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Use of Platelet-Rich Plasma in the prevention of cardiovascular surgical wound infections: Integrative review

Uso de Plasma Rico em Plaquetas na prevenção de infecções após cirurgias cardiovasculares: Revisão integrativa

Uso del Plasma Rico en Plaquetas para prevenir infecciones tras cirugía cardiovascular: Revisión integrativa

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Abstract
This integrative review seeks to evaluate the effectiveness of the use of platelet-rich plasma in preventing infections after cardiovascular surgeries through the analysis and comparison of existing studies in the database, given that sternal infections are common complications in cardiac surgeries and the search for its prevention is of high importance in medical care. Articles were searched using the descriptors: Surgical wound infection and Platelet-rich plasma, on the platforms: PubMed, Scielo, and BVS. The inclusion criteria used were: articles related to the area of cardiovascular surgery with the use of PRP, published in the last 10 years and written in Portuguese or English. 7 articles were selected and later analyzed according to their degree of recommendation and level of evidence. The study concluded that the use of PRP is effective in reducing post-surgical complications and improving wound healing, however, the lack of studies in the area makes it necessary to carry out more high-quality studies.
Keywords: Platelet-rich plasma; Surgical wound infection; Cardiovascular surgical procedures; Wound healing.

Resumo
Essa revisão integrativa busca avaliar a eficácia do uso de plasma rico em plaquetas na prevenção de infecções após cirurgias cardiovasculares através da análise e comparação de estudos existentes na base de dados, visto que infecções esternais são complicações comuns em cirurgias cardíacas e a busca de tratamentos para a sua prevenção são de alta importância nos cuidados médicos. Foram coletados trabalhos utilizando os descritores: Surgical wound infection e Platelet-rich plasma, publicados nas plataformas PubMed, Scielo e BVS. Os critérios de inclusão utilizados foram: artigos relacionados à área de cirurgia cardiovascular com uso de PRP, publicados nos últimos 10 anos e escritos em português ou inglês, sendo selecionados 7 artigos que posteriormente foram analisados de acordo com o seu grau de recomendação e nível de evidência. Concluiu-se que o uso do PRP é eficaz na diminuição de complicações pós cirúrgicas e auxilia na cicatrização, no entanto há uma escassez de estudos na área, sendo necessário a realização de mais estudos de alta qualidade.
Palavras-chave: Plasma rico em plaquetas; Infecção de ferida cirúrgica; Cirurgia cardiovascular; Cicatrização de feridas.

Resumen
Esta revisión integradora busca evaluar la efectividad del uso de plasma rico en plaquetas en la prevención de infecciones después de cirugías cardiovasculares a través del análisis y comparación de estudios existentes en la base de datos, dado que las infecciones esternales son complicaciones comunes en las cirugías cardíacas y la búsqueda de tratamientos para su prevención. es de gran importancia en la atención médica. Los trabajos fueron recolectados utilizando los descriptores: Infección de herida quirúrgica y Plasma rico en plaquetas, publicados en las plataformas PubMed, Scielo y BVS. Los criterios de inclusión utilizados fueron: artículos relacionados con el área de cirugía cardiovascular con uso de PRP, publicados en los últimos 10 años y escritos en portugués o inglés, seleccionándose 7 artículos que luego fueron analizados según su grado de recomendación y nivel de evidencia. Se concluyó que el uso del PRP es efectivo para reducir las complicaciones posquirúrgicas y coadyuva en la cicatrización, sin embargo faltan estudios en el área, por lo que es necesario realizar más estudios de alta calidad.
Palabras clave: Plasma Rico en plaquetas; Infección de la herida quirúrgica; Procedimientos quirúrgicos cardiovasculares; Cicatrización de heridas.

1. Introduction

Surgical site infections occur when microorganisms enter the surgical incision and proliferate, which can be a major complication after cardiac procedures (Gelape, 2007). These infections are often associated with sternal infections and graft harvesting and can be categorized as superficial (SSWI) or deep (DSWI), with the first affecting the skin and subcutaneous tissue and the second the tissues below the fascia. The patient's skin is the main source of contamination, and various risk factors can increase the likelihood of infection such as age, diabetes, comorbidities, obesity, smoking, malnutrition, and intra- and postoperative conditions (Gelape, 2007; Phoon & Hwang, 2020). Due to the large extent and aggressiveness of heart surgeries, the risk of infection becomes even higher, with rates ranging from 3.5% to 26.8%. This poses a significant threat to patient health and can lead to increased morbidity and mortality rates (Zukowska & Zukowski, 2022).

Platelet-rich plasma (PRP) is a biological product made from the patient's blood and collected through centrifugation, which allows the extraction of plasma with a platelet concentration up to five times greater than in regular blood. One of the major benefits of PRP is its ease of extraction, preparation, and storage, as well as being an autologous derivative, which poses fewer challenges than compounds that require donation or transplantation (Giannotti et al., 2023). PRP helps reduce the incidence of surgical infections by utilizing the growth factors, immunological messengers, and enzymes found in platelets, which, when in their active form, assist in healing and tissue regeneration, as well as control bacteria and coagulation, assisting in tissue repair and wound healing through cell proliferation and migration (Sethi et al., 2021). This compound has shown a significant role in various medical fields, including the stimulation of tissue growth in dermatology, gynecology, orthopedics, plastic surgery, veterinary medicine, and dentistry (Alves & Grimalt 2017; Giannotti et al., 2023).

More recently, randomized clinical trials have explored the usage of PRP in patients who have undergone cardiovascular surgery. However, a consistent analysis of the recently obtained results has yet to be conducted. To enrich the literature on this subject, this integrative review seeks to evaluate the effectiveness of the use of platelet-rich plasma in preventing infections after cardiovascular surgeries through the analysis and comparison of existing studies in the database.

2. Methodology

This article presents an integrative review written based on the following steps: formulation of the research question using the PICO strategy, construction of research searches based on the research question, search for eligible articles in the literature, determining inclusion and exclusion criteria, selection of the articles based on the established criteria, analysis of possible biases, data extraction, summarizing the results and conclusion of the study (Rodrigues et al., 2022).

Therefore, following the PICO strategy (Methley et al., 2014), the following research question was established: “Is there an association between the use of Platelet-rich plasma and the reduction of surgical site infections after cardiovascular surgery?”, as shown in Figure 1.

Figure 1 - PICO used for formulating the research question.

P:	Patients undergoing cardiovascular surgery
I:	Use of PRP
C:	Standard procedure
O:	Reduction of surgical site infection

Source: Authors.

Research searches were determined through the Medical Subject Headings (MeSH), being: Surgical wound infection and Platelet-rich plasma. The boolean operator AND was used for an advanced search that was carried out in the following databases: Medical Literature Analyses and Retrial System Online (MEDLINE) (through PubMed), Brasil Scientific Electronic Library Online (Scielo), and Biblioteca Virtual em Saúde (BVS), between October and November of 2023.

Inclusion criteria such as scientific articles related to cardiovascular surgery using PRP, published in the last 10 years, and written in English or Portuguese were applied to determine article eligibility. Additionally, exclusion criteria such as dental scientific articles, animal studies, meta-analyses, case reports, and revision articles were implemented.

After identifying relevant articles through title and resume screening the articles were read in full and selected, a citation search was conducted on the selected articles, and an analysis of possible biases was performed.

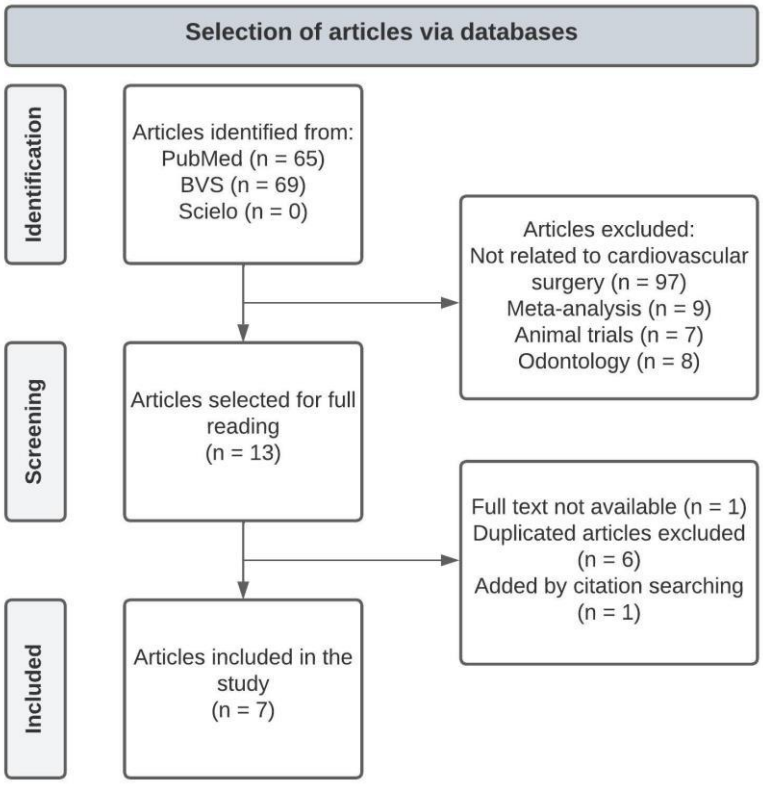
An analysis of the level of evidence and degree of recommendation of the selected studies was carried out using the Oxford Center for Evidence-Based Medicine (2009) methodology, which categorizes studies based on their type and data collection quality. This measure assures the reliability of this summary.

This review was conducted according to the PRISMA protocol to ensure transparency and credibility in information dissemination, reducing the risk of bias (Page et al., 2021).

3. Results

The literature search in the databases resulted in 134 articles. After screening the titles and abstracts and applying eligibility criteria, 13 of these articles were selected for full reading. Consequently, 7 studies underwent final analysis, as shown in the flowchart. (Figure 2).

Figure 2 - Flow chart of the search and selection of articles.



Source: Authors.

3.1 Primary information of the articles

Table 1 showcases the articles categorized based on their source and country of publication. The data reveals that out of the total number of articles, 57.14% (n=4) were published in Europe while the remaining 42.86% (n=3) were published in the United States (USA).

Table 1 - Characteristics of articles concerning the source and country of origin.

Nº	Reference	Title	Source	Country
1	Dörge et al. (2013)	Incidence of Deep Sternal Wound Infection Is Not Reduced with Autologous Platelet Rich Plasma in High-Risk Cardiac Surgery Patients.	BVS	Germany
2	Hamman et al. (2014)	Relation Between Topical Application of Platelet-Rich Plasma and Vancomycin and Severe Deep Sternal Wound Infections After a First Median Sternotomy.	PubMed BVS	USA
3	Jiritano et al. (2022)	Efficacy of prophylactic platelet-rich plasma (PRP) following open saphenous vein harvesting in cardiac surgery.	PubMed BVS	Italy
4	Patel et al. (2016)	Evaluation of autologous platelet-rich plasma for cardiac surgery: outcome analysis of 2000 patients.	PubMed BVS	USA
5	Serraino et al. (2013)	Platelet-rich plasma inside the sternotomy wound reduces the incidence of sternal wound infections.	PubMed BVS	Italy
6	Vermeer et al. (2019)	Platelet-leukocyte rich gel application in the prevention of deep sternal wound problems after cardiac surgery in obese diabetic patients.	PubMed BVS	Netherlands
7	Zhou et al. (2013)	Analysis of Autologous Platelet-Rich Plasma During Ascending and Transverse Aortic Arch Surgery.	Citation Tracking	USA

Source: Authors.

3.2 Characteristics of the Articles

Chart 1 presents the type of study, the methodology used, and the main conclusions. Of the selected studies, only one is a randomized clinical trial (14.28%). The others are retrospective cohorts (71.4%) and non-randomized clinical trials (14.28%).

Chart 1 - Analysis of selected articles.

Reference	Study type	Methodology	Conclusions
Dörge et al. (2013)	Randomized clinical trial	196 patients at risk of Deep sternal wound infections (DSWI) were ramdomically selected for the application of autologous PRP and thrombin simultaneously between the sternal edges after the sternal wires (97) or for the control group (99). The endpoint was the occurrence of DSWI requiring revision surgery.	The application of autologous PRP in patients undergoing cardiac surgery who possess a high risk of sternal complications did not reduce the incidence of DSWI.
Hamman et al. (2014)	Clinical trial and Retrospective Cohort study	1866 patients undergoing cardiac surgery participated in the study, in which 548 received the PRP paste on the edges of the sternal wounds before closure, and 1,318 were historical controls.	Patients who did not receive the PRP paste were 18 times more likely to develop DSWI than the ones who did receive it. The association between the intervention and the incidence of severe DSWI was statistically significant.
Jiritano et al. (2022)	Retrospective Cohort study.	953 patients who underwent coronary artery bypass graft surgery (CABG using saphenous vein as a conduction graft) participated and were retrospectively divided into two groups. The treatment group (n=452), who received topical application of PRP, and the control group (n=501). The primary outcome was the occurrence of surgical site infection.	The use of autologous PRP may have a positive impact in lowering the occurrence of surgical site infection. This benefit is significantly more pronounced in individuals with diabetes.
Patel et al. (2016)	Non-randomized clinical trial	In the study, 2000 patients undergoing cardiac surgery participated, in which 1000 got PRP applied to the sternum and soft tissues during the sternal closure, and 1000 were controls. The outcomes analyzed included wound healing, infections, remission, and costs.	The use of PRP efficiently reduces the incidence of wound healing complications and subsequently reduces associated costs. Therefore, it is recommended that PRP be incorporated as a standard practice in sternotomy procedures.
Serraino et al. (2013)	Retrospective Cohort study	In the study, 1093 patients undergoing cardiac surgery through a median sternotomy participated, in which 641 got PRP applied to the sternum before sternal closure, and 422 were controls. The primary outcome was the occurrence of DSWI and SSWI was the secondary outcome analysed.	The use of PRP significantly reduces the occurrence of DSWI and SSWI.
Vermmer et al. (2019)	Clinical trial and Retrospective Cohort study	The study analyzed the occurrence of Deep sternal wound problems (DSWP) in obese DM 2 patients undergoing cardiac surgery through a median sternotomy. The study group (n=144) received PRP gel between the sternal halves before closure and the control group (n=118) consisted of patients who underwent surgery in the 2 years before the use of PRP.	The use of PRPgel can be useful in the prevention of DSWP in high-risk patients.
Zhou et al. (2013)	Retrospective Cohort study	The study is a retrospective analysis of 685 cases of ascending aorta and transverse arch repair, in which 287 patients were treated with autologous platelet-rich plasma (PRP) while 398 patients underwent the standard procedure without PRP. The study aimed to evaluate the efficacy of PRP treatment in reducing the need for blood transfusions and postoperative morbidity.	Platelet-rich plasma (PRP) has been shown to significantly reduce the requirement for blood transfusions while also decreasing the incidence of early mortality, the need for dialysis, and the length of stay in the intensive care unit.

Source: Authors.

In methodological terms, 7055 patients were evaluated in total, including those who underwent PRP administration and patients in the control group. Of all the studies included, only one study did not obtain positive outcomes with the use of PRP (Dörge et al., 2013).

3.3 Bias and limitations

Dörge et al. (2013) presented two limitations in their research. Firstly, the use of bone wax to close the sternum may have impacted the application of platelet-rich plasma (PRP). Secondly, the study was limited by a small sample size.

Hamman et al. (2014) had limitations related to the use of retrospective controls, as there were changes and advances in surgical technique, wound care, and antibiotics that may have benefited the group that received PRP. Furthermore, the surgeries in the study group were more complex, which may have underestimated the effectiveness of the intervention.

Jiritano et al. (2022) contain selection bias as it is not a randomized study. Additionally, all data was collected from a single institution, which limits the generalizability of the findings. Furthermore, the study did not consider the severity of diabetes mellitus (DM) and its treatment when analyzing the diabetic population.

Patel et al. (2016) demonstrates selection bias as it is not randomized or blind, in addition to presenting several confounding variables.

Serraino et al. (2013) has certain limitations. Firstly, it is an observational study, which may limit the validity of the results. Secondly, the surgeries included in the study were performed in different periods, despite being consecutive. Added to this, the complications of PRP can raise ethical questions when conducting randomized studies.

Vermmer et al. (2019) main limitation is related to the use of a retrospective reference group.

Zhou et al. (2013) demonstrate information bias as it is a retrospective study, as the author himself reports in the text the need to take a generalized approach. In addition, there was a significant difference in preoperative variables between the study groups.

Furthermore, the studies found were analyzed and classified according to the level of scientific evidence and their degree of recommendation following the Oxford Center for Evidence-Based Medicine model (2009), as shown in Table 2.

Table 2 - Levels of evidence - "Oxford Center for Evidence-based Medicine"

Reference	Grades of recommendation	Evidence level
Dörge et al. (2013)	A	1B
Hamman et al. (2014)	B	2B
Jiritano et al. (2022)	B	2B
Patel et al. (2016)	B	2B
Serraino et al. (2013)	B	2B
Vermeer et al. (2019)	B	2B
Zhou et al. (2013)	B	2B

Source: Authors.

The research conducted by Dörge et al. (2013) holds superior scientific evidence and minimal bias potential, resulting in a more precise and trustworthy study. Consequently, it is recommended above all others. The remaining studies are similarly rated with their recommendation level being second only to the aforementioned research and their level of evidence, although slightly lower, is still deemed substantial.

4. Discussion

4.1 PRP preparation and application

Dörge et al. (2013) performed cardiac surgery with full sternotomy on cardiopulmonary bypass. PRP and thrombin were injected simultaneously, via spray, between the sternal edges after the sternal wires had been placed. To produce the PRP, 54 and 11 ml of patient blood were taken, which were mixed with 6 and 1.2 ml of 5.5% anticoagulant calcium citrate,

respectively. The anticoagulated blood was then processed to separate the platelets, obtaining 2 ml of autologous PRP and 8 ml of thrombin, which were stored at 8°C until 30 minutes before surgery, when it was reheated until it reached room temperature.

Hamman et al. (2014) performed surgeries on patients who had not previously undergone procedures requiring sternotomy and applied PRP paste to the edges of the sternum before closure. The PRP paste was produced by combining 5 ml of 10% calcium chloride solution with 5,000 IUs of topical thrombin of bovine origin, forming a suspension from which 0.6 ml was removed and combined with 3 ml of PRP. Subsequently, 2 grams of vancomycin hydrochloride powder were added to this mixture, forming a paste. The PRP added to the paste was obtained by processing 60 ml of the patient's blood, producing approximately 7 ml of PRP with a concentration of platelets ranging from 1.5 to 2 million, considered 4.8 times greater than that found in the blood, a great concentration for stimulating angiogenesis.

Jiritano et al. (2022) performed a coronary artery bypass surgery procedure in which PRP gel was applied to the extraction region before closing the incision. The PRP was prepared by collecting 18 ml of the patient's blood and was processed to obtain 8 ml of platelet gel, rich in growth factors, which was stored vertically at room temperature until application.

Patel et al. (2016) performed open cardiac surgery requiring a sternotomy. PRP was applied along with calcium chloride and thrombin to the exposed edges of the sternum and subcutaneous tissue before closing the sternal wound. To produce the PRP, 52 ml of the patient's blood was collected and mixed with 8 ml of anticoagulant dextrose citrate formula A., the anticoagulated blood was processed by an autologous platelet separator system producing 6 ml of PRP to be used in the procedure.

Serraino et al. (2013) performed complete sternotomy surgery with the application of autologous PRP on the sternum before closing the subcutaneous tissue. The PRP was prepared by removing 18 ml of blood from the patient in the operating room, during anesthetic induction. The blood was centrifuged and separated into 3 layers of which 2 ml of plasma was removed, to which 0.5 ml of calcium chloride was added. The solution obtained was left to rest horizontally to activate coagulation. The rest of the collected blood was added to a petri dish along with the already activated plasma, gradually, obtaining a platelet gel.

Vermmer et al. (2019) performed cardiac surgery involving a median sternotomy and cardiopulmonary bypass in patients with a BMI >30 and diagnosed with type 2 diabetes mellitus. The PRP was added, along with thrombin, between the halves of the sternum immediately before closure. To produce the PRP, 100 ml of blood was collected from the patient before the application of heparin and the beginning of the surgery to minimize platelet activation. The blood was anticoagulated using ACD-A (9:1) and centrifuged, obtaining 8 to 10 ml of PRP which were stored at room temperature.

Zhou et al. (2013) performed the repair of the ascending or transverse arch using PHCA and transfused autologous PRP during surgery aiming to recover cells. The PRP was collected from a large-caliber central venous access and approximately 15-20 ml/kg of blood was collected before administering heparin to the patient. The blood was processed by an autologous transfusion system to obtain 10 ml/kg of PRP. The PRP was stored at room temperature in a citrate collection bag for a new transfusion later, inside the operating room. The decision to perform PRP was left to the discretion of the anesthesiologist who performed each surgery.

4.2 Literature comparison

It is possible to compare the findings of the present study with the meta-analyses found in the literature. In the study Yao et al. (2021), the authors analyzed studies published in both English and Chinese. Retrospective cohort studies and randomized clinical trials that used PRP in surgeries with thoracic incisions were analyzed, separately. The results obtained by this work demonstrate that PRP is effective only in the retrospective cohort subgroup, while the clinical trial subgroup did not

obtain major differences. Therefore, PRP can be considered for the treatment of DSWI and SWI, however with a low level of evidence and with the need to carry out more high-quality clinical trials to ensure its effectiveness. Finally, the low number of randomized studies included in this publication may indicate publication bias.

Kirmani et al. (2017) only investigated papers published in English, considering only the topical use of PRP, and also included both observational studies and randomized clinical trials. This meta-analysis concluded that there is great efficiency of the treatment in the studies observed and states that the use of PRP can significantly reduce the occurrence of SWI.

The third meta-analysis used as a comparison was Zhu et al. (2023), this paper demonstrated that the use of PRP reduces the chances of DSWI and SWI after thoracic surgeries, however, the authors highlight the possibility of bias as the sample used was small and, in addition, the meta-analysis may present selection bias since other researches were not included.

5. Conclusion

According to the review, utilizing PRP to treat wounds post cardiovascular surgery significantly decreases the likelihood of DSWI and SWI in patients, while remaining cost-effective and user-friendly. Despite these promising findings, the limited number of studies available, coupled with small group sizes, raises concerns regarding the potential for bias and limits the level of evidence.

To ensure the validity and effectiveness of this treatment, additional research must be conducted, including larger and higher-quality studies. These studies should adhere to rigorous standards, such as randomized clinical trials with sizable sample sizes, double-blind protocols, and detailed accounts of methodology, data, and results. By doing so, we can enhance the practical impact of PRP and promote its safe and frequent use.

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