Fat embolism syndrome secondary to the use of polymethylmethacrylate in bioplasty: a systematic review

Síndrome da embolia gordurosa secundária ao uso de polimetilmetacrilato na bioplastia: uma revisão sistemática

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ABSTRACT

Fat embolism syndrome (FES) is defined as the presence of fatty emboli, not only in the pulmonary system, but also in the systemic circulation, with inflammatory, neurological and cutaneous manifestations. Currently, in cosmetic surgery, the polymethylmethacrylate (PMMA) material is indicated for skin filling techniques used in injectable form in small non-incisional aesthetic procedures, known as bioplasty. The objective of this study was to carry out a systematic review of the literature to show clinical studies that addressed the appearance of fat embolism syndrome in patients who underwent PMMA (polymethylmethacrylate) infiltration in bioplasty. Even with the exhaustion of sources and the expansion of systematic research that followed the precepts of the PRISMA protocol, the answer was only one article that was added to the present study. Unfortunately, no reviews or experimental studies are looking at FES in PMMA infiltration. Most of the available reports are about liposuction and correlate with bone trauma when PMMA use is mentioned. This review serves as a wake-up call for nonscientific studies and reports on the risks of using PMMA in bioplasty, but no reports or articles were obtained related to life-threatening fat embolism.

Keywords: Polymethylmethacrylate; Fat embolism; Dermal fillers; Plastic surgery; Long-term adverse effects.
The ideal filler applied to treat signs of aging or to increase soft tissue should provide good cosmetic results and have a long-term effect. It must also be safe, biocompatible, and stable at the implantation site, with low-risk, non-migratory complications6.

According to Lemperle et al., in 20067, all injectable dermal fillers can cause complications. Late side effects can be divided into those caused by insufficient training or technical errors during the injection, and those caused by immune reactions (allergic and non-allergic) to the injected substance. Granuloma formations are rare events that result from type IV hypersensitivity reaction to a foreign body. They usually occur over months to years after the injection3.

Currently, there are a large number of fillers available for this purpose, each with its chemical composition, specific indications, and effectiveness5,6. This wide range of available materials requires aesthetic specialists and plastic surgeons to choose the appropriate filler for each aesthetic complaint of their patients5,6.

The histological reaction is always similar, and the trigger for this sudden stimulation of macrophages may be a systemic infection of the patient. Dermal fillers such as silicone, bovine collagen, ArtecollTM (Hafod B.V, Rotterdam, The Netherlands), and...
Restylane™ (Q-Med AB, Stockholm, Sweden) have been used worldwide. Bovine collagen (Zyderm™, Zyplasta™, McGhan Medical Corporation 3M, USA) was introduced between 1981 and 1983, becoming the standard for injectables. Articoll™ (Canderm Pharma Inc., Canada) was distributed between 1994 and 2006, and Restylane™ (Q-Med AB, Stockholm, Sweden) began its triumphal advance in 1997. Since then, a variety of materials have been introduced, such as Radiesse™ (Merz, Brazil), which is approved for facial bone augmentation and has been used off-label since 2003 for the treatment of wrinkles; and Sculptra™ (Aventis, USA), which is approved for facial lipodystrophy of the human immunodeficiency virus, but has been used to treat wrinkles since 2005. The Food and Drug Administration (FDA - USA) approved Restylane™ in 2003, Hylaform™ (Genzyme Biosurgery, USA) in 2004, Captique™ in 2005 and Juvederm™ 2006 (both from Allergan, USA) for the treatment of facial wrinkles.

The polymethylmethacrylate (PMMA) molecule does not have any animal component in its structure, which makes this molecule a biocompatible material and also provides stability even decades after the initial implantation. Its commercial applications are PMMA microspheres suspended in bovine collagen.

In the context of the indications of the PMMA compound, the filling of grooves, deep wrinkles, scars, dermal defects, soft and bone tissues stands out. It is also used in restorative procedures for volumetric facial and body correction of lipodystrophy syndrome, a result of the use of antiretrovirals in patients with the human immunodeficiency virus.

Fat embolism syndrome (FES) is a poorly defined clinical entity that arises from systemic manifestations of fat embolism within the microcirculation. Embolized fat in the capillary beds causes direct tissue damage, in addition to inducing a systemic inflammatory response, which produces pulmonary, cutaneous, neurological, and retinal symptoms. It occurs more frequently after orthopedic trauma, as well as in patients with many clinical conditions, including liposuction, bone marrow transplantation, pancreatitis, however, as observed in the present study, rarely in bioplasty procedures using PMMA.

**OBJECTIVE**

The present study aimed to carry out a systematic review of the literature in order to highlight the clinical studies that included FES in patients undergoing PMMA infiltration in bioplasty.

**METHODS**

**Search strategies and eligibility criteria**

A search of the PubMed/MEDLINE and LILACS/BVS databases was performed, including articles that addressed the topic “fat embolism syndrome secondary to the use of PMMA in bioplasty.”

We included studies in humans, older than 18 years (adults), whose publication in English was between January 1, 2000, and January 8, 2019, and the text published with full access reported on FES after bioplasty with use. PMMA intervention.

Review articles (meta-analyses and systematics), letters to the editor, case reports, and experimental studies in which the complication after using PMMA did not include FES were not added.

After the response of the electronic databases, a manual search of relevant articles was carried out, since the sample was not adequate. In this way, the search date was extended from January 1970 to January 2019.

The following search terms were included in English: “fat embolism syndrome,” “polymethylmethacrylate,” and “fat embolism syndrome.” In Portuguese: “PMMA,” “polimetilmetacrilato,” “síndrome embolia gordurosa,” “embolia lipídica.” In Spanish: “PMMA,” “polimetilmetacrilato,” “embolia grasa,” “embolia lipídica.” As protocols, the recommendations of the Preferred reporting elements for systematic reviews and meta-analyses were followed.

**Data extraction**

Research data, after extraction, was included, and the authors of this article reviewed controversies. Information such as: authors, year of publication, and country of origin was reviewed to identify and exclude duplicate publications from the same cohort. The extracted data included the total number of patients and injuries, age, sex, and occurrence.

**RESULTS**

In the PubMed/MEDLINE electronic search, 20 research article references were found. After reading the titles, 18 references were excluded, leaving two references. When read in full, two studies were excluded as they did not include bioplasty and the use of PMMA. The exclusion of these articles was based on the inclusion and exclusion criteria described above.

In the LILACS/VHL database, 59 references to research articles were found (subject index). After
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reading the titles, 50 references were excluded, leaving nine references. When reading in their entirety, three studies that did not contemplate bioplasty and the use of PMMA were excluded, and the remaining six were also excluded because they are liposuction related studies that do not consider the use of PMMA. The exclusion of these articles was based on the inclusion and exclusion criteria described above.

In this way, a manual search was performed in the three languages (English, Portuguese, and Spanish), and the search date was extended from January 1970 to January 8, 2019. As a result, only one article was available for a complete reading. (Spanish language). The selection criteria are described in Figure 1.

DISCUSSION

The bibliographic search resulted in a single article, according to the descriptors, and the inclusion and exclusion requirements. Unfortunately, there is no significant number of articles that address FES in PMMA infiltration. Most of the available reports come from liposuction and correlate with bone trauma when PMMA use is mentioned.

The subject of the only report was a 26-year-old woman who started the condition 24 hours after PMMA injection into the bilateral gluteal region at a cosmetic clinic. The patient presented fever, anxiety, diaphoresis, headache, dizziness, drowsiness, and dysarthria13.

On physical examination at admission, blood pressure of 110/70mmHg was presented, heart rate of 113 beats per minute, respiratory rate of 21 respiratory incursions per minute, with supplemental support of oxygen by mask and nebulizer; body temperature of 38.4° C, with Glasgow of 12. She was aware13.

Pelvic tomography revealed abundant, diffuse, non-encapsulated material between the skin and the gluteus maximus. Her management was in the Intensive Care Unit, with general support, mechanical ventilation in the volume control in assisted mode. Broad-spectrum antibiotics and anticoagulation with low molecular weight heparin were also prescribed13.

The patient developed pneumonia, systemic inflammatory response syndrome, and cerebral edema. Due to prolonged intubation and inadequate management of secretions, it was necessary to perform a tracheostomy. She had a prolonged clinical evolution; however, satisfactory, allowing her to remain without mechanical ventilation support. The infectious respiratory focus was controlled, and the patient evolved with hemodynamic stability. The patient was discharged after three weeks of hospitalization. In this case report, massive PMMA infiltration destroyed adipose tissue, which, together with the microspheres of this product, provoked fat embolism in the patient13.

The case presented by Salgado and Olvera in 200813 was of non-medical professionals who performed the procedure. This type of practice has generated a public health problem, since most of the time, the subjects do not have medical training, and there are no reliable statistics on the incidence or prevalence of patient complications concerning the substances used. FES

Chart 1. Included studies: country of origin, methods and objectives and characteristics of the study.

| Author/year          | Country of Origin | Methods and Objectives                        | Study characteristics                                      |
|----------------------|-------------------|-----------------------------------------------|-----------------------------------------------------------|
| Salgado and Olvera,  | México            | Presentation of clinical case and outcomes.    | Clinical case report with outcomes after FES in a post-procedure patient with PMMA infiltration |

Source: Elaborated by the author.
was first described in 1862, by Zenker, who visualized fat cells in the pulmonary circulation of a polytraumatized individual after performing a biopsy\(^4\). The term FES is a severe consequence of fatty emboli that causes a distinct pattern of symptoms and clinical signs\(^5\).

The typical clinical manifestation is the triad of acute respiratory failure, thrombocytopenia, and neurological dysfunction\(^5\). No definitive diagnostic criteria or tests have been developed, which makes the diagnosis of FES more difficult. It usually occurs within 48 hours after the trauma or during surgical procedures in most patients\(^12\).

There are two main theories for the genesis of fat embolism; they are the mechanical theory and the biochemical theory. The first suggests that the obstruction of the systemic vasculature by fat embolism results from the direct release of the bone marrow into the venous system after the trauma. High intramedullary pressure after trauma causes the release of fat through open venous sinusoid. This embolized fat favors the obstruction of the capillary beds\(^12\).

The second theory proposes that the inflammatory response to trauma causes the release of free fatty acids from the bone marrow into the venous system. Elevations in free fatty acids and inflammatory mediators damage the capillary beds. Elevated levels of free fatty acids have been correlated with hypoxemia and the induction of pulmonary inflammation\(^12\).

Regarding the therapeutic approach, there is no specific treatment for FES. The procedures are based on clinical support measures, hemodynamic stabilization, volume replacement, nutrition and oxygen therapy or mechanical ventilation with alveolar recruitment in more severe cases\(^14\). There is insufficient data to support the initiation of steroid therapy, once FES is established. The proposed mechanism of action is generally an anti-inflammatory agent that reduces perivascular hemorrhage and edema. An experimental study did not show a beneficial effect and there were no prospective, randomized, and controlled clinical studies that demonstrated a significant benefit with its use\(^15\).

**CONCLUSION**

In the current aesthetic situation, there is a significant increase in minimally invasive techniques that favor non-incisional methods, such as the implantation of PMMA, to minimize the effects of aging and correct body defects. It is known that in order to prevent or treat disorders, such as FES with dermal implants, it is essential to know their composition, the physiological reactions of the tissue, the time of absorption, and persistence. There is an urgent need for more studies targeting PMMA in cosmetic procedures, their risks, and clinical cases that identify FES and other potentially fatal postoperative problems for the patient.

**COLLABORATIONS**

**CGAO**
- Analysis and/or data interpretation,
- Conceptualization, Data Curation,
- Final manuscript approval,
- Formal Analysis, Investigation, Methodology,
- Project Administration, Resources,
- Supervision, Validation, Visualization,
- Writing - Original Draft Preparation,
- Writing - Review & Editing

**FRS**
- Analysis and/or data interpretation,
- Conceptualization, Final manuscript approval,
- Investigation, Resources,
- Supervision, Validation,
- Visualization

**FAAF**
- Conceptualization, Data Curation,
- Final manuscript approval,
- Supervision, Visualization,
- Writing - Original Draft Preparation

**RZDF**
- Final manuscript approval,
- Data Curation,
- Conceptualization, Writing - Original Draft Preparation,
- Supervision, Visualization.

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