Comparing the fibrosis inhibition effect of bevacizumab, 5-fluorouracil, and mitomycin C in trabeculectomy in dogs with glaucoma: A series of six cases

Comparación de bevacizumab, 5-fluorouracilo y mitomicina C en trabeculectomía como tratamiento quirúrgico del glaucoma en perros: una serie de seis casos

Comparação de bevacizumab, 5-fluorouracil e mitomicina c em trabeculectomia como tratamento cirúrgico de glaucoma em cães: uma série de seis casos

Sandra Patricia Acevedo¹,²*; Nathalia María Correa Valencia²

¹ Private practice, Unidad Oftalmológica Ocularvet (Medellín, Colombia).
² CENTAURO Research Group, School of Veterinary Medicine, Faculty of Agricultural Sciences, Universidad de Antioquia (Medellín, Colombia).

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*Corresponding author. Unidad Oftalmológica Ocularvet (Medellín, Colombia). Tel: +57 311 3046136. Email: ocularvetmedellin@gmail.com

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Abstract

Anamnesis: A descriptive series of six cases in dogs with glaucoma are presented, aiming to compare the fibrosis inhibition effect of three pharmacological principles applied during trabeculectomy. Clinical findings: The patients obtained a diagnosis of primary chronic closed-angle glaucoma, refractory to topical medical treatment, with no pupillary light reflex, a negative visual threat eyeblink response, and ocular pain. Therapeutic approach: Two patients received an intraoperative application of bevacizumab, two received 5-fluorouracil, and two, mitomycin C. The intraocular pressure (IOP) and the filtering ampoule were observed on days 1, 7, 30, 60, and 90 of postsurgical evolution. Conclusion: According to our results, the bevacizumab manages to regulate the IOP under 25 mmHg and constitutes the drug of potential choice in dogs with primary closed-angle glaucoma, without a previous positive response to topical therapy and subjected to TEC, when compared with 5-fluorouracil and MMC regarding the inhibition effects of fibrosis.

Keywords: dog; fibrinolytic; glaucoma; intraocular pressure; ocular disease; ocular hypertension.

Resumen

Anamnesis: Se presenta una serie descriptiva de seis casos de perros con glaucoma, con el objetivo de comparar el efecto de inhibición de la fibrosis tres principios farmacológicos aplicados durante la trabeculectomía. Hallazgos clínicos: Los pacientes obtuvieron un diagnóstico de glaucoma primario crónico de ángulo cerrado, refractario al tratamiento médico tópico, sin reflejo pupilar a la luz, respuesta negativa de parpadeo ante amenaza y dolor ocular. Aproximación terapéutica: Dos pacientes recibieron aplicación intraoperatoria de bevacizumab, dos recibieron 5-fluorouracilo y dos, mitomicina C. La presión intraocular (PIO) y la ampolla filtrante se observaron los días 1, 7, 30, 60 y 90 de evolución posquirúrgica. Conclusión: De acuerdo con nuestros resultados, el bevacizumab logra regular la PIO por debajo de 25 mmHg y constituye el fármaco de elección potencial en perros con glaucoma primario de ángulo cerrado, sin respuesta positiva previa a la terapia tópica y sometidos a TEC, cuando se compara con 5-fluorouracilo y mitomicina C en cuanto a los efectos de inhibición de la fibrosis.
Palavras clave: enfermedad ocular; fibrinolítico; glaucoma; hipertensión ocular; perro; presión intraocular.

Resumo

Anamnese: Apresenta-se uma série descritiva de seis casos de cães com glaucoma, com o objetivo de comparar o efeito da inibição da fibrose de três princípios farmacológicos aplicados durante a trabeculectomia. Achados clínicos: Os pacientes foram diagnosticados com glaucoma primário crônico de ângulo fechado, refratário ao tratamento medicamentoso tópico, sem reflexo pupilar à luz, piscamento negativo à ameaça e dor ocular. Abordagem terapêutica: Dois pacientes receberam aplicação intraoperatoria de bevacizumabe, dois receberam 5-fluorouracil e dois mitomicina C. A pressão intraocular (PIO) e a bolha vazante foram observadas nos dias 1, 7, 30, 60 e 90 de pós-operatório. Conclusão: De acordo com nossos resultados, o bevacizumabe consegue regular a PIO abaixo de 25 mmHg e é a droga de escolha potencial em cães com glaucoma primário de ângulo fechado, sem resposta positiva prévia à terapia tópica e submetidos à TEC, quando comparado com 5-fluorouracil e mitomicina C em termos de efeitos de inibição de fibrose.

Palavras-chave: cão; doença ocular; fibrinolítico; glaucoma; hipertensão ocular; pressão intraocular.

Introduction

Glaucoma is a multifactorial disease; it is the main cause of irreversible blindness in humans worldwide (Chou et al., 2017). In dogs, it presents with progressive disorders, characterized by apoptosis of retinal ganglion cells, and optic neuropathy associated with a graying of the optic nerve (Pizzirani, 2015). In brief, the patient suffers from visual acuity loss, in addition to clear signs of pain due to an increased Intraocular Pressure (IOP). Bilateral blepharospasm, episcleral vascular congestion and corneal edema, and the presentation of behavioral changes, such as sleepiness, reluctance to exercise, and even loss of appetite and depression are also observed (Miller and Bentley, 2015).
Glaucoma is classified as open-angle (OAG) or closed-angle (CAG), depending on whether there is a defect in the elimination of aqueous humor. The OAG is known as primary when it occurs without an underlying disease (ocular or systemic), or secondary when it is due to filter obstruction due to protein material associated with goniodysgenesis, resulting from an abnormal biochemical metabolism of the trabecular cells of the aqueous humor outflow system. In turn, the increase in IOP is due to an increase in the resistance in the drainage channels (Gellat, 2014). The CAG represents around 20% of glaucoma in dogs, with a broad breed predisposition, being hereditary and bilateral. It is due to a poor conformation of the anterior chamber, the iridocorneal angle, the trabecular meshwork, or any other part of the ciliary cleft (Baro-Lorenzo et al., 2018). Its pathogenesis progresses with an evolution in which the patient presents, 1) intermittent episode(s) of increased IOP — which are too high for axoplasmic flow from the optic nerve; 2) aqueous humor outflow obstruction; 3) retinal ganglion cell dysfunction — leading to optic nerve atrophy or degeneration; and, finally, 4) visual field loss and blindness (Miller and Bentley, 2015).

Considering that a high IOP is only one of the risk factors for the development of glaucoma, the reduction in the production of aqueous humor or its outflow would favor the therapeutic solution of the disease. In this sense, medical treatments with topical drugs are proposed. However, these methods may not control it on a long-term basis, and since it is a progressive disease, some patients may require surgical intervention to reduce IOP and thus slow the progression of glaucoma (Chen and Moeller, 2019).

The trabeculectomy (TEC) consists of establishing an exit route for the aqueous humor from the anterior chamber of the eye to the subconjunctival space, creating a filtration bleb under the conjunctiva, through a small hole in the sclera. With this procedure, the drainage of the aqueous humor is favored and, consequently, the IOP is reduced (Urcelay et al., 2015).

The success of TEC in the treatment of glaucoma in dogs is based on the development of a fistula between two anatomical spaces that does not heal. The viability of this fistula is influenced by the connective tissue, the aqueous humor, and the vascular tissue. Failure of the procedure refers to scleral fibrosis, which inhibits adequate drainage of aqueous humor (Zheng et al., 2016). In this sense, one of the aspects to consider for the success of the procedure is the use of fibrinolytics, with the aim of preserving the filtering ampule over time. Its intraoperative
application is performed below the subconjunctival and scleral flap (Zheng et al., 2016) at the end of TEC. The bevacizumab (Quiroz-Mercado et al., 2008; Herrera-Herrera and Bermúdez-Cruz, 2015), 5-fluorouracil (Alegre et al., 2002), and mitomycin C (Chen and Moeller, 2019) are drugs used to inhibit the activity of fibroblasts and the subsequent development of scarring fibrosis in the TEC’s filtering ampoule (Güerri and Calvo, 2011).

The bevacizumab is a monoclonal antibody against vascular endothelial growth factor (VEGF) that binds to all the active isoforms of the molecule (Quiroz-Mercado et al., 2008). In humans, it is used to treat macular degeneration and block angiogenesis after performing filtering surgery—as is the case of TEC. The use of this drug reduces the fibroblasts proliferation and migration to the surgical wound and, consequently, a slowdown in healing (Herrera-Herrera and Bermúdez-Cruz, 2015). In addition, it has an ocular anti-inflammatory effect attributed to its ability to bind the VEGF, since they are known leukocyte chemotaxis mediators (via VEGFR-1), which is expressed on the surface of subpopulations of leukocytes, particularly macrophages and neutrophils (Azanza-Perea and Sábado, 2015).

The 5-fluorouracil belongs to the category of chemotherapy drugs called antimetabolites. These substances are similar to those normally found inside somatic cells. When cells incorporate these substances into their cellular metabolism, they lose the ability to divide. This action inhibits fibroblastic proliferation and increases the success rates of TEC (Güerri and Calvo, 2011).

The mitomycin C (MMC) is an antimitotic antibiotic isolated from Streptomyces caespitosus. Its mechanism of action consists of the formation of irreversible bonds between the two DNA chains, preventing their duplication. Its intraocular action is aimed at inhibiting the growth and proliferation of cells with fibroblast activity (Villarreal et al., 2009) and has demonstrated its efficacy in prolonging the half-life of filtration bullae in TEC surgery, by inhibiting the growth of fibroblasts and, therefore, scar formation (Alegre et al., 2002).

Given the evolution of veterinary ophthalmology in recent decades, knowledge on glaucoma and its treatment is needed. Therefore, this report aims to compare the fibrosis inhibition degree of the filtering ampoule after intraoperative application of bevacizumab, 5-fluorouracil, or
MMC in six dogs with primary chronic glaucoma subjected to TEC. To the author's knowledge, this is the first approach to compare these three fibrinolytic drugs in veterinary medicine.

**Examination of the patient**

*Clinical findings*

Characterization of the patients that attended a consultation at a veterinary ophthalmological unit in Medellín (province of Antioquia, Colombia) is shown (Table 1). The dogs were diagnosed with a primary chronic closed-angle glaucoma refractory to topical treatment (applied for at least 2 months) and an IOP >25 mmHg.

**Table 1.** Characterization of the study patients.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Breed</th>
<th>Sex</th>
<th>Age (in years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Basset hound</td>
<td>Female</td>
<td>6</td>
</tr>
<tr>
<td>2</td>
<td>Bulldog</td>
<td>Male</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>Crossbreed (Labrador retriever × German shepherd)</td>
<td>Male</td>
<td>3</td>
</tr>
<tr>
<td>4</td>
<td>Labrador retriever</td>
<td>Male</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>Springer Spaniel</td>
<td>Female</td>
<td>8</td>
</tr>
<tr>
<td>6</td>
<td>Siberian husky</td>
<td>Female</td>
<td>7</td>
</tr>
</tbody>
</table>

As clinical findings, the patients presented no pupillary light reflex, a negative visual threat eyeblink response, ocular pain associated with ocular hypertension, loss of appetite, behavioral changes (e.g. aggressiveness, apathy, depression), with abrupt rubbing of the affected eye and leaning head up against wall; in addition to other signs evaluated during the ophthalmological consultation, such as episcleritis, corneal ulceration and desiccation, buphthalmus, mydriasis, and visual deficit.

*Surgical and therapeutic approach*

Each of the six patients underwent conventional TEC, a surgical procedure performed under general anesthesia with propofol induction and maintenance with isoflurane. All surgeries were performed by the same surgeon. Briefly, conjunctival dissection was performed, cauterizing the
scleral vessels. The trabecular window was made at 12 o'clock from the eyeball, achieving a superficial scleral flap of 3 to 5 mm on each side, with medium scleral thickness, leaving a thin layer of underlying scleral bed. Conjunctival antimitotic drugs were applied to reduce subconjunctival scarring. A fragment was extracted from the cornea to the sclera, including the trabeculum and angular structures, in addition to the iridian resection in its most peripheral part, achieving communication between the anterior and posterior chambers with the subconjunctival space through the TEC (Urcelay et al., 2015). The suture of the superficial scleral flap was completed, allowing the apposition of the tapetum on the deep bed, carrying out a repositioning to modulate the aqueous humor outflow. A resorbable material (polyglycolic acid 8/0) was used. Once the conjunctiva was sutured, the anterior chamber was washed with a balanced saline solution, allowing tissue or blood debris to be removed, and simultaneously checking the operation of the filtering procedure and the formation of a correct subconjunctival filtration bleb (Alegre et al., García, 2002; Chou et al., 2017).

For the following process, patients were randomly assigned to three groups, obtaining two patients for each of the fibrinolytic drugs for intraoperative application, as follows: Group 1 (bevacizumab — Avastin®, Genetech Inc. San Francisco, CA), a single dose of 2 mg in 40 µL, injected with an intradermal syringe under the subconjunctival and scleral flap; Group 2 (5-fluorouracil — Acoflut®, Seven Pharma Colombia. S.A.S, Bogotá, Colombia), a single dose of 25 mg/mL, topically applied by embedded surgical sponge under the subconjunctival and scleral flap for 5 min; and Group 3 (MMC — Mitomycin C®, Quiminet, Bogotá, Colombia), a single dose of 0.5 mg/mL, topically applied by embedded surgical sponge under the subconjunctival and scleral flap for 5 min.

The IOP was measured by flattening tonometry in each patient who underwent surgery, and the filtering ampoule was evaluated on days 1, 7, 30, 60, and 90 of postsurgical evolution by two different veterinarians.

Postoperative treatment for all patients included 1% prednisolone acetate (topical ophthalmic solution; 1 drop applied to the operated eye every 4 hours for 15 days, decreasing frequency every 2 weeks to 6, 8 and then 12 hours until completing 8 weeks of treatment), moxifloxacin (topical ophthalmic solution; 1 drop applied to the operated eye every 6 hours for 20 days), cefovecin sodium (a single dose of 0.1 mL/Kg PV, SC). All patients were initially medicated
with dorzolamide + timolol and the frequency of the medication was adjusted according to the evolution of each patient.

Data analysis

Data were collected regarding the demographic characterization of the population (e.g. breed, sex, age). The progress scale was established in three levels, being 1, little progress; 2, moderate progress; and 3, excellent recovery, defined according to the comparative evolution with the photographic record of each previous ophthalmological examination. The variables that contributed to the definition of the progress scale for each patient at each evaluation time (days 1, 7, 30, 60, and 90 of postsurgical evolution) were the eyeball closure degree (i.e. complete palpebral closure, partial eyelid—central cleft of 0.5 mm or more, buftalmus without eyelid closure, complete corneal exposure), signs of pain (i.e. mild blepharospasm, severe blepharospasm accompanied by epiphora, no signs of pain), iris coloration (i.e. normal, with moderate rubeosis —orange coloration with severe rubeosis, reddish coloration), and patient behavior (i.e. apathy/loss of appetite/aggressiveness to handling/constant head movements, no change in behavior). The IOP was classified as satisfactory (15-25 mmHg) or unsatisfactory (≥26 mmHg), as previously established (Chen and Moeller, 2019). Data were manually recorded in Excel spreadsheets (Microsoft Corp., Redmond, WA, USA) and then exported to Stata 16.0 (StataCorp 2020, Texas, USA) for descriptive statistical analysis for all study variables of interest.

Results

Treatment allocation of the six patients, as well as the follow-up of the progress scale and IOP for each of the evaluation moments is presented (Table 2).

The first measurements showed unsatisfactory IOP values (≥26 mmHg), with signs of eye pain still evident, episcleritis, and enlargement of the eyeball. Evaluation of clinical progress — based on clinical signs, started as excellent from day 30 in all patients. The IOP evolution obtained at the time of each revision time was initially unsatisfactory, beginning to be controlled from day 30 in five of the six patients, and being satisfactory on day 60 for all patients (Table 2, Figures 1 and 2). By day 90, one of the patients presented an increase in IOP and with it all the associated ocular clinical signs (Table 2; Figure 3).
Table 2. Intraoperative fibrinolytic treatment allocation and monitoring on days 1, 7, 30, 60, and 90 of postsurgical evolution.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Treatment</th>
<th>Intraocular pressure (classification†; progress scale‡)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day 1</td>
</tr>
<tr>
<td>1</td>
<td>Mitomycin C</td>
<td>40 mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(NS; 2)</td>
</tr>
<tr>
<td>2</td>
<td>5-fluorouracil</td>
<td>38 mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(NS; 1)</td>
</tr>
<tr>
<td>3</td>
<td>Bevacizumab</td>
<td>25 mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(S; 3)</td>
</tr>
<tr>
<td>4</td>
<td>Mitomycin C</td>
<td>37 mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(NS; 2)</td>
</tr>
<tr>
<td>5</td>
<td>5-fluorouracil</td>
<td>38 mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(NS; 2)</td>
</tr>
<tr>
<td>6</td>
<td>Bevacizumab</td>
<td>23 mmHg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(S; 2)</td>
</tr>
</tbody>
</table>

†S: Satisfactory (15-25 mmHg); NS: Not satisfactory (≥ 26 mmHg).
‡1, little progress; 2, moderate progress; and 3, excellent recovery, defined according to the comparative evolution with the photographic record of each previous ophthalmological examination.
**Figure 1.** Comparative evolution of the intraocular pressure (IOP) results at each postsurgical evaluation time of the six patients in the study.
Figure 2. Comparative evolution of the progress scale at each postsurgical evaluation time of the six patients in the study.

1, little progress; 2, moderate progress; and 3, excellent recovery, defined according to the comparative evolution with the photographic record of each previous ophthalmological examination.

The photographic evidence of each patient during the postsurgical evaluation times is presented (Figures 3-8). For all cases A, corresponds to the day of the TEC and B, day 1; C, day 7; D, day 30; E, day 60; and F, day 90 post surgery.

Figure 3. Photographic comparative evolution of each ophthalmological evaluation of patient 1 (TEC + MMC). A. Creation of filtering ampoule; B. Active subconjunctival filtration bleb, but without adequate evacuation of aqueous humor; C. Active ampoule, but with congestion and active hypertension; D, E. Active ampoule with IOP control; F. Moderate fibrosis of the ampoule.
**Figure 4.** Photographic comparative evolution of each ophthalmological evaluation of patient 2 (TEC + 5-fluorouracil); A. Creation of filtering ampoule; B. Active subconjunctival filtration bleb, but without adequate evacuation of aqueous humor; C. Partially active ampoule, but with hypertension; D. Partially active ampoule; E, F. Active ampoule with IOP control.

**Figure 5.** Photographic comparative evolution of each ophthalmological evaluation of patient 3 (TEC + bevacizumab). A. Creation of filtering ampoule; B. Active subconjunctival filtration bleb, but with localized hyphema around infiltration; C, D, E, F. Active ampoule with IOP control.
Figure 6. Photographic comparative evolution of each ophthalmological evaluation of patient 4 (TEC + MMC); A. Creation of filtering ampoule; B. Active subconjunctival filtration bleb, but without adequate evacuation of aqueous humor; C. Filtering ampoule without adequate flow, showing buftalmus and secondary ulcerative keratitis; D. Active ampoule, improving the evacuation of aqueous humor; E, F. Active ampoule with IOP control.

Figure 7. Photographic comparative evolution of each ophthalmological evaluation of patient 5 (TEC + 5-fluorouracil); A. Creation of filtering ampoule; B. Active subconjunctival filtration bleb, but without adequate evacuation of aqueous humor; C. Filtering ampoule without...
adequate Flow, showing a localized hyphema in the incisional area; D. Active ampoule with IOP control and mild diffuse edema; E, F. Active ampoule with IOP control.

Figure 8. Photographic comparative evolution of each ophthalmological evaluation of patient 6 (TEC + bevacizumab). A. Creation of filtering ampoule; B. Active subconjunctival filtration bleb with an adequate evacuation of aqueous humor; C, D, E, F. Active ampoule with IOP control.

Discussion

The objective of this case series report was comparing the fibrosis inhibition degree of the filtering ampoule after intraoperative application of bevacizumab, 5-fluorouracil, or mitomycin C (MMC) in six dogs with primary chronic glaucoma subjected to TEC. Patients presented a satisfactory outcome, with the PIO compensation by tonometry, being even faster —although not immediately, after the surgical procedure.

It is essential to mention that patients not adequately responding to glaucoma medical therapy are more and more frequently found in daily practice, having to resort to surgical treatments for the management of this pathology. Therefore, it is necessary to resort to techniques such as TEC to stabilize patients diagnosed with glaucoma and help control IOP when tonometry values continue to be high after 2-3 months of topical treatment (Maggio and Bras, 2015). Nevertheless, this technique may also be insufficient in controlling IOP, being reported that the
The main cause of technique failure lies in conjunctival and episcleral fibrosis at the filtration ampoule level. This led to the understanding that TEC requires a filtering ampoule that remains active over time, including the use of drug principles to reduce or prevent the formation of scar or fibrotic tissue, characteristic of good resolution of wounds (Chen and Moeller, 2019).

According to our results, a comparative difference was found between the drugs used, in relation to the IOP reduction and the clinical evolution of the patients included in the study, requiring 2 months (60 days) of treatment and follow-up to manage to stabilize the patient and observe the decrease in the clinical signs of ocular discomfort, pain, and inflammation — characteristic of glaucoma, regardless of the fibrinolytic drug used. However, we believe that the revision of patients should not take so long after observing improvement, since it is necessary to adjust the doses of antiglaucomatous drugs, which cannot be suspended even when IOP is within normal ranges. This case was observed in one of the patients in this report, who presented a regression 90 days after performing the TEC.

Scleral congestion was maintained in all patients until day 30, even if IOP was controlled. This may be associated not only with the IOP itself, but also with the healing process that can be generated from the scleral vessels and that manages to stabilize with the effect of the fibrinolytic drugs used. The decrease in diffuse corneal edema and corneal opacity improved immediately in patients in whom bevacizumab was used. In the case of patients treated with 5-fluorouracil and MMC, an improvement could only be observed up to postoperative day 30. In addition, mydriasis reappeared on day 30 in the patients treated with 5-fluorouracil, but it only persisted in one of them during follow-up, in which the IOP again increased above 25 mmHg. It is worth mentioning that the patients treated with MMC presented moderate scleral congestion again by postoperative day 90. Therefore, the analysis of the effect of the three fibrosis inhibitory principles (i.e. bevacizumab, 5-fluorouracil, MMC) evidences the favorable response of the filtering bleb with bevacizumab when IOP and patient progress scale is considered.

These results do not coincide with studies published in human medicine, where MMC is the drug of choice in the active maintenance of the filtering bleb (Wilkins et al., 2001; Quintero-Delgado, 2013; Hu et al., 2021). This may be due to the lack of comparative studies of the action of other drugs with a similar mechanism in animals.
From this case series report, it is concluded that bevacizumab—as a fibrinolytic drug for intraoperative application—achieves IOP regulation under 25 mmHg after performing TEC, when carried out as a treatment for chronic glaucoma not controlled with topical treatment; it is, therefore, the drug of potential choice in dogs for the maintenance of the filtering bleb, helping to improve the signs of glaucoma. The other two fibrinolytic drugs used in this report (i.e. 5-fluorouracil, MMC) achieved improvement in the clinical signs associated with glaucoma, but did not completely prevent tissue fibrosis; therefore, there were relapses in IOP control up to 3 months after the surgical procedure.

With the increase in the diagnosis of glaucoma in dogs and its resistance to topical treatment, the purpose is to develop strategies at modulating post-surgical conjunctival and episcleral healing to prolong the survival of the filtering bleb, a key aspect in the success of the surgical procedure. Therefore, it is pertinent to conduct research with a larger number of patients and verify the effectiveness reported herein.

Declarations

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Conflicts of interest and sources of funding
The authors declare they have no conflicts of interest with regard to the work presented in this report.

Author contributions
Sandra Acevedo: Conception and acquisition, analysis, and interpretation of data, as well as drafting of the manuscript. Nathalia Correa: Analysis, and interpretation of data as well as substantial contributions and revision of the manuscript. Both authors have gave the final approval of the version to be submitted.

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