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Phacoemulsification associated with loss of endothelial cells in cataract surgery: a systematic review of main surgical techniques

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Abstract

Introduction: Phacoemulsification (PE) cataract surgery is the gold standard in ophthalmology, being effective in improving vision in more than 90.0% of patients. In this context, authors found that PE was associated with 16.67% of endothelial cell loss, which correlated with the degree of trauma during surgery. Endothelial changes are considered an important parameter for assessing trauma and for estimating the safety of a surgical technique. In this sense, more modern PE machines are capable of removing cataracts using optimized parameters such as high vacuum, aspiration flow, and low amount of ultrasonic energy. **Objective:** It was to present and discuss the main phacoemulsification techniques for optimizing the treatment of cataracts, in an attempt to reduce the loss of corneal endothelial cells. **Methods:** Experimental and clinical studies were included (case reports, retrospective, prospective, and randomized studies) with qualitative and/or quantitative analysis. Initially, the keywords were determined by searching the DeCS tool (Descriptors in Health Sciences, BIREME base) and later verified and validated by MeSH Terms. The search literature was carried out from January to April 2023 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. **Results:** A total of 122 articles involving phacoemulsification and endothelial cells were found. Initially, the existing title and duplications were excluded according to the interest described in this work. After this process, the abstracts were evaluated and a new exclusion was performed. A total of 80 articles were evaluated in full and 59 were included and discussed in this study. At the beginning of treatment with PE, without the endothelial protection of viscoelastic agents and the use of ultrasound in the anterior chamber, the endothelial loss was greater than in extracapsular cataract extraction. With the modernization of PE, the use of viscoelastic agents, the emergence of techniques for fracture of the nucleus within the capsular bag, and the use of ultrasound in the posterior chamber, the loss of endothelial cells reduced from 7 to 12% on average. **Conclusion:** Endothelial changes are considered an important parameter to assess trauma and estimate the safety of a surgical technique. Highlighted, the main predictors associated with the loss of corneal endothelial cells are the duration of the ultrasound used in the surgery, the turbulence of the liquid in the anterior chamber, and the mechanical trauma.

Keywords: Phacoemulsification. Techniques. Cataract. Endothelial cells. Endothelial thickness.

Introduction

Cataract surgery by phacoemulsification (PE) is the gold standard in ophthalmology, being effective in improving vision in more than 90.0% of patients [1]. PE appeared in 1967, with Charles Kelman, allowing a smaller surgical incision, without the need for sutures, less induction of astigmatism, less postoperative inflammation, and the conversion of this surgical procedure into an outpatient setting [2-6]. Furthermore, PE currently has low complication rates and high patient satisfaction rates [7-9].

In the technique, a small incision is made in the cornea and the lens is removed through ultrasonic fragmentation, leaving the posterior capsule intact so that a synthetic intraocular lens can be inserted into the capsular bag through the corneal incision and maintaining a low risk of complications from the cornea. posterior segment [10]. Thus, the large incision dimensions in cataract surgery, astigmatism induced by the procedure, intra and postoperative complications, and length of hospital stay were solved. Thus, the basic procedures of phacoemulsification in the last twenty years have shown a high success rate, with more than 95.0% of surgeries [1].

In this context, Pirazzoli et al. (1996) [11] found that PE was associated with 16.67% of endothelial cell loss which correlated with the degree of trauma during surgery. The corneal endothelium is a single-cell layer of approximately 500,000 cells located on the posterior surface of the cornea. It derives from the neural crest and has a low capacity for regeneration. With cell loss, surviving cells fill in the resulting gaps, increasing in size and also losing their regularity in size and shape.

Also, endothelial changes are considered an important parameter for assessing trauma and for estimating the safety of a surgical technique. Thus, the analysis of the shape and regularity of the endothelium is an indicator of endothelial damage. As a corollary, the malfunction of the corneal endothelium causes corneal edema and a consequent increase in corneal thickness [12].

In this sense, more modern PE machines are capable of removing cataracts using optimized parameters such as high vacuum, aspiration flow, and low amount of ultrasonic energy [12-14]. This allowed very fast techniques for cataract extraction, such as the "quick chop" technique, also known as "vertical chop" [15-21]. This technique is performed using a high vacuum, a small amount of ultrasound, and a pointed chopper. The "chopper" and the PE tip are placed side by side in the center of the lens [15].

Thus, the fracture of the cataract occurs through a vigorous bimanual maneuver, by which the chopper is depressed and the tip is raised in the center of the lens. After the fracture, it becomes easier to remove the cataract. However, surgical trauma occurring during PE leads to the loss of corneal endothelial cells [16, 22-24]. As these cells do not regenerate, most studies evaluating the safety of new techniques involve evaluating the reduction in corneal endothelial cell density by specular microscopy [19, 25-27]. Highlighted, the main predictors associated with the loss of corneal endothelial cells are the duration of the ultrasound used in the surgery, the turbulence of the liquid in the anterior chamber, and the mechanical trauma [28-33].

Added to this, the "divide and conquer" technique, modified by Shepherd in 1990, is quite popular because it is very systematic, uses more ultrasound than the "quick chop" technique, and does not require such a high vacuum [34-37]. Crema, in 1996, verified that the reduction of the corneal endothelial cell density by this technique is small and, therefore, safe [19].

In addition to these techniques, others have been developed and some are under development with the use of PE in an attempt to reduce the loss of endothelial cells. Thus, to justify the present work, it is necessary to know the main PE techniques for optimizing the treatment of cataracts [1].

Therefore, the present study aimed to present and discuss the main phacoemulsification techniques for optimizing the treatment of cataracts, in an attempt to reduce the loss of corneal endothelial cells, through a systematic review.

Methods

Study Design and Elegibilidade

Clinical studies were included (case reports, retrospective, prospective, and randomized studies) with qualitative and/or quantitative analysis. Initially, the keywords were determined by searching the DeCS tool (Descriptors in Health Sciences, BIREME base) and later verified and validated by the MeSh system (Medical Subject Headings, National Library of Medicine of the United States) with the objective of consistent search. The search literature was carried out from January to April 2023 in Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. In addition, a combination of keywords with the Booleans "OR", "AND" and the "NOT" operator was used to target scientific articles of interest.

Descriptors (Mesh Terms) And Guidelines

The main descriptors (Mesh Terms) used were *"Phacoemulsification. Techniques. Cataract. Endothelial cells. Endothelial thickness"*. For greater specification, the description of "loss of endothelial cells" for refinement was added during the searches, following the rules of the systematic review - PRISMA (Transparent reporting of systematic reviews and metaanalysis. Available at: www.prisma-statement.org/). Accessed on 05-10-2023.

Study Quality and Risk of Bias

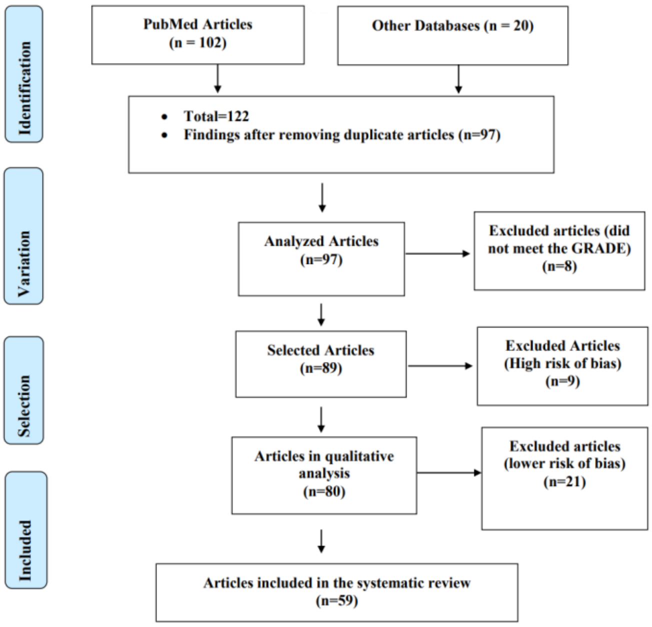
The quality of the studies was based on the GRADE instrument. The highest ratings were for controlled clinical studies with a sample size with statistical significance. The risk of bias was analyzed using the Cochrane instrument, based on the effect size of each study versus the sample size.

Results

Summary of Findings

A total of 122 articles involving phacoemulsification and endothelial cells were found. Initially, the existing title and duplications were excluded according to the interest described in this work. After this process, the abstracts were evaluated and a new exclusion was performed. A total of 80 articles were evaluated in full and 59 were included and discussed in this study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 9 studies with a high risk of bias and 8 studies that did not meet the GRADE that was removed (Figure 1).

Figure 1. Flowchart of the article selection process for the systematic review.



Source: Own authorship.

Major Findings and Discussion

In phacoemulsification (PE) surgery, protection of the corneal endothelium with viscoelastic is necessary, especially in hypermetropic patients. Thus, the loss of endothelial cells is significant and the thickness of the cornea may increase by 3 microns after surgery. The current standard procedure starts with a small incision in the cornea, filling the anterior chamber with viscoelastic material, opening a second corneal incision, and manually opening the anterior lens capsule [1]. Subsequently, cataract hydro dissection and hydro delamination are performed, followed by ultrasound-assisted PE and its complete aspiration and capsular polishing [37].

Finally, an intracapsular lens is implanted. However, these procedures are considered likely to be improved in their effectiveness and safety. The most common intraoperative complications with PE are anterior and posterior capsular rupture, followed by vitreous dislocation. In addition, other complications can be a refractive target not achieved, posterior capsular opacification, and cystoid macular edema [38].

Also, the total emission time of ultrasound in PE is considered a major risk factor for the development of postoperative corneal edema, delaying the usual visual rehabilitation. The indication of the best technique for the treatment of cataracts with hard cores is still a challenge [39-41]. PE has the advantage of a smaller incision with faster recovery and the disadvantage of requiring a greater amount of ultrasonic energy for hard nuclei, increasing damage to the corneal endothelium [42,43].

In this sense, at the beginning of treatment with PE, without the endothelial protection of viscoelastic agents and the use of ultrasound in the anterior chamber, the endothelial loss was greater than in extracapsular cataract extraction [43]. With the modernization of PE, the use of viscoelastic agents, the emergence of techniques for fracture of the nucleus within the capsular bag, and the use of ultrasound in the posterior chamber, the loss of endothelial cells reduced from 7 to 12% on average [44-47].

In this context, studies that prospectively analyzed the endothelial damage that occurred in surgeries for non-dense cataracts, comparing extracapsular cataract extraction and modernized and optimized PE, observed similar endothelial loss with the techniques (7-12% and 7-11%, respectively), with no statistically significant difference [47]. In addition, some authors prospectively studied the effect of PE in 167 cases of dense cataracts, with endothelial loss one year postoperatively of 13.05% in hard cataracts and 15.0% in black cataracts. The technique used was the "step-by-step chop in situ and separation", with the Legacy® 20000 phacoemulsification equipment, 2% hydroxypropylmethylcellulose viscoelastic (Viscomet®), and balanced saline solution (BSS®) [41].

Added to this, another study analyzed a series of 15 eyes with black cataracts, finding an average endothelial loss of 25.59%. The technique used was the "stop and chop", the phacoemulsification device was the Legacy® 20000 and the viscoelastic used was sodium hyaluronate 3.0% - chondroitin sulfate 4.0% (Viscoat®) [40]. In addition, the positive correlation between endothelial loss and ultrasound duration, used in PE surgeries in this study, confirms the findings of other studies that point to ultrasound energy as a harmful factor to the corneal endothelium [43,47-51].

Also, in a prospective study with 843 eyes, to identify the main risk factors for endothelial damage during PE, endothelial density was evaluated preoperatively and three months after surgery. As findings, a significant correlation of endothelial loss was analyzed concerning advanced age, small pupil diameter, hard lenticular nucleus, large nucleus, large irrigation volume, and prolonged ultrasound time [43].

Other authors compared the loss of corneal endothelial cells after PE according to different anterior chamber depths (ACD). The study followed a prospective model in 135 eyes with senile cataracts. Eyes with nuclear density from 2 to 4 were divided into three groups according to ACD: ACD I, 1.5 < ACD ≤ 2.5 mm; ACD II, 2.5 < ACD < 3.5 mm; or ACD III, 3.5 <ACD <4.5 mm. Endothelial cell loss was significantly greater in CAD I than in CAD III, 2 months after PE ($p < 0.05$). Therefore, eyes with superficial CAD, especially those with relatively hard cataract densities, may be vulnerable to further endothelial cell loss [52].

Furthermore, Nayak et al. (2012) [53] compared the difference in corneal endothelium in terms of cell density and morphology after PE using Ringer Lactate (RL) and balanced salt solution (BSS). The study was a prospective randomized controlled study with 52 human eyes with senile cataracts. Participants were divided into two groups, one with 26 patients undergoing the PE procedure using RL irrigation solution and the other 26 patients with BSS irrigation solution. The same surgeon was retained. At 1, 7, and 28 days postoperatively, an evaluation was performed to measure corneal endothelial cell density and morphology, as well as the inflammation variable in both groups. On the 28th postoperative day, the reduction of endothelial cells in the BSS group (173.96 cells/mm2, 8.12%) was lower than that of the RL group (253.20 cells/mm2, 10.25%). The percentage of increased corneal thickness in the BSS group (2.92%, 8.36%) was lower than in the RL group (3.42%, 9.96%). The decrease of hexagonal cells in the percentage of endothelium cell presentation in the BSS group (4.30%, 8.17%) was lower compared to the RL group (4.84%, 8.97%). However, all the results referring to the difference in the density and morphology of the corneal endothelium between the two groups did not present a statistically significant difference ($p > 0.05$).

Another work carried out by Maggon et al. (2017) [50] compares endothelial cell loss after PE via a prospective double-blind observational study. A total of 150 eyes of 150 patients between 50 and 70 years of age with grade II nuclear sclerosis senile cataracts were included. Patients were allocated into three groups of 50 eyes each in Group A (pupil size <5 mm), Group B (pupil size 5-7 mm), and Group C (pupil size > 7 mm). PE was performed by the same specialist surgeon using a "vertical chop" technique and a foldable intraocular lens was implanted in the capsular bag. Measurements were taken preoperatively and postoperatively on day 1, day 7, and day 30. The mean loss of endothelial cell counts on postoperative day 1 in Group A was 19.45%, Group B 14.89 %, Group C 10.19% with a statistically significant difference between Group A and Group B, as well as Group A and Group C. The difference was not significant between Group B and Group C, although there was a drop in cell counts in Group C. The increase in corneal thickness on the 1st postoperative day in Group A was 5.43%, Group B 3.55%, and Group C 2.14% with a statistically significant difference between Group A and Group B, as well as Group A and Group C, with no difference between Group B and Group C. Therefore, PE performed in eyes with maximum pupillary dilation <5 mm causes greater loss of endothelial cells and results in thicker corneas postoperatively in comparison with eyes with pupillary dilation > 5 mm at the end of one month.

In this context, in the "divide and conquer" technique by Shepherd, 1990, the fracture occurs after making, at the expense of the ultrasonic vibration of the tip, 2 central cross grooves in the core, of sufficiently tenuous thickness to allow the fracture of the core in 4 quadrants, by imposing, with the tip and spatula, lateral pressure on the grooves separating the quadrants [54-59].

The "quick chop" uses ultrasound for fractions of seconds together with a high vacuum to seize and retain the core in the tip. The fracture in the "quick chop" technique is, therefore, faster, as it does not require the creation of grooves, making the total use of ultrasound significantly less. In the capture of the crystalline lens by the tip to cause a fracture of the nucleus in the "quick chop" technique, it is necessary to use a high vacuum and a high flow of aspiration [1,59].

Thus, modern devices with computerized fluid control systems allow the use of a vacuum of up to 500 mmHg and an aspiration flow of 40 mL/min with anterior chamber stability. In the "divide and conquer" technique, the nucleus is sculpted using high ultrasound (70.0 %), low aspiration flow (20 mL/min), and the lowest possible vacuum (1 mmHg), as we do not want to seize any crystalline fragments at that time. In both techniques, we used the pulsatile mode and vacuum between 100 and 150 mmHg to phaco-emulsify the lens fragments [59].

In addition, for endothelial protection, 2.0% methylcellulose can be used. It has a low molecular weight, is dispersive, is a little pseudoplastic, and does not form chemical bonds with the endothelial cell layer [1]. It remains in the anterior chamber for longer than cohesive viscoelastic materials, but high molecular weight substances protect the endothelium more by occupying the anterior chamber space better, and substances composed of sodium hyaluronate favor chemical bonds with the hyaluronic acid of the endothelial cells, forming a layer protective of the endothelium [59].

In this sense, the high aspiration flow generates greater liquid turbulence in the anterior chamber and removes the viscoelastic more quickly, thus, in the "quick chop", 2.0% methylcellulose is removed more promptly than in "divide and conquer". Swirling is considered a cause of endothelial loss in PE. Corneal endothelial cell loss due to PE is due to several factors, not all easily measurable [1,2]. Damage to the endothelium begins with the incision, and continues during surgery with the volume, quality of the irrigation solution, and the turbulence of liquid inside the anterior chamber, in addition to microtrauma caused by instruments and lens fragments inside the eye. and by implanting an intraocular lens [3,4].

Added to this, the time and amount of ultrasound used in surgery have been widely discussed and studied as causes of corneal endothelial damage. Some authors reported that no correlation was found between endothelial cell loss and ultrasound time, or between it and the time or volume of irrigation, and that endothelial cell loss must be caused by factors such as instruments and intraocular maneuvers. In addition, they reported that the position of the PE tip concerning the eye (anterior or posterior chamber) can determine greater or lesser endothelial damage. PE in the anterior chamber can cause greater endothelial cell loss [57,58].

Another factor related to corneal endothelial injury in several studies was the quality and volume of the balanced saline solution used. Based on this, we studied 2 groups of patients, those who used more (≥250 mL) or less (≤ 200 mL) solution during surgery. However, no difference was found in the variation in corneal pachymetry or the variation in corneal endothelial cell density at 1 month postoperatively between the two groups [59].

Other factors implicated in endothelial injury by PE, such as mechanical trauma by instruments and lens fragments, the occurrence of air bubbles, the turbulence of balanced saline solution in the anterior chamber, and oscillation of the anterior chamber with the "surge" effect are not that can be quantified and perhaps play an important role in the endothelial loss. In addition, it is convenient to remember that the most modern devices and viscoelastic make surgeries with high flow and vacuum safer and more comfortable for the surgeon, probably reducing liquid turbulence, the "surge" effect, and even the ultrasound time, and a study similar conditions under such conditions could provide favorable results to the "quick chop" technique [59].

A study carried out by Perone et al. (2018) [4] analyzed the correlation between postoperative corneal edema and endothelial cell loss after cataract surgery by micro coaxial PE. Eighty-five eyes of 85 consecutive patients with mild cataracts (up to C5, N4, and P5: by LOCS III classification) were included in the prospective study. Pachymetry and endothelial cell density measurements were performed preoperatively, 2 hours after surgery, and 4 days, 15 days, and 1 month after surgery using non-contact specular microscopy CEM-530 (Nidek CO Ltd, Japan). Each surgery was performed using the Stellaris device (Bausch & Lomb, Bridgewater, NJ) in a micro coaxial mode with 2.2 mm incisions. The mean age was 73 ± 2.1 years, with 41 women (48%) and 44 men (52%). The mean operative time was 8 ± 5.5 minutes and the mean effective PE time was 7 ± 3.7 seconds. The mean increase in central corneal thickness was 46.68 ± 10 μm (8.39%) 2 hours after surgery, 10 ± 18 μm (1.8%) 4 days after surgery, and only 0.76 ± 11, 4 μm (0.1%) 15 days after surgery. Mean endothelial cell loss was 3.0 ± 1.5% at 2 hours, 9.0 ± 3.3% at D4, 10 ± 4.6% at D15, and 11 ± 4.7% at 1 month. On D4, significant endothelial loss (>15%) was mainly related to significant immediate corneal edema (>15%), while low postoperative edema (<5%) did not lead to significant endothelial loss (<5% loss). At D15 and D30, endothelial cell loss appeared to be closely correlated with immediate postoperative edema ($p < 0.0001$). Postoperative measurement of corneal thickness may therefore become a marker of endothelial damage after PE.

Another study evaluated the intrinsic correlations between lens density based on the Scheimpflug Imaging System, power used during surgery, duration of surgery, and endothelial cell loss in eyes with nuclear cataracts. A prospective cross-sectional observational study was carried out with 62 patients (71 eyes) with a mean age of 58.56 ± 10.4 years. The mean lens density measured by Scheimpflug was 13.93 ± 3.27. The mean parameters of power, ultrasound time, and elliptical movement were 13.63 ± 6.38, 1.27 ± 1.12, and 50.56 ± 50.06, respectively. In conclusion, positive correlations were observed between the lens density measured by Scheimpflug with the power parameters, ultrasound time and elliptical movement, duration of surgery, and endothelial loss [49].

Another important technique was demonstrated by Schmidt et al. (2018) [54], in which the "twist mode" PE results in a more effective fragmentation of the nucleus due to a different movement of the drug. Thus, we investigated the influence of a modified tip design and active fluid on PE efficacy and safety for the corneal endothelium. A prospective randomized study was carried out in which 40 patients were operated on with the Kelman Tip, using the Infiniti® system (group 1), and 20 patients were operated on with the Intrepid® Balanced Tip and the Centurion® System. Both groups did not differ preoperatively in age, sex, axial globe length or corneal endothelium cell density, or cataract density (LOCS3). The loss of endothelial cells was 8% in group 1 and 10.3% in group 2 ($p>0.05$). Cell size increased significantly in both groups with +37 μm in group 1 ($p<0.05$) and +54 μm in group 2 ($p<0.05$). There was no statistically significant difference between the two groups ($p> 0.05$). Therefore, endothelial cell loss occurs similarly using both systems. Furthermore, postoperative changes in cell size, number of hexagonal cells, and corneal thickness were similar between the two systems.

In the same sense, Sorrentino et al. (2017) [55] also studied the effect of torsional PE energy on the corneal endothelium, evaluating the relationship between changes in endothelial cells and postoperative visual acuity. This was followed by a prospective observational cohort study with 50 patients with cataracts. Sequential analyzes of morphometric and quantitative corneal endothelial cells were performed four weeks before surgery and six weeks after surgery using non-contact specular microscopy. There was an important correlation between the percentage of endothelial cell loss and the 5-point damage scale.

Furthermore, a meta-analysis study with 13 identified studies found that morphological abnormalities of the corneal endothelium result in fluid imbalance, stromal edema, and loss of transparency, impairing visual function. Recently, an increasing number of studies have focused on diabetic corneal abnormalities after cataract surgery, and their comparison with nondiabetic patients, results remain conflicting. For dynamic changes between pre- and postoperative values, significant differences were identified between the two groups in endothelial cell and hexagonal cell density at 1 day, 1 week, 1 month, and 3 months postoperatively, in the central cornea, thickness at 1 month postoperatively, and coefficient of variation at 1 week and 1 month postoperatively. However, no significant differences were observed in thickness at 1 day, 1 week, and 3 months postoperatively or in endothelial cells at 1 day and 3 months postoperatively [56].

Still, other authors studied the effects of 1.5% phenylephrine on the loss of corneal endothelial cells and morphological changes in patients who had PE surgery. A randomized controlled double-blind study followed, with 295 patients randomized into the intracameral mydriatic or topical mydriatic groups, analyzed preoperatively and postoperatively at 1 week, 6 weeks, and 3 months under a specular microscope. There was no significant difference in endothelial cell density and endothelial cell loss between topical and intracameral groups. At 3 months, the mean endothelial cell density in the intracameral group was 2129.76 ± 423.53 cells/mm2 and 2100.54 ± 393.00 cells/mm2 in the topical group ($p = 0.539$). The loss of endothelial cells was 18.60 ± 12.79% in the intracameral group and 19.44 ± 11.24% in the topical group ($p=0.550$). Therefore, intracameral phenylephrine was not associated with an increased risk of postoperative endothelial cell loss or morphological changes [58].

Conclusion

The basic procedures of phacoemulsification in the last twenty years have shown a high success rate, with more than 95.0% of surgeries. Endothelial changes are considered an important parameter for assessing trauma and for estimating the safety of a surgical technique. Highlighted, the main predictors associated with the loss of corneal endothelial cells are the duration of the ultrasound used in the surgery, the turbulence of the liquid in the anterior chamber, and the mechanical trauma.

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Data sharing statement
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Conflict of interest
The authors declare no conflict of interest.

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