analysis (censored).

Statistical analysis

Demographic and medical variables were determined by the mean and standard deviation for parametric data and median and range for nonparametric one. Comparisons were performed by $\chi 2$ test for proportions, Student's t test for parametric independent samples, Mann-Whitney U test for nonparametric independent samples, and Pearson's correlation coefficient for correlations; distribution of the samples was assessed by Shapiro-Wilk test. Data were considered statistically significant when $p < 0.05$. Time-to-event analyses used a Kaplan-Meier survival approach, and log-rank tests were used to compare survival times for the different variables. Statistical analysis was performed with SPSS 20.0 (SPSS, Chicago, IL).

Results

Approach 1: PRP application for KOA delays the need for TKA

Out of the 331 patients who underwent TKA between 2014 and 2019, 186 met the criteria to be included in this retrospective study, and 138 patients (74.2%) were considered responders since they managed to delay joint replacement by more than 1.5 years (Fig. 1). The median delay in TKA for all patients was 4.1 years (0.3–14.7), increasing in responders up to 5.6 years (1.6–14.7) ($p < 0.01$). There was a delay during the first five years after the initiation of PRP treatment in 52.9% of the responder patients. 30.4% of patients underwent surgery within five to ten years after the beginning of PRP treatment, and 16.7% of the patients delayed TKA for more than ten years (Fig. 2a). The mean age at which patients started treatment with PRP was 67.3 ± 7.4, being significantly lower among respondents (66.7 ± 7.6 years) compared with nonresponders (70.9 ± 5.9 years) ($p < 0.01$). The application of PRP shifted the age of the patients for TKA, from 60–70 years to 70–80 (Fig. 2b).

Regarding the number of treatment cycles, a significant correlation was observed between the number of cycles received and the number of years of delay of the surgical procedure ($r = 0.758$; $p < 0.01$). The median of the total patients analyzed was 2 cycles (1–19), with a significant increase in responders (3.5 cycles, 1–19) ($p < 0.01$), with a higher number of PRP cycles at a higher number of delay years (Fig. 2A).

Approach 2: Age, treatment cycles, and route of administration influence the delay of TKA

Out of the 753 patients (905 knees) who received PRP during 2014, 481 patients (601 knees) met the inclusion criteria in the final analysis (Fig. 3), with a total of 78 cases that dropped out. All these patients received PRP treatment during the year 2014, of which 225 patients (273 knees) received their first treatment cycle that same year. The remaining 256 (328 knees) patients received the first cycle during 2007–2013. Survival data for the different years showed percentages of patients without TKA ranging from 68.4 (9-year follow-up) to 90.6% (6-year follow-up) (Table 1).

Since the largest number of patients was included in the five year analysis, these data were the most representative with a survival rate of 85.7% (Table 1), including 41 censored events that were lost to follow-up before the five year timepoint. When analyzing the 273 cases that started PRP treatment in 2014 (5-year follow-up) (Fig. 4), it was observed that in patients who began treatment at an age below 65 years, the percentage of those with joint replacement decreased significantly ($p < 0.01$). 19.4% of cases received three or more cycles of PRP, while 27.1% received at some point intraosseous PRP. The number of PRP cycles and the inclusion intraosseous PRP did not significantly influence the percentage of patients with TKA. In contrast, the severity of KOA does influence survival values, being significantly higher in patients with non-severe KOA ($p < 0.01$). There were no significant differences between the median age of the non-severe (64 years, 36–89) and severe KOA group (67 years, 36–88). When the 91 patients who presented severe KOA were analyzed separately (Fig. 5), it was observed that the age of treatment initiation below 65 years, three or more PRP cycles (28.6% of severe cases) and the inclusion of intraosseous PRP (59.3% of severe cases) significantly improved the percentage of patients with severe KOA who did not undergo TKA at five years ($p < 0.05$).

Discussion

The main finding of this study is that the application of PRP in KOA patients could be a therapeutic tool for maintaining the

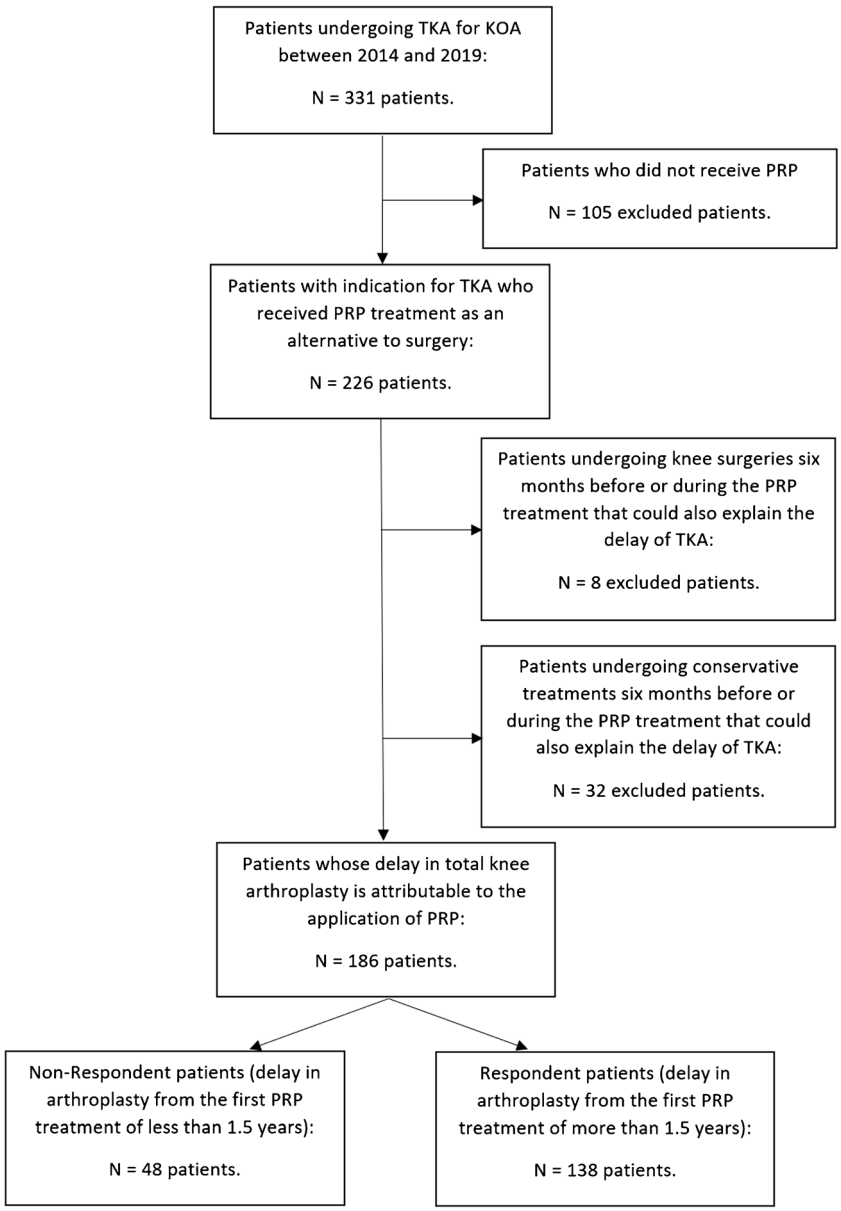

Fig. 1 Flowchart of cohort patients' selection for retrospective study (approach 1). Patients who underwent TKA between 2014 and 2019 were reviewed to determine the delay in surgery after PRP infiltrations. TKA, total knee arthroplasty; KOA, knee osteoarthritis; PRP, platelet-rich plasma

patient's quality of life and delaying surgery. Two types of analyses were performed with two different patient cohorts, to collect complementary data to address this issue.

Regarding the retrospective study, a TKA delay of at least 1.5 years was established to define a positive response [10]. Although the response could be defined at six months after the application, the 1.5-year limit was set because some patients often opt for a second PRP cycle even though the first cycle does not provide positive results, after which a TKA was performed. The median delay of all patients analyzed in this first approach analysis was 4.1 years. However, the delay increased up to 5.6 years in responders with more than 15% of patients whose joint replacement was delayed for more than ten years. These data are very promising when compared with other studies where this effect was analyzed after the administration of hyaluronic acid. Altman et al. [11] conducted a study in which the intra-articular administration of hyaluronic acid delayed surgical intervention by 2.5 years (908 days). Similar data were observed in a study where patients treated with hyaluronic acid achieved a 2.4-year delay in joint replacement (864 days) [12]. Ong et al., however, reported a mean delay of just 1.6 years (19.5 months) [13].

It should be noted that this retrospective analysis is very restrictive since it only considered patients who inevitably had to undergo TKA. Although this approach divides patients into responders and nonresponders, all patients eventually failed to respond to treatment. Therefore, a second approach based on survival analysis was performed selecting all patients who received PRP in 2014, including all KOA

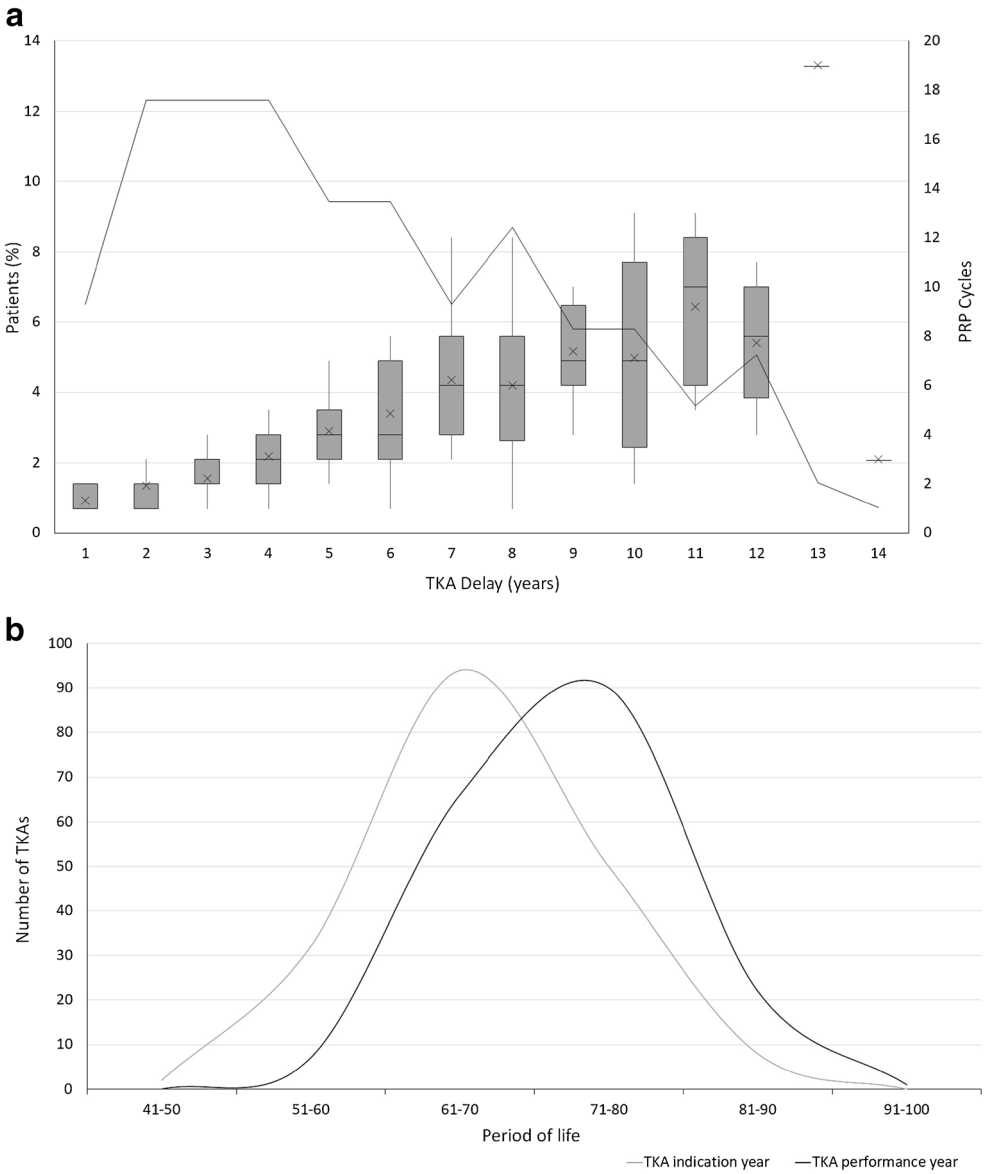

Fig. 2 Distribution of the percentage of responder patients (line, primary axis) and the number of PRP cycles (boxplot, secondary axis) by the number of years of delay in total knee arthroplasty (**a**). Delay in the age of patients to undergo total knee arthroplasty (**b**). TKA, total knee arthroplasty; PRP, platelet-rich plasma

patients regardless of the severity degree. In this second analysis, several patients started PRP treatment for KOA before 2014 allowing for longer term follow-up data, which showed survival rates of more than 70% follow-ups of up to 12 years. However, most patients received their first PRP cycle in 2014, reporting a percentage of 85% of patients who did not have TKA in a 5-year follow-up. This survival percentage was higher than that achieved in similar studies. A previous study showed that viscosupplementation with Hylan GF-20 achieved a 5-year survival of 67%, 18 points lower than that achieved with PRP in the present study [14].

This complementary dual approach allows the analysis of variables that could influence PRP effectiveness. Regarding age, respondent patients of the retrospective analysis represented a significantly younger age than patients with a negative response, suggesting that early initiation of PRP application may improve their clinical response. This finding was also observed in the survival analysis, in which patients who started treatment under the age of 65 achieved a higher percentage of survival, increasing the difference when analyzing patients with severe KOA. This is in accordance with other studies in which younger patients have a better response [15]. However, survival analysis also showed that severity is a factor that influences the efficacy of PRP, being the response better in patients with non-severe KOA. Although the younger patients tend to have a lower degree of KOA, in the present study, such correlation was not found so that other factors could contribute to age influence. The age of the patients could have an important

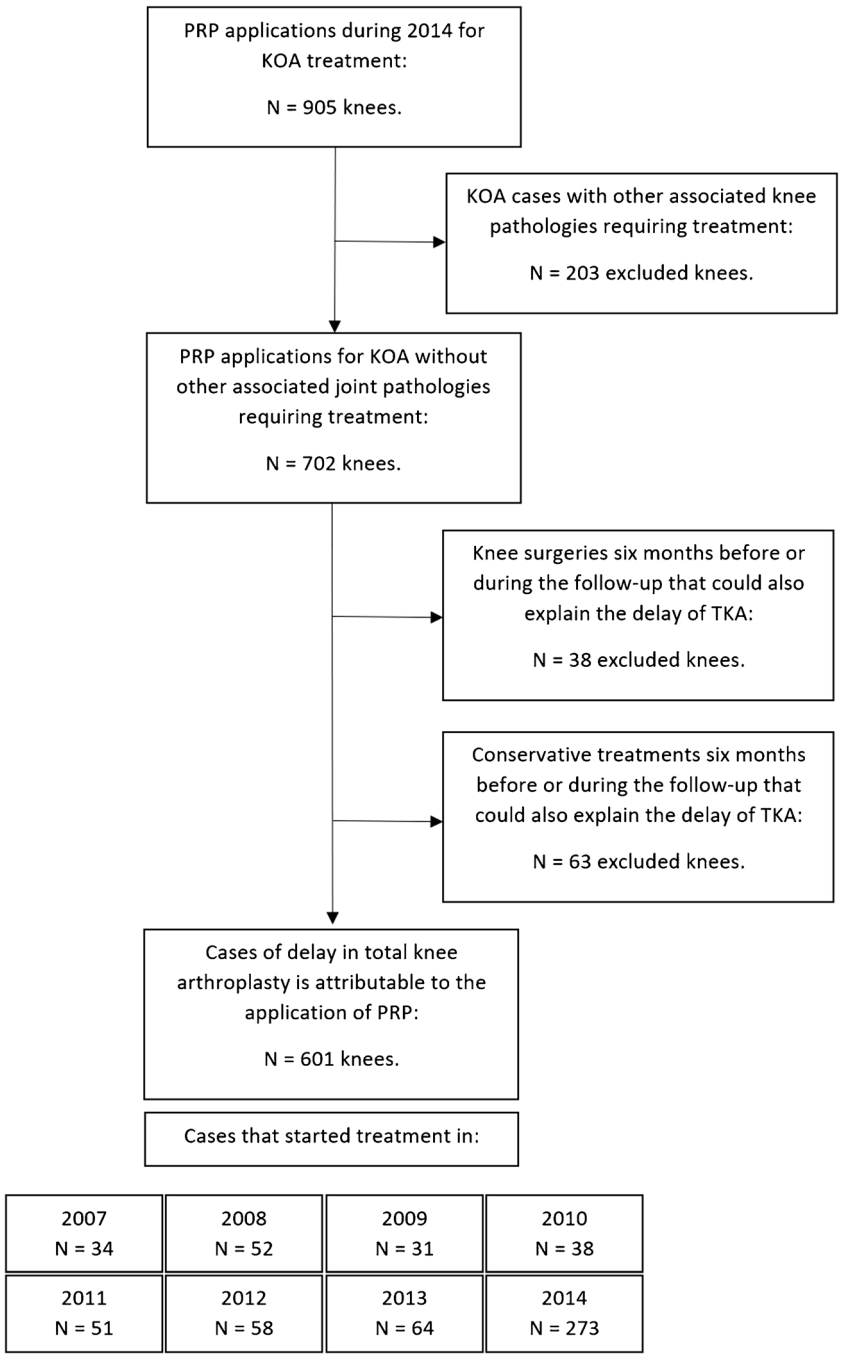

Fig. 3 Flowchart of cohort patients' selection for survival analysis (approach 2). Patients who received PRP during 2014 were reviewed to know the survival rate of patients who did not undergo TKA until 2019. TKA, total knee arthroplasty; KOA, knee osteoarthritis; PRP, platelet-rich plasma

effect on the composition of PRP, being aged PRP more pro-inflammatory due to the higher levels in inflammatory molecules [16, 17]. This may be related to the efficacy of PRP according to in vivo studies that showed better results with PRP from young donors and with PRP without inflammatory molecules [18, 19].

The composition of PRP is one of the variables that could influence the effectiveness of PRP. The large number of products with different compositions that are covered by the term PRP makes research in this field confusing. Products with different levels of platelets and leukocytes or with different methods of activation could be mistakenly considered the same since different concentrations of platelets or the presence of leukocytes can have different biological effects [20]. For this study, PRP presented two times the concentration of platelets compared with peripheral blood, and it did not contain leukocytes. Although this type of PRP seems to be more effective in this type of pathology [8], more studies related to this issue are needed.

The number of treatment cycles was also positive for the delay of surgery in both analyses, increasing the effectiveness with a higher number of cycles. This result is consistent with

Table 1 Demographic characteristics of KOA patients with PRP during 2014 (approach 2)

Starting treatment	2007	2008	2009	2010	2011	2012	2013	2014	Total
Patients, *N* (%)[a]	22 (4.6)	38 (7.9)	26 (5.4)	31 (6.4)	40 (8.3)	46 (9.6)	53 (11.0)	225 (46.8)	481
Gender									
Male, *N* (%)	13 (59.1)	16 (42.1)	15 (57.7)	15 (48.4)	19 (47.5)	16 (34.8)	29 (54.7)	121 (53.8)	244 (50.7)
Female, *N* (%)	9 (40.9)	22 (57.9)	11 (42.3)	16 (51.6)	21 (52.5)	30 (65.2)	24 (45.3)	104 (46.2)	237 (49.3)
Age at diagnosis									
Mean ± S.D.	66.2 ± 10.0	61.9 ± 8.6	63.4 ± 10.61	66.0 ± 10.2	66.7 ± 8.7	62.1 ± 10.6	65.5 ± 9.3	63.4 ± 12.4	63.9 ± 11.1
Range	47–82	41–81	38–78	42–82	50–82	36–82	43–81	36–89	36–89
Bilateral injections patients, *N* (%)	12 (54.5)	14 (36.8)	5 (19.2)	7 (22.6)	11 (27.5)	12 (26.1)	11 (20.6)	48 (21.3)	120 (24.9)
Knees, *N* (%)[a]	34 (5.7)	52 (8.7)	31 (5.2)	38 (6.3)	51 (8.5)	58 (9.7)	64 (10.7)	273 (45.4)	601
Severe Knee OA, *N* (%)	11 (32.4)	14 (26.9)	10 (32.3)	21 (55.3)	20 (39.2)	24 (41.4)	20 (31.3)	91 (33.3)	211 (35.1)
Censored, *N* (%)	5 (14.7)	1 (1.9)	5 (16.1)	7 (18.4)	9 (17.6)	3 (5.2)	7 (10.9)	41 (15.0)	78 (12.9)
Patients without TKA (survival), %	73.5	71.2	71.0	68.4	88.2	75.9	90.6	85.7	

KOA knee osteoarthritis, *PRP* platelet-rich plasma, *a* percentage of total cases, *TKA* total knee arthroplasty

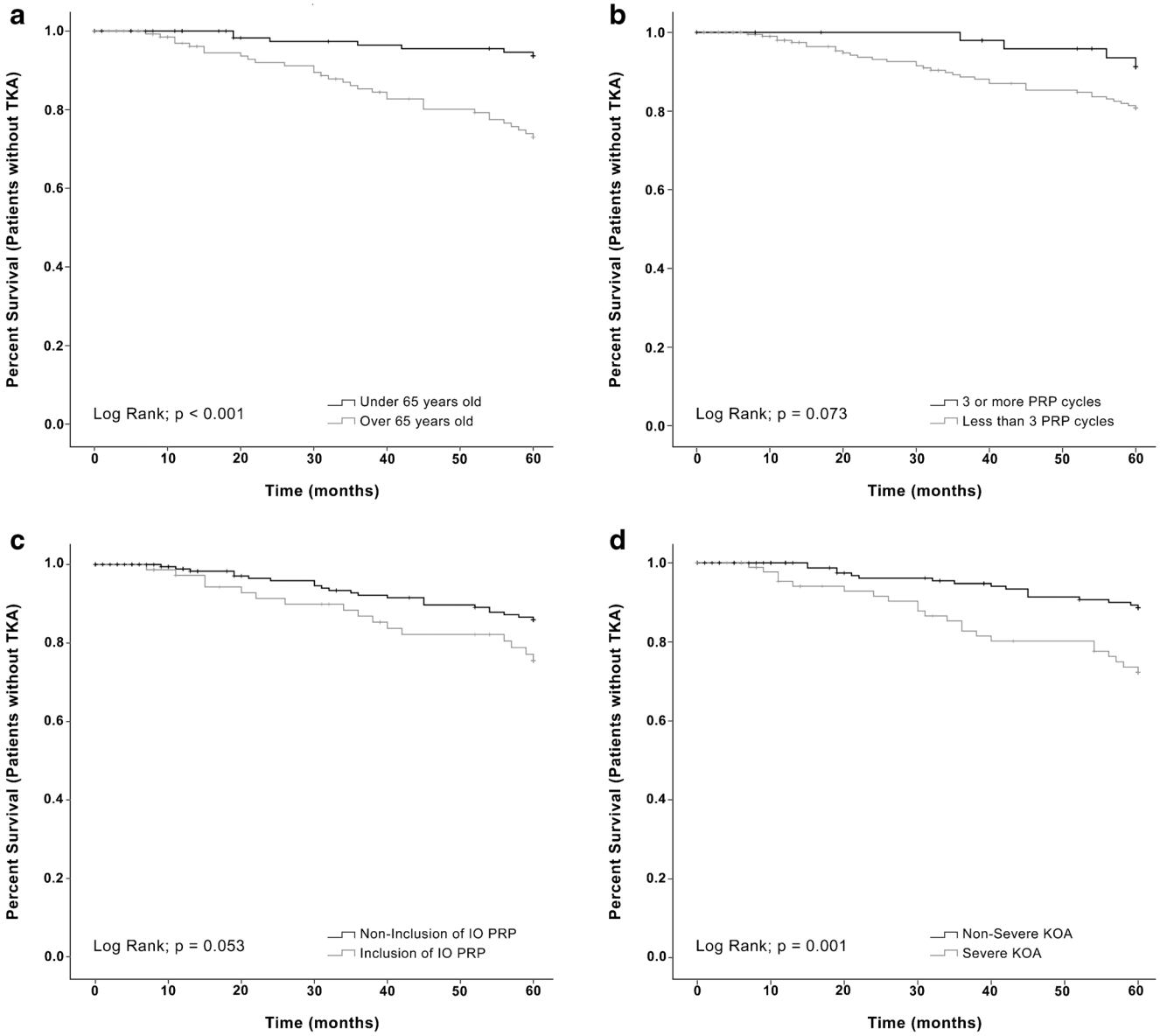

Fig. 4 Kaplan-Meier survival analysis with total knee arthroplasty as the endpoint with a 5-year follow-up on total KOA patients. **a** Influence of age on PRP efficacy. **b** Influence of the number of treatment cycles on PRP efficacy. **c** Influence of intraosseous administration on PRP efficacy. TKA, total knee arthroplasty; PRP, platelet-rich plasma; IO, intraosseous

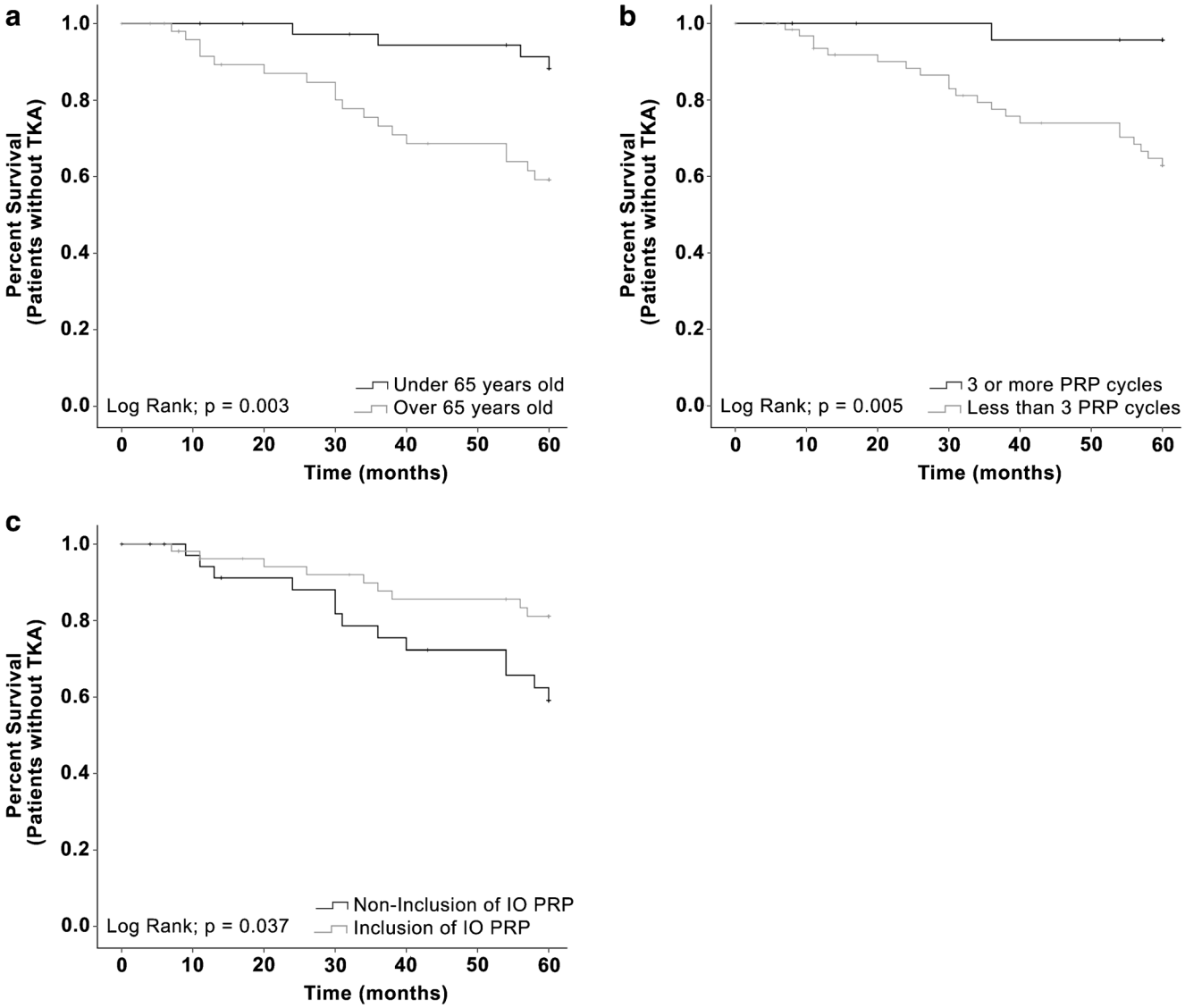

Fig. 5 Kaplan-Meier survival analysis with total knee arthroplasty as the endpoint with a 5-year follow-up on severe KOA patients. **a** Influence of age on PRP efficacy. **b** Influence of the number of treatment cycles on PRP efficacy. **c** Influence of intraosseous administration on PRP efficacy TKA, total knee arthroplasty; PRP, platelet-rich plasma; IO, intraosseous

previous studies in which repeated administration of PRP improved the response. Vaquerizo et al. observed at six month follow-up an improvement in the functionality of patients treated with repeated cycles compared with those who received only one [21]. A clinical trial with a 24-month follow-up showed that patients treated with repeated cycles of PRP presented a greater long-term improvement than those who received only one cycle [22]. Although it is a treatment that in the long term is superior to other conservative treatments [23], these findings as well as others from in vivo studies [24] suggest that the effect of PRP decreases over time and that new doses are needed to prolong its effect in the long term. Periodic repetitions of PRP infiltrations may contribute to maintaining the biological balance in the joint over time, slowing down the degenerative processes.

The route of administration should also be considered for optimizing the clinical outcomes. The combination of intraosseous and intra-articular administration of PRP might increase its range of action and the therapeutic effect, acting directly on the subchondral bone which is the key in the KOA pathophysiology [25]. In the survival analysis, the influence of intraosseous administration was not observed when analyzing all the patients included in the study. However, significant improvement was found in patients with severe KOA. Indeed, intraosseous PRP administration is indicated for patients with advanced KOA [26]. Therefore, although intra-articular administrations of PRP are effective in patients with less advanced KOA and have some influence on severe KOA, the latter might present a more positive response to intraosseous administration.

Despite the therapeutic effect of PRP observed in this study and the influence of the variables analyzed, it is necessary to consider the placebo effect. Recent studies have shown that this effect is a component of intra-articular injections that should not be ignored and it is therefore present in PRP infiltrations [27, 28]. However, an increasing number of studies both "in vitro" and "in vivo" are finding mechanisms of action that explain in part their effect on pain, inflammation, lubrication, or tissue repair [25]. Conducting not only preclinical but also clinical studies to provide more insight into the mechanisms of action of PRP is necessary to optimize and enhance this therapy.

The present work suggests that the application of PRP is a valid treatment to avoid or delay surgery and it supports other findings in elbow [29] and ankle [30], although further clinical studies are needed to optimize protocols that improve clinical outcomes. In addition to the inherent limitation of a retrospective study, one of the major difficulties of this study was to establish a clear date of diagnosis due to the nature of this pathology, so the dates of treatment were used as a reference. Another limitation of this study was the lack of X-ray images in some medical records, so additional criteria and image studies were considered for the KOA classification. Besides, during the follow-up of some patients, the application of other conservative treatments was unclear, and they were excluded from the analysis. Finally, multicenter studies with control groups are needed to make progress on the issue raised by this work.

Conclusion

The application of PRP in KOA patients is a treatment that could delay TKA. Variables such as KOA degree, age, PRP cycles, and the type of administration influence the clinical outcomes, although further studies are needed to understand PRP mechanisms and to design protocols that improve its efficacy.

Authors' contributions All authors equally contributed to this paper, in terms of the conception and design of the study, literature review and analysis, drafting and critical revision and editing, and final approval of the final version.

Data availability Not applicable.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethics approval The present study was carried out in accordance with the international standard on clinical studies: Declaration of Helsinki in its latest revised version (Fortaleza, Brazil; 2013), and Good Clinical Practice Regulations (International Conference for Harmonization). Ethical approval for this study was obtained from the Ethics Committee of the Basque Country.

Consent to participate Not applicable.

Consent for publication Not applicable.

Code availability Not applicable.

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