Level of Evidence and Industry Sponsorship Associated with Favorable Outcomes in Publications on Platelet-Rich-Plasma Therapy in Musculoskeletal Disorders*

Nível de evidência e patrocínio industrial associados a desfechos favoráveis nas publicações sobre terapia de plasma rico em plaquetas em doenças osteomusculares

Pietro Felice Tomazini Nesello[1] Allan Cassio Baroni[1] Luciano da Silva Selistre[2]

[1] Institute of Sports Medicine and Sciences Applied to Human Movement, Universidade de Caxias do Sul, RS, Brazil
[2] Department of Biostatistics, Hospital Geral, Universidade de of Caxias do Sul, RS, Brazil

Address for correspondence Pietro Felice Tomazini Nesello, MD, Instituto de Medicina do Esporte e Ciências Aplicadas ao Movimento Humano, Universidade de Caxias do Sul, Rua Francisco Getúlio Vargas 1.130, Caxias do Sul, RS, 95070-560, Brazil (e-mail: pietrofelicenesello@gmail.com).

Rev Bras Ortop 2020;55(3):263–268.

Abstract

Platelet-rich plasma is derived from centrifuging whole blood. There is increasing interest in the sports medicine and athlete community about providing endogenous growth factors directly to the injury site, using autologous blood products such as platelet-rich plasma. The aim of the present study is to evaluate the association between research financing, conflict of interests, level of evidence and author affiliation with the interpretation of results in articles published on platelet-rich plasma therapy in musculoskeletal ailments. A review of the current literature was performed. The outcome was classified as favorable or unfavorable. The declaration of conflict of interests and the type of funding was extracted from each article. The financing was classified as industry-sponsored; not industry-sponsored; or unidentifiable. The level of evidence was categorized from I to IV. Higher positive outcomes were observed in 134 studies with industry sponsorship compared with not industry-sponsored studies (odds ratio [OR]: 0.26; 95% confidence interval [95%CI]: 0.08–0.85; $p < 0.05$). Compared with level of evidence I, levels II and IV increase the probability of positive outcomes by 12.42 times ($p < 0.01$) and 10.97 times ($p < 0.01$) respectively. Proportionally, industry-sponsored studies are more likely to present positive results, as well as articles with a lower quality of evidence.

Keywords

- platelet-rich plasma
- musculoskeletal diseases
- industry
- conflict of interest
- ethics

Resumo

O plasma rico em plaquetas é derivado da centrifugação do sangue total. Há um interesse crescente, na medicina esportiva e na comunidade atlética, no fornecimento de fatores de crescimento endógeno diretamente ao sítio da lesão, usando

* *Work conducted at the Institute of Sports Medicine and Sciences Applied to Human Movement, Universidade de Caxias do Sul, RS, Brazil.*

received
April 24, 2018
accepted
October 16, 2018

DOI https://doi.org/10.1055/s-0039-1700834.
ISSN 0102-3616.

componentes sanguíneos autólogos, como o plasma rico em plaquetas. O objetivo deste estudo é avaliar a associação entre financiamento de pesquisa, conflito de interesses, nível de evidência e afiliação dos autores com a interpretação dos resultados em publicações sobre terapia com plasma rico em plaquetas nas doenças osteomusculares. Foi realizada uma revisão da literatura atual. O desfecho foi classificado como favorável ou desfavorável. A declaração de conflito de interesses e o tipo de financiamento foram extraídos de cada artigo. O financiamento foi qualificado em patrocínio industrial; não patrocinado pela indústria; ou não identificável. O nível de evidência foi categorizado de I a IV. Foram obtidos os resultados positivos mais altos com 134 estudos financiados pelo setor industrial, em comparação com estudos não financiados pela indústria (razão de probabilidades [RP]: 0,26; intervalo de confiança de 95% [95% IC]: 0,08–0,85; $p < 0,05$). Em comparação com o nível de evidência I, os níveis II e IV aumentam a probabilidade de resultado positivo em 12,42 vezes ($p < 0,01$) e 10,97 vezes ($p < 0,01$), respectivamente. Demonstrou-se que, proporcionalmente, estudos patrocinados pela indústria têm maior probabilidade de apresentar resultados positivos, bem como artigos com menor qualidade de evidência.

Palavras-chave
- plasma rico em plaquetas
- doenças musculoesqueléticas
- indústria
- conflito de interesses
- ética

Introduction

Platelet-rich plasma (PRP) is obtained by centrifuging the blood of the patient, resulting in a fraction rich in platelets higher than the serum concentration.[1] Therapy with this preparation consists of activating growth factors that migrate to the sick spot, namely the region in which an improvement in tissue regeneration and angiogenesis are necessary. As such, the biological effect of this blood preparation takes form, facilitating the biocellular environment and theoretically accelerating the process of cicatrization.[2]

Recently, the use of PRP has been observed in the treatment of some osteomuscular injuries.[3,4] However, many of these studies have small sample sizes and high risk of bias.[5–7] It is known that financial backing from the industry is associated with favorable findings in many studies in the literature regarding orthopedic surgery.[8,9]

The aim of the present paper is to describe and investigate the association between research financing, conflict of interests, level of evidence and author affiliation with the interpretation of results in studies published on PRP therapy in musculoskeletal diseases (MSDs).

Methods

Research Strategy

We included papers about platelet-rich plasma therapy in cases of MSDs published in journals. Then, a review was performed in the PubMed and Scielo databases. The research of articles published over the past 10 years was conducted with keywords in the titles, and it ended on August 12th, 2016. The following keywords were researched: *Platelet rich plasma[Title] AND (hamstring[Title] OR achilles[Title] OR tunnel[Title] OR patellar[Title] OR plantar[Title] OR talar[Title] OR talus[Title] OR calcaneal[Title] OR calcaneus[Title] OR cruciate [Title] OR ulnar[Title] OR radial[Title] OR tibial[Title] OR knee [Title] OR shoulder[Title] OR elbow[Title] OR ankle[Title] OR hip [Title] OR rotator cuff[Title] OR handle[Title] OR low back[Title] OR spinal[Title] OR cervical[Title] OR arm[Title] OR forearm [Title] OR gluteal[Title] OR gluteus[Title] OR calf[Title] OR leg [Title] OR gastrocnemius[Title] OR quadriceps[Title] OR abductor[Title] OR adductor[Title] OR abdominal[Title] OR biceps [Title] OR triceps[Title] OR pectoral[Title] OR joint[Title] OR articular[Title] OR chondral[Title] OR tendon[Title] OR tendinous[Title] OR soft tissue[Title] OR muscle[Title] OR muscles [Title] OR muscular[Title] OR musculoskeletal[Title] OR bone [Title] OR bones[Title] OR skeletal[Title] OR cartilage[Title] OR cartilaginous[Title] OR ligament[Title] OR ligaments[Title] OR osteochondral[Title] OR damage[Title] OR damages[Title] OR harm[Title] OR harms[Title] OR contusion[Title] OR contusions[Title] OR sprain[Title] OR sprains[Title] OR twist[Title] OR twists[Title] OR torsion[Title] OR torsions[Title] OR fractures[Title] OR rupture[Title] OR ruptures[Title] OR dislocation [Title] OR dislocations[Title] OR luxation[Title] OR luxations [Title] OR strain[Title] OR strains[Title] OR tendinitis[Title] OR tendinopathy[Title] OR tendinopathies[Title] OR tendinosis[Title] OR fasciitis[Title] OR arthritis[Title] OR osteoarthritis[Title] OR arthrosis[Title] OR osteoarthrosis[Title] OR osteoporosis [Title] OR osteomyelitis[Title] OR bursitis[Title] OR lesion[Title] OR lesions[Title] OR synovitis[Title] OR trauma[Title] OR traumatic[Title] OR injury[Title] OR injuries[Title] OR epicondylitis [Title] OR sport[Title] OR sports[Title] OR athletes[Title] OR degenerative[Title]) AND ("2008/09/23"[PDat]: "2016/08/12"[PDat] AND "humans"[MeSH Terms] AND (Portuguese [lang] OR English[lang]) AND "adult"[MeSH Terms])*.

The inclusion criteria were: papers published about PRP therapy and MSDs, describing studies in humans > 18 years of age, written in English or Portuguese, with the full text available. The exclusion criteria were: papers on topics that differed from the one of the present research, experimental and protocol studies, and studies with quality of evidence level V on the Oxford scale.[10]

Collection of Data

Two authors independently reviewed each paper and collected the following data: quality of the outcomes, level of evidence, authorship, financing, and conflict of interests.

In keeping with the hypotheses of the authors of each article, the conclusions and discussions were reviewed to evaluate the interpretation of the results. Key expressions such as "more effective," "superior," "is better," "more efficient," "is safe," "is recommended," "should be used" qualified the outcome as favorable. And the expressions: "is the same," "did not display any difference," "there is no evidence to support the use" denoted an unfavorable outcome. Each article was evaluated according to the directives of the Oxford Center for Clinical Evidence.[10] The classification of the level of evidence varied from I to V, with level I being the highest quality and V being the worst. The authorship, in turn, was considered academic if all authors presented academic affiliations: faculty of medicine, university, medical school or hospital. If one or more authors disclosed laboratorial, industrial or any other company affiliations, that type of authorship was considered industrial. The financing of the study was categorized as follows: industry-sponsored, not industry-sponsored or unidentifiable. If any of the authors were linked to a pharmaceutical company, if financial support was declared, or if gratitude was expressed to any industry, the study was considered industry-sponsored. In the case of financial support from public, governmental academic and research institutions, then the financing was considered not industry-sponsored. If the financial support was not possible to classify, then it was deemed unidentifiable. The declaration of conflict of interests was classified as present or absent. If there was no declaration, the conflict of interests was considered unclassified.

In cases in which the authors of the present paper were not in agreement, the article was revised and discussed until agreement was reached.

Statistical Analysis

The level of interobserver agreement was measured with kappa (κ) statistics, and the values were described in accordance with the Fleiss criteria.[11] A descriptive statistic with frequencies and percentages was used. The Chi-squared test was used to evaluate the relationship between the quality of the outcome and the other variables. A posterior binary logical regression was planned and used to diminish the confusion bias and to measure the adjusted odds ratio (OR) (exponentiation of the B coefficient [Exp B]). The variables with p-values < 0.20 in the Chi-squared test were selected for the binary logistic regression. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS, IBM Corp., Armonk, NY, US) software, version 22. Values of $p < 0.05$ from both sides were considered significant, with a 95% confidence interval (95%CI) .

Results

Our electronic research identified 204 studies published since August 16, 2006. After excluding 70 (34.3%) studies, 134 (65,7%) publications were included for analysis (►**Table 1**). The frequency of favorable outcomes was of 96 (71,6%), differing significantly from the negative outcome ($p < 0.001$). The interobserver κ value for the outcome was of 0.89 ($p < 0.001$), displaying an index of excellence.

Table 1 Flowchart of the search strategy to identify studies on the use of platelet-rich therapy in diseases of the musculoskeletal system

1. Identification
2. Selection
3. Elegibility
4. Included
5. Articles found in the electronic search (n = 204)
6. Articles selected for the review (n = 188)
7. Articles evaluated for elegibility (n = 134)
8. Included studies (n = 134)
9. Excluded studies (16):
• Studies in Spanish (3) and Czech (1);
• Full text not available (12);
10. Excluded (54):
• Studies not regarding the research topic (26);
• Protocol studies (2);
• Experimental/Laboratory studies (20);
• Studies with level V of evidence (6);

The industry was identified as a sponsor of the study in 26.1% of the cases (►**Table 2**); nonetheless, in almost half of the cases, it was not possible to classify the financer. Conflict of interests was present in 15.7% of the total, and a larger proportion of papers was at level IV on the Oxford scale. We noted that, in all of the described variables, the frequencies were different from what was expected ($p < 0.001$). The κ indexes were all in the "excellent" category ($p < 0.001$).

The relationship between the variables investigated denotes that the industry-sponsored studies had a higher frequency of positive outcomes in relation to notindustry-sponsored studies. On the other hand, in relation to levels of evidence, we significantly observed ($p < 0.001$) that the lower the quality of a study, the greater the frequency of positive outcomes (►**Table 3**).

In the multivariate analysis, the participating variables of the model were: financing and level of evidence. The overall statistics for the Chi-squared of the residues was of 27.44 ($p < 0.001$). Based on the analysis of the model, a significant relationship was detected between industry sponsorship and non-industry sponsorship. The adjusted OR for positive outcomes decreased by ~ 74% in the non-industry studies in relation to the industry studies (OR: 0.26; 95%CI: 0.08–0.85; $p < 0.05$). On the other hand, as for the level of evidence, we observed that, compared with evidence level I, levels II and IV increased (OR: 12.42; 95%CI: 3.79–40.67; $p < 0.001$; and OR: 10.97; 95%CI: 2.33–51.51; $p < 0.01$) respectively for a positive outcome (►**Table 4**).

Table 2 Expected frequency and level of interobserver agreement

		Frequency (%)	Qui-squared*	*p*-value	Kappa (κ) value	*p*-value
Outcome	Favorable	96 (71.6)	25.10	< 0.001	0.89	< 0.001
	Unfavorable	38 (27.9)				
Financing	Industry-sponsored	35 (26.1)	25.80	< 0.001	0.85	< 0.001
	Not industry-sponsored	27 (20.1)				
	Unclassified	72 (53.7)				
Authorship	Academic	46 (34.3)	13.16	< 0.001	0. 83	< 0.001
	Industrial	88 (65.7)				
Conflict of interests	Yes	21 (15.7)	39.50	< 0.001	0.87	< 0.001
	No	78 (58.2)				
	Unclassified	35 (26.1)				
Level of evidence	I	27 (20.1)	38.32	< 0.001	0.80	< 0.001
	II	39 (29.1)				
	III	10 (7.5)				
	IV	58 (43.3)				

Note: *Chi-squared analysis for a sample of expected equivalent frequency.

Table 3 Association between the quality of the outcome and the studied variables

		Outcome		*p*-value
		Favorable ($n = 96$)	Unfavorable ($n = 38$)	
Financing	Industry-sponsored ($n = 35$)	29 (30.2%)	6 (15.8%)	0.159
	Not industry-sponsored ($n = 27$)	20 (20.8%)	7 (18.4%)	
	Unidentifiable ($n = 72$)	47 (49%)	25 (65.8.%)	
Autorship	Academic ($n = 46$)	31 (32.3%)	15 (39.5%)	0.430
	Industrial ($n = 88$)	65 (67.7%)	23 (60.5%)	
Conflict of interests	Yes ($n = 21$)	16 (16.7%)	5 (13.2%)	0.638
	No ($n = 78$)	57 (59.4%)	21 (55.3%)	
	Unclassified ($n = 35$)	23 (24%)	12 (31.6%)	
Level of evidence	I ($n = 27$)	12 (12.5%)	15 (39.5%)	< 0.001*
	II ($n = 39$)	29 (30.2%)	10 (26.3%)	
	III ($n = 10$)	4 (4.2%)	6 (15.8%)	
	IV ($n = 58$)	51 (53.1%)	7 (18.4%)	

Note: *Linear association.

Discussion

Our findings showed that industry financing of publications on PRP therapy is significantly associated with favorable outcomes. In addition, we observed that the greater the level of evidence, the lower the proportion of favorable outcomes. We also recognize the limitations of our analysis, like that fact that we were unable to evaluate and detect significant findings in relation to the type of financing. In many cases, we did not qualify the support because it was not described. However, the present article is the first to describe variables that might influence the outcomes of publications on PRP therapy.

The clinical therapeutic use of PRP has been studied by many authors.[7,12,13] A systematic review[7] that assessed the effects (benefits and harms) of PRP in the treatment of MSDs concluded in general that there currently is insufficient evidence to support its use.[7] Another systematic review[12] evaluated the effects of PRP in the treatment of long bone osteotomies, acute fractures, ununited fractures and defects, and the authors showed that the currently available evidence is insufficient to support the routine use of this intervention in the clinical practice.[12] A meta-analysis[13] studied the efficacy of PRP treatment for hamstring injury and showed no effect when the patients were compared with the control group (OR: 1.03; 95%CI: 0.87–1.22; $p = 0.73$)[13] These reviews seem to show that there are studies with poor quality of evidence and that there currently is insufficient data showing the clinical benefit of the use of PRP.

Table 4 Binary logistic regression of the variables associated with favorable outcomes

		B coefficient	Adjusted odds ratio (95% confidence interval)	*p*-value
Financing	Industry-sponsored	–	–	0.058
	Not industry-sponsored	-1.32	0.26 (0.08–0.85)	0.026
	Unidentifiable	-0.91	0.39 (0.12–1.30)	0.130
Level of evidence	I	–	–	< 0.001
	II	2.52	12.42 (3.79–40.67)	< 0.001
	III	0.82	2.27 (0.76–6.78)	0.141
	IV	2.39	10.97 (2.33–51.51)	0.002

Amiri et al[14] found favorable outcomes in the association between research financing and favorable conclusions in 81% of spine research. In another article,[15] the rate of researches with positive outcomes was of 48.8%. Nonetheless, these authors considered the outcome "neutral", with a frequency of 41.4% in the respective paper, and in cases of arthroplasty of the hip and of the knee, they showed that 70.81% of papers had positive outcomes. Generally, most papers displayed favorable outcome biases. Similarly, low rates of unfavorable conclusions were also reported by other authors in research on general orthopedics.[16]

There has been a lot of debate surrounding the research financing and how much this sponsorship can influence the publication of favorable studies.[11,15,16] Our findings showed that the industry was the sponsor of the research in 26.1% of the cases, but in almost half of the studies, it was not possible to classify the financer. A review of 886 articles described that 246 (27.7%) of research projects were sponsored by the industry.[11] Printz et al[16] performed a critical review of 48 studies on injections of hyaluronic acid for osteoarthritis of the knee. The authors found that 35% of the publications were financed by the industry.

Noordin et al[15] found that studies sponsored by the industry had a higher probability of reporting favorable outcomes in relation to studies with other sources of financing.[15] Other authors reviewed the relationship of financial support with positive conclusions in spinal research,[12] and they showed that the OR was of 3.3 (95%CI: 2.0–5.5). In our research, we noted that the adjusted OR was of 0.26 (95%CI: 0.08–0.85) in the publications not sponsored by the industry. It becomes difficult to compare the results with the amount of studies in the present paper that were deemed "unidentifiable."

Our results also show the articles without due declaration of financial support for the research. Other authors corroborated these data, with 41.3% of the articles without information relating to the financial backing.[17] Therefore, we believe that the frequency of articles sponsored by health industries cannot be precisely determined by the methodology used. Even if the industry, the profession and the patient have many shared interests, they also may have real or potential conflicting interests.[18] A study[19] that analyzed the disclosure of conflict of interests among orthopedic doctors in a meeting of the American Academy of Orthopaedic Surgeons[19] showed that 20.7% of professionals did not disclose their directly-related payments. Therefore, we noted that policies concerning conflicting interests and their disclosure are in constant flux, and that maybe additional clarification to people regarding the demands for disclosure is necessary.[11]

The challenge is to identify and manage the conflict, and from there comes the authors' obligation to disclose the conflict of interests.[20] By contrast, in our analysis, which is corroborated by other authors, many journals do not mandatorily require the declaration of conflict of interests.[11]

Our work showed the presence of more articles with level IV of evidence. Pinski et al[21] evaluated the evidence level in research on the surgical treatment of osteochondral injuries, and they showed that 90% of papers were at level IV of evidence. Cunningham et al[22] showed that publications with levels I and II, as much as those with levels III and IV, increased significantly from 2000 to 2010. Despite that, a proportion of level-IV studies was always greater during the 10 years of analysis.

Amiri et al[12] showed that, among the positive outcomes (80% of cases), 85% of level-IV and 63% of the level-I articles were reflected.[12] By contrast, among the unfavorable outcomes 14% of level-I studies and 6% of level-IV studies were observed. These findings showed a significant linear relation: the greater the level of evidence, the lower the frequency of favorable studies.[23]

Conclusion

Thus, our paper showed that, in general, positive outcomes are more frequent in publications about PRP therapy in MSDs. Most of the papers were not academically affiliated, did not declare financial support for the research, and had level IV of evidence. We noted that industry-sponsored studies were more likely to present positive results, as well as articles with a lower quality of evidence. It is crucial to critically evaluate each scientific article and to not blindly trust the authors' conclusions, as well as to be aware of potential conflict of interests on the part of the authors investigating this field.

Conflict of Interests

The authors have no conflict of interests to declare.

Acknowledgments

We would like to express our gratitude to the professor of biostatistics and epidemiology Petrônio Fagundes de Oliveira Filho, for his help and his teachings. We are also grateful to Professor Robert Sweeney for his support with English. We would also like to thank the Institute of Sports Medicine and Sciences Applied to Human Movement at Universidade de Caxias do Sul and all its collaborators, especially Eduardo Pflug Comparsi and Olga Sergueevna Tairova, friends and sports physicians.

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