Injection of platelet aggregates in facial rejuvenation: a systematic review

Injeção de agregados plaquetários no rejuvenecimento facial: uma revisão sistemática

CARMEN LUCIA MUELLER STORRER 1*
CARLA FREHNER ANDRADE 1
LUÍS HENRIQUE KOHLER CHAVES 1
LETÍCIA MAÍRA WAMBIER 1
JULIANA LAROCCA DE-GEUS 1
JOÃO CÉZAR ZIELAK 1

Institution: Universidade Positivo, Curitiba, PR, Brazil


Conflicts of interest: none.

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ABSTRACT

Introduction: This systematic review was conducted to assess whether the use of a platelet aggregate injection with or without associated facial rejuvenation techniques favors facial rejuvenation in adult patients. Methods: Randomized clinical trials that compared the use of techniques for facial rejuvenation alone with the same techniques coupled with the injection of platelet aggregates were searched. The search was performed in indexed databases and in the gray literature. The Cochrane Collaboration bias risk tool was applied to assess the quality of the studies. Results: In total, 7137 articles were identified. Only four studies remained in the qualitative synthesis, and the others were considered as having undefined bias risk in the key domains. Conclusion: There are few studies in the literature that compare the use of platelet aggregates in facial rejuvenation and those that are available have a risk of “undefined” or “high” bias. There is a need for more well-designed clinical studies comparing the use of platelet aggregate injection with or without associated facial rejuvenation techniques.

Keywords: Skin; Rejuvenation; Platelet-rich plasma; Platelets; Fibrin; Review.
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INTRODUCTION

Currently, physical appearance is directly related to self-esteem, which also influences the acceptance of others\(^1\). A decrease of vascularization, the replacement of cells, fat atrophy, and loss of muscle tonus are some of the factors that trigger skin aging\(^2\). In addition, the combination of genetic factors (intrinsic aging) with environmental factors (photo aging) directly influences skin aging, a common biological process, which triggers clinical manifestations such as wrinkles, alteration of surface texture, and pigmentation, among others\(^2\). Thus, the treatment of facial rejuvenation is increasingly being exploited for a more effective and lasting achievement\(^1\).

Aesthetic facial rejuvenation can be divided into operational and non-operational procedures\(^3\). Operating procedures include facial liposculpture surgery, a procedure in which the tissues are carved with filling using intricate layers of infiltrated autologous tissue like fat for example\(^4\).

The prevention and treatment of skin aging are leveraging technological innovations in the cosmetic field; these innovations include mesotherapy and platelet-rich plasma (PRP), a potential tool for skin rejuvenation, capable of promoting the remodeling of the tissue as it is an autologous human platelet concentrate in a small volume of plasma, containing large reservoirs of bioactive proteins, including growth factors, which are able to facilitate collagen fibroblasts, increasing the proliferation of keratinocytes and the generation of hyaluronic acid, thus increasing, dermal elasticity\(^1,3,5\). In addition, a study proved that PRP in conjunction with aesthetic facial fat filling significantly reduced the post-treatment recovery time, thus favoring overall patient satisfaction\(^6\).

OBJECTIVE

There are many methods and techniques used in the treatment of facial rejuvenation, making it difficult to understand which facial therapies best favor this rejuvenation. We conducted a systematic review to compare the injection of platelet aggregates to other facial therapies in the facial rejuvenation of adult patients.

METHODS

Protocol and record

This study protocol was recorded in the PROSPERO database (CRD42017075650) and followed the recommendations of PRISMA\(^7\), held from August to December 2017 at the Universidade Positivo in Curitiba, Paraná, Brazil.
The following controlled vocabulary search (MeSH terms) and keywords of the search strategy were established based on the acronym PICOS:
1. Population (P): Adult patients
2. Intervention (I): Injection of platelet aggregates
3. Comparison (C): Other facial therapies
4. Primary outcome (O): Facial rejuvenation
5. Study design (S): Randomized clinical trials (RCTs)

The search included indexed electronic databases such as PubMed, Scopus, Web of Science, the Latin American Health Sciences Literature database (LILACS), the Brazilian Library of Dentistry (BBO), and the Cochrane Library (Chart 1).

In addition, a search was made in the gray literature including: abstracts of the annual conference of the International Association for Dental Research (IADR) and its regional divisions (1990-2017), ProQuest databases, Capes Journals database, clinical trial records: Current Controlled Trials, International Clinical Trials Registry Platform, ClinicalTrials.gov, and EU Clinical Trials Register. No language, date, and publication restrictions were applied.

Eligibility criteria

Randomized clinical trials (RCTs) with parallel or split face designs in humans comparing the technical use of facial rejuvenation alone versus the technical use of facial rejuvenation together with platelet aggregates were included. The RCTs were excluded if: 1) they performed different rejuvenating treatments associated with platelet aggregates on both sides; 2) the comparison of the use of the treatment together or separate from the platelet aggregates was not directly related to facial rejuvenation.

Study selection and data collection process

Articles were selected considering the titles first, followed by the abstract, and then articles in their entirety, in accordance with the eligibility criteria described. Relevant information from each article selected such as the study design, number and age of participants, interventions, evaluation time, and number of patients lost during treatment (Chart 2), as well as the methods of evaluations of the results (Chart 3) were extracted by researchers (C.F.A, C.T.T) using a personalized file.

Risk of bias of individual studies

The assays were examined using the Cochrane risk-of-bias tool of the Cochrane Collaboration.

The evaluation criteria included five items: suitable generation of sequences, allocation concealment, blinding of evaluators and participants, incomplete data results and reports, and selective outcome. The risk of bias for each aspect of quality assessment was in accordance with the recommendations described in the Cochrane Handbook for Systematic Reviews 5.1.0 (http://handbook.cochrane.org).

Two of the five areas of Cochrane risk of bias were considered as key areas (randomization and allocation), thus qualifying the studies as “Low risk” of bias if there was an adequate sequence generation and allocation concealment. If one or more criteria were not met, the study would be considered “high” risk of bias and judged as “undefined” when the authors did not report how randomization or allocation was performed.

RESULTS

Study selection

After screening the databases and removing duplicates, 5918 studies were identified (Figure 1). After the removal by titles, 378 studies remained. This number was reduced to 10 after reading the abstracts and full texts were evaluated to verify eligibility. Among them, 6 were excluded: 1) four for not including rejuvenation, 2) one for not comparing one technique to another, 3) one due to unavailable full text, and 1 pilot clinical case was added because the information provided fit the proposed subject.

Characteristics of the studies included

The qualitative synthesis of the four studies included in this review revealed that three presented a study design with a split face and one was a pilot study. The studies included presented the following comparisons of Fat + PRP x Fat + FRP (Fibrin Rich Plasma), in which the main expectation was facial rejuvenation through facial filling in the cheek/malar region, to refine the facial contour; mesotherapy x PRP, in which the expectation was facial rejuvenation by intradermal injection of a solution of readymade growth factors - mesotherapy (side A) and PRP (side B) to decrease the signs of aging such as wrinkles, sagging, and pigmented changes (Chart 4).

In the study comparing mesotherapy x PRP, evaluations were performed by the evaluators one and six months after the last treatment session by using the Global Aesthetic Improvement Scale (GAIS) through a comparison of photos, besides the Patient Satisfaction Level (PSL), registering their opinion on the benefits of the treatment, and by Optical Coherence Tomography.
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Chart 1. Electronic databases and search strategy.

<table>
<thead>
<tr>
<th>Database</th>
<th>Pubmed</th>
<th>Scopus</th>
<th>Web of Science</th>
<th>Lilacs and BBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pubmed</td>
<td>714</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Scopus</td>
<td>5467</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Web of Science</td>
<td>752</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lilacs and BBO</td>
<td>06</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#1 (TITLE-ABS-KEY (rejuvenation) OR TITLE-ABS-KEY (Skin Aging) OR TITLE-ABS-KEY (Adult human) OR TITLE-ABS-KEY (wrinkles) OR TITLE-ABS-KEY (Expression marks))

#2 (TITLE-ABS-KEY (Plasma skin regeneration) OR TITLE-ABS-KEY (Platelet rich plasma) OR TITLE-ABS-KEY (Platelet aggregation) OR TITLE-ABS-KEY (Blood platelets) OR TITLE-ABS-KEY (Growth factors) OR TITLE-ABS-KEY (injection) OR TITLE-ABS-KEY (rejuvenation) OR TITLE-ABS-KEY (Platelet rich fibrin) OR TITLE-ABS-KEY (PRP) OR TITLE-ABS-KEY (PRF) OR TITLE-ABS-KEY (Skin regeneration) OR TITLE-ABS-KEY (Platelet concentration)) AND (LIMIT-TO (SUBJAREA, "MEDI") OR LIMIT-TO (SUBJAREA, "PHAR") OR LIMIT-TO (SUBJAREA, "DENT") OR LIMIT-TO (SUBJAREA, "DENT"))


#1 AND #2 AND #3

continue...
Chart 1. Electronic databases and search strategy.

<table>
<thead>
<tr>
<th>#1 AND #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cochrane Library = 181  (09/10/2017)</td>
</tr>
</tbody>
</table>

#1 MeSH descriptor: [Rejuvenation] explode all trees
#2 MeSH descriptor: [Skin Aging] explode all trees
#3 “Adults humans”:ti,ab,kw or “Adult Human” or Wrinkles or “Expression Marks” (Word variations have been searched)
#4 #1 or #2 or #3

#5 MeSH descriptor: [Plasma Skin Regeneration] explode all trees
#6 MeSH descriptor: [Platelet-Rich Plasma] explode all trees
#7 MeSH descriptor: [Fibrin] explode all trees
#8 MeSH descriptor: [Platelet Aggregation] explode all trees
#9 MeSH descriptor: [Blood Platelets] explode all trees
#10 MeSH descriptor: [Injections] explode all trees
#11 “Growth factors”:ti,ab,kw or “Platelet rich fibrin” or PRP or PRF or “Skin regeneration” (Word variations have been searched)
#12 “Platelet concentration”:ti,ab,kw (Word variations have been searched)
#13 #5 or #6 or #7 or #8 or #9 or #10 or #11

#4 AND #13

Chart 2. Summary of studies selected for the systematic review.

<table>
<thead>
<tr>
<th>Study (ID/year)</th>
<th>Study Design</th>
<th>Mean age (±SD)</th>
<th>Male patients</th>
<th>Total number of patients</th>
<th>Treatment</th>
<th>Evaluation Time</th>
<th>Patients lost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seied Omid Keyhan 2013</td>
<td>Clinical face divided</td>
<td>46.5 ± 31.81</td>
<td>8 (32%)</td>
<td>25</td>
<td>Fat + PRP  Fat + FRP</td>
<td>1 and 12 months after the procedure</td>
<td>0</td>
</tr>
<tr>
<td>Heba I Gawdat 2017</td>
<td>Clinical face divided</td>
<td>41 ± 5.15</td>
<td>0</td>
<td>20</td>
<td>Side A (mesotherapy) Side B (PRP)</td>
<td>1 and 6 months after the final session</td>
<td>30% - 6 Patients</td>
</tr>
<tr>
<td>Qiang Hui 2016</td>
<td>Clinical face divided</td>
<td>42.1 ± 7.37</td>
<td>0</td>
<td>13</td>
<td>Side PRP + Ultra-pulsed fractional CO₂ laser Saline side + Ultra-pulsed fractional CO₂ laser</td>
<td>3 months after the final session</td>
<td>0</td>
</tr>
<tr>
<td>Min Kyung Shin 2012</td>
<td>Clinical pilot</td>
<td>43.7 ± 6.0</td>
<td>0</td>
<td>22</td>
<td>11 – laser 11 – laser + PRP</td>
<td>1 month after the final session</td>
<td>0</td>
</tr>
</tbody>
</table>

ID: identification; SD: Standard deviation.

Chart 3. Summary of the assessments made in each selected study.

<table>
<thead>
<tr>
<th>Treatments</th>
<th>Expectation</th>
<th>Pictures</th>
<th>Objective clinical evaluation</th>
<th>OCT</th>
<th>PSL</th>
<th>Histological Analysis</th>
<th>Adverse Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat + PRP x Fat + FRP</td>
<td>Filling/ Rejuvenation</td>
<td>X</td>
<td>X</td>
<td>NR</td>
<td>N.R</td>
<td>NR</td>
<td>X</td>
</tr>
<tr>
<td>Mesotherapy x PRP</td>
<td>Rejuvenation</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>NR</td>
<td>X</td>
</tr>
<tr>
<td>CO₂ Laser x CO₂ Laser + PRP</td>
<td>Rejuvenation</td>
<td>X</td>
<td>X</td>
<td>NR</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Laser x Laser + PRP</td>
<td>Rejuvenation</td>
<td>X</td>
<td>X</td>
<td>NR</td>
<td>X</td>
<td>NR</td>
<td>X</td>
</tr>
</tbody>
</table>

NR: Not reported.
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Results

<table>
<thead>
<tr>
<th>Objective Clinical evaluation</th>
<th>OCT</th>
<th>PSL</th>
<th>Histological Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fat + PRP x Fat + FRP</td>
<td>p &lt; 0.05</td>
<td>N.R</td>
<td>N.R</td>
</tr>
<tr>
<td>Mesotherapy x PRP</td>
<td>p &gt; 0.05</td>
<td>p &gt; 0.05</td>
<td>p &lt; 0.05 + PRP</td>
</tr>
<tr>
<td>CO2 Laser x CO2 Laser + PRP</td>
<td>p &lt; 0.05</td>
<td>N.R</td>
<td>p &lt; 0.05 + PRP</td>
</tr>
<tr>
<td>Laser x Laser + PRP</td>
<td>p &gt; 0.05</td>
<td>N.R</td>
<td>p &gt; 0.05</td>
</tr>
</tbody>
</table>

NR: not reported; PSL: patient satisfaction level; OCT: Optical Coherence Tomography.

Comparison of photos and PSL, registering their opinion about the benefits of the treatment; and, by the histological analysis in which 3 of 7 factors analyzed presented a statistically significant difference (p<0.05), which were higher for the Fractional Laser therapy + PRP.

Regarding adverse effects, there were no cases of massive edema, prolonged hematomas, or severe pain in the study of facial liposculpture surgery. When comparing the mesotherapy and PRP treatments, a transient erythema was observed on both sides, which resolved in two days; there was a statistically significant difference in relation to burning sensation (p > 0.01), which was higher on the mesotherapy side. Erythema, edema, and crusting were evaluated, and were significantly (p > 0.05) lower on the ultra-pulsed fractional CO2 laser + PRP side. In the pilot study, there were no serious or persistent side effects during treatment. The duration of erythema was 1-3 days, with no significant difference between the two groups (p > 0.05).

Compared to the FRP, PRP presented lower efficacy in relation to the maintenance of facial filling with fat. However, when associated with the other treatment and when compared to mesotherapy, its effectiveness was superior both in the improvement of rejuvenation and the reduction of adverse effects.

**Assessment of risk of bias**

The assessment of risk of bias of the articles selected is shown in Figure 2. Some authors did not report how concealment of allocation was performed. One study was determined to have a “low” risk of bias (reference), one study presented an “undefined” risk of bias, and the other two were classified as having a “high” risk of bias.

**DISCUSSION**

The main idea behind the use of platelet aggregates together with another technique of facial rejuvenation involves the bioregenerative action of PRP that stimulates the removal of components of the extracellular matrix and induces the synthesis of new collagen by dermal fibroblasts, thus increasing skin thickness (OCT), comparing epidermal and dermal thickness. Despite the absence of a significant difference (p > 0.05) in improvement between the two treated areas by the GAIS and OCT, PSL was significantly higher (p < 0.05) in area B (PRP).

In the study with ultra-pulsed fractional CO2 laser + injection of PRP, evaluations were performed three months after the last treatment session by using the VISIA Complexion Analysis System, also by the comparison of photos, which presented a statistical difference in texture and elasticity (p < 0.05) that was higher for the side with the application of ultra-pulsed fractional CO2 laser + injection of PRP. Moreover, the PSL of patients who registered their opinion about the benefits of the treatment also showed no significant difference (p > 0.05), with results favorable to the ultra-pulsed fractional CO2 laser experimental group + injection of PRP.

In the pilot study, the evaluations were performed one month after the last treatment session, through the application of the GAIS Scale by evaluators through comparison of photos and PSL, registering their opinion about the benefits of the treatment; and, by the histological analysis in which 3 of 7 factors analyzed presented a statistically significant difference (p < 0.05), which were higher for the Fractional Laser therapy + PRP.

Figure 1. Flowchart of the study.
The present systematic review was carried out to clarify this issue. Half of the studies included in this systematic review reported no significant differences in the results when comparing the two types of treatment. Although all selected papers reported expected results in accordance with the objective, the other key areas were classified as “undefined” or with a “high” risk of bias, thus reducing the reliability of the results.

Fat grafts have always been a challenge when inducing the necessary neoangiogenesis in facial liposculpture surgery, which results in significant resorption. Some studies have indicated that FRP provides better fat graft survival compared to PRP due to its retention and the slow release of platelet growth factors.

To reduce this resorption, a study was carried out to compare the efficiency of PRP versus FRP combined with a fat graft. The results indicated that FRP associated with fat is more effective than a combination of PRP and fat. The difficult injection technique and the lack of FRP fibrin clot are the main disadvantages of FRP and fat compared to PRP.

In a critical review of the current literature, five of the six selected studies showed an improvement in fat graft survival with the addition of platelet preparation.

Liang et al. assessed the efficacy of nanofat-derived stem cells (NFSCs) in facial rejuvenation by intradermal injection of nanofat combined with FRP applied in 103 patients compared to a control group of 128 patients undergoing hyaluronic acid (HA) injections. They concluded that both the injection of nanofat-FRP and HA showed an improvement in the condition of the skin, but the first was associated with a greater patient satisfaction, as well as an improvement in skin texture, suggesting that the injection of nanofat-FRP is safe, highly effective, and a long-lasting method for skin rejuvenation.

Compared to mesotherapy, PRP was superior due to increased patient satisfaction, fewer side effects, and more sustainable results, without a significant difference between the two areas treated regarding improvement according to GAIS and OCT. However, the durability of PRP compared to mesotherapy needs to be better evaluated, since the superiority of PRP was only perceived at the 6-month follow-up. This suggests a shorter life of readymade products when compared to the longevity of the effects of growth factors induced naturally by PRP, a point that suggests more detailed research with longer follow-up periods.

In addition to a reduction in adverse effects, several studies have reported that PRP led to a clinical improvement when analyzing the effectiveness of PRP combined with fractional carbon dioxide laser ablation in the treatment of atrophic acne scars. As the MTZ produced by ultra-pulsed CO2 laser has similar histopathological changes to those of wounds, laser therapy associated with PRP accelerates healing and reduces the adverse effects.

The results of a study involving PRP associated with an ablative carbon dioxide laser showed that despite greater patient satisfaction, there was a greater duration of adverse effects on the experimental side (with the association of PRP), although this was not statistically significant. This worsening of adverse effects can be attributed to the accumulated evidence, demonstrating that platelets contribute to the initiation and propagation of the inflammatory process.

When PRP was combined with microneedling, no articles were found relating to facial rejuvenation per se, but mostly the safety and efficacy of treatment in facial aesthetics was assessed, together with the improvement of post-acne atrophic scars.

Facial harmonization is a set of aesthetic procedures that aim to harmonize the teeth aesthetically and functionally with the mouth and face. Although it is not yet a specialty in dentistry, it is important to know the definition of the area of action, which, according to Resolution 176, dated September 6, 2016, authorizes the use of platelet aggregates and mesotherapy.
for non-transfusion purposes in dentistry, making it possible to collect blood to obtain PRP and FRP in a dental or surgical center. This establishes that not only dermatologists, but also the qualified dental surgeons, have the possibility and competence to perform a facial rejuvenation treatment with the use of platelet aggregates.

This systematic review showed that, due to the scarce evidence and the risk of “undefined” bias, there is need for further research, especially randomized controlled trials, that test alternatives to assess the best form of application of platelet aggregates for facial rejuvenation.

Therefore, further randomized controlled clinical studies should be performed that compare the use of platelet aggregates with other facial rejuvenation techniques, since even with good results, few are found in the literature.

CONCLUSION

This systematic review found that there are few studies in the literature that compare the use of platelet aggregates in facial rejuvenation, and those that are available have an “undefined” or “high” risk of bias. Further well-designed clinical studies are needed that compare the use of platelet aggregates associated with facial rejuvenation techniques.

COLLABORATIONS

CLMS Final manuscript approval, supervision.
CFA Data curation, writing - original draft preparation.
LHKC Data curation.
LMW Analysis and/or data interpretation, conception and design study, formal analysis.
JLG Analysis and/or data interpretation, conception and design study.
JCZ Writing - review & editing.

REFERENCES


*Corresponding author: Carmen Lucia Mueller Storrer
Rua Professor Pedro Viriato Parigot de Souza, 5300, Campo Comprido, Curitiba, PR, Brazil
Zip Code: 81280-330
E-mail: carmen.storrer@gmail.com