UPDATE IN RADIOLOGY

Assisted techniques for the endovascular treatment of complex or atypical cerebral aneurysms

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Abstract In the last ten years, the endovascular approach to the management of cerebral aneurysms has gone from being an alternative to surgery to being the first-choice technique in the vast majority of cases. The continuous development of new assisted techniques and of new materials for embolization has multiplied its therapeutic possibilities, so that safe and efficacious endovascular treatment is now possible for aneurysms that would have required surgery only a few years ago. These continuous technological advances require the professionals who treat patients with cerebral aneurysms to achieve a high degree of specialization and to keep up to date through continuous training. In this article, we review some of the most widely used assisted techniques in the endovascular treatment of cerebral aneurysms, discussing their main indications, their advantages over conventional embolization techniques, and their possible limitations.

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TÉCNICAS ASISTIDAS PARA EL TRATAMIENTO ENDOVASCULAR DE ANEURISMAS CEREBRALES COMPLEJOS O ATÍPICOS

Resumen A lo largo de los últimos 10 años, el abordaje endovascular de los aneurismas cerebrales ha pasado de ser una alternativa a la cirugía para convertirse en la terapia de elección en la inmensa mayoría de los casos. El constante desarrollo de técnicas asistidas y de nuevos materiales de embolización ha multiplicado sus posibilidades terapéuticas, de modo que en la actualidad es posible tratar con eficacia y seguridad aneurismas que hace tan solo unos años hubiesen sido considerados quirúrgicos. Este continuo avance tecnológico exige a los profesionales implicados en el tratamiento de pacientes con aneurismas cerebrales un alto grado de especialización y una actualización formativa permanente. En el presente trabajo repasamos algunas de las técnicas asistidas más empleadas en la actualidad para el tratamiento...
Assisted techniques for the endovascular treatment of cerebral aneurysms

Introduction

The management of patients with cerebral aneurysms has undergone a radical change throughout the last decade. Since the publication of the ISAT (International Subarachnoid Aneurysm Trial)\(^1\) in 2002 and of the ISUIA (International Study of Unruptured Intracranial Aneurysms)\(^2\) in 2003, the neurosurgical treatment has gradually been replaced by the endovascular approach as the first-choice technique for ruptured aneurysms and for a large proportion of incidental aneurysms.

The increasingly widespread use of this therapeutic modality not only has enabled operators to gain experience and improve their skills, but it has also promoted the development of new techniques and materials. These advances have made the classical indications to become obsolete, allowing the treatment of increasingly complex and atypical aneurysms in a safe and effective way.

Assisted techniques for the treatment of patients with cerebral aneurysms can be used in addition to or as alternative to conventional embolization. Much of the effort used to develop these techniques has been aimed at achieving stable closures and recanalization rates close to those of surgery, because the main advantage of neurosurgical treatment over endovascular treatment is a lower recanalization rate in the long term, resulting in a reduced need for repeat surgery and lower risk of rebleeding.

The objective of this article is to review some of the main assisted techniques for the endovascular treatment of cerebral aneurysms, discussing their main indications, their advantages over conventional embolization techniques, and their possible limitations.

Remodeling techniques

One of the major factors limiting the endovascular treatment of cerebral aneurysms is the neck width.\(^3\) Wide-necked aneurysms (>4 mm) or with a dome-to-neck ratio less than 1.2 can only be treated endovascularly if assisted techniques are employed. The reason for this lies in the morphological characteristics of these aneurysms, which highly increase the risk of coil migration or protrusion into the parent artery.\(^4\)

The remodeling technique, also known as “balloon-assisted embolization”, was one of the first techniques introduced in the routine practice for the treatment of wide-necked aneurysms or aneurysms with unfavorable morphology.\(^3\) This technique involves the placement of a balloon-catheter in the neck of the aneurysm that is inflated temporarily during coil deployment (Fig. 1). At the end of the procedure, the balloon is removed and no device is left in place in the parent vessel, unless stent placement is subsequently performed.\(^5\)

In addition, to avoid coil protrusion into the parent vessel, the remodeling technique has further advantages: the balloon provides an excellent control of the neck, increases endosaccular stabilization of the microcatheter, and permits a denser packing of the aneurysm. Another advantage is that the inflated balloon inside the parent artery will help control the bleeding in the event of aneurysmal rupture during the procedure.

As a result of the development of ever more sophisticated balloons, the remodeling technique has gradually been improved, to such an extent that many centers currently use it on a routine basis.\(^6\) In addition, the launch of compliant balloons, able to protrude into the aneurysm sac and to conform to the anatomy of arterial bifurcations, has broadened the indications of the technique to also include the treatment of distal aneurysms and bifurcations.\(^7,8\)

The safety of remodeling has been a subject of much controversy\(^9-11\) because this technique is supposedly associated with a higher risk of thromboembolism and arterial rupture or dissection secondary to the simultaneous use of multiple devices, balloon inflation, and temporary parent artery occlusion. A critical review of the recently published literature\(^5\) has analyzed the outcomes of remodeling in different series of patients with cerebral aneurysms who received endovascular treatment, including the multicentre and prospective ATENA (incidental aneurysms)\(^12\) and CLARITY (ruptured aneurysms)\(^13\) series. The review concluded that the rate of complications, morbidity and mortality associated with remodeling is similar to that of conventional embolization. The review also provided evidence of the superiority of remodeling in terms of anatomic outcomes and degree of aneurysm occlusion in the immediate post-operative period. Based on these results, and considering the lack of randomized studies that assess the efficacy and safety of remodeling, the authors of the review advocate for the routine use of this technique.

A variant of the remodeling technique is the double-balloon remodeling, involving the simultaneous use of two balloons that are placed in each side branch of the bifurcation or in an X-shaped configuration (Fig. 2). Double-balloon remodeling provides a better sealing of the neck and better side-branch protection than inflation of one single compliant balloon, especially in wide-necked aneurysms and bifurcations.\(^14,15\) However, double-balloon remodeling is not without its risks, since the simultaneous use of three microcatheters increases the technical complexity of the procedure and the risk of thromboembolic complications.

Combined use of coils and stents

The combined use of coils and stents is another alternative for the treatment of wide-necked aneurysms or aneurysms with a dome-to-neck ratio less than 1.2.

In complex aneurysms with unfavorable anatomy, the remodeling balloon may be insufficient to prevent coil protrusion into the parent vessel and to ensure an adequate arterial reconstruction and packing of the aneurysm sac.
Figure 1  Ruptured wide-necked aneurysm located at the origin of the posterior communicating artery (PCA). (A) Preoperative digital subtraction angiogram (DSA) in the working projection. (B and C) Angiographic images without subtraction showing an inflated balloon covering the aneurysm neck (arrows) during coil delivery into the sac (arrowhead). After the procedure, optimal packing (white arrowhead) and the deflated balloon catheter in the parent artery (thin arrows) are observed. (D) Postoperative DSA after withdrawal of the balloon catheter, complete sac sealing and optimal parent artery reconstruction.

In these cases, stent implantation not only provides support during embolization, but it also redirects the flow of the parent artery, and serves as a scaffold to artery reendothelialization.\textsuperscript{16-18} The use of this type of devices would mean a conceptual advance in the management of cerebral aneurysm because it would enable the treatment of both the aneurysm and the underlying abnormality in the parent artery.\textsuperscript{19}

Figure 2  Anterior communicating artery (ACoA) aneurysm that was previously clipped, with growth of the surgical remnant. (A and B) 3D reconstructions show configuration and neck width of the aneurysm, which is untreatable with simple remodeling. (C) Digital subtraction angiogram (DSA) in the working projection shows placement of the first remodeling balloon in the anterior cerebral artery (ACA) (arrows). (D) Angiography without subtraction shows both balloons covering the neck (arrows) to prevent coil protrusion (asterisk). (E) The final DSA demonstrates complete occlusion of the surgical remnant. (F) Detail of the coils and surgical clips at the end of the procedure.
poor flexibility and navigability through intracranial vasculature entail a great technical difficulty and a significant risk of ischemic and hemorrhagic complications.\textsuperscript{20}

The development of self-expandable stents specifically engineered for stent-assisted embolization of cerebral aneurysms was a new landmark in neuroendovascular surgery. These devices are very flexible and manageable, and thus, can easily change their shape to conform to vascular morphology even in curved or very elongated segments. As a result, they are less traumatic, entail lower risk of artery dissection or rupture, and have broadened the indications for the treatment of aneurysms with unfavorable locations.\textsuperscript{21,22} Stents are made of nitinol, so they do not produce any artifacts on MR images. For this reason, MRI can be safely used for follow-up.\textsuperscript{23} Except for the first model launched to the market—Neuroform\textsuperscript{®} (Boston Scientific, Fremont, CA, USA)—, which is an open-cell design, all models in this group—Leo Plus\textsuperscript{®} (Balt Extrusion, Montmorency, France), Enterprise\textsuperscript{®} (Cordis Neurovascular, Miami, Florida, USA) and Solitaire\textsuperscript{®} (EV3 Neurovascular, Inc Irvine, California, USA)—have a closed-cell design. Although these latter models presumably provide a wider coverage of the aneurysm neck, none of them has proved superior to the others in terms of efficacy, safety, indications or long-term outcome.\textsuperscript{24}

A second group of stents specifically engineered for intracranial use is balloon-expandable stents, which are normally used for the treatment of artery stenosis because they are less compliant. However, the use of models such as Pharos\textsuperscript{®} (Micrus Endovascular, San Jose, California, USA) has been approved for the treatment of cerebral aneurysms.\textsuperscript{25}

Stents provide excellent support during embolization, allowing high packing density and decreasing the risk of delayed coil compaction by redirecting blood flow to the parent artery. Once the stent is placed in the target position, coil delivery inside the aneurysm is performed with a microcatheter, which can be inserted in the sac after or prior to stent deployment. If it is inserted prior to stent deployment, one of the cells is used as the gateway to the sac. Opting for one or other technique is ultimately at the operator’s discretion (Fig. 3).

Double stenting (placement of two stents in an X- or Y-shaped configuration) is a variant that allows the treatment of bifurcation aneurysms that cannot be properly packed by means of one single device\textsuperscript{26,27} (Fig. 4).

Most of the data on stent-assisted embolization published to date focus on the treatment of incidental aneurysms. The use of stent-assisted embolization in patients with ruptured aneurysms is controversial because the thrombogenic potential of stents makes it necessary to follow a strict antplatelet regimen before, during and after the procedure. In spite of preventing thromboembolic events, antplatelet agent administration in patients with subarachnoid hemorrhage increases the risk of serious hemorrhagic complications associated with relatively common circumstances in routine practice, such as aneurysm re-rupture, need for surgery after the neuroendovascular procedure, and aneurysm perforation during the procedure. For these reasons, and despite a number of series that report on the good outcomes of stent-assisted embolization in acute settings,\textsuperscript{4} most interventional radiologists are currently reluctant to use stents for the management of subarachnoid hemorrhage.

**Treatment assisted by stand-alone stents: flow diversion**

Since their incorporation into routine practice, the role of stents to obtain higher packing density has been highlighted. However, a good number of laboratory experiments and cases studies suggest that stents are able to promote stable occlusion even with low packing densities.\textsuperscript{18,29} Stents have proved to trigger a set of hemodynamic changes that induce contrast ectasia in the sac and thrombosis of the aneurysm, effects that would be influenced both by porosity (proportion of open area with respect to the total area of the stent) and by the geometry of the stent deployed.\textsuperscript{30–32} The extreme case involves covered stents\textsuperscript{33,34} (Fig. 5), but there are reports of aneurysms that have undergone spontaneous thrombosis after placement of a single non-covered stent\textsuperscript{35} (Fig. 6) or several overlapping stents\textsuperscript{29} without coiling. These observations have led to a conceptual change in the application of stents for the treatment of cerebral aneurysm, where instead of using stents as mere adjuncts to assist embolization, they would now be used as stand-alone devices for functional and anatomic reconstruction of the parent artery.\textsuperscript{32}

Pipeline\textsuperscript{®} (Ev3-MTI, Irvine, CA, USA) and Silk\textsuperscript{®} (Balt, Montmorency, France) embolization devices are specifically designed as stand-alone stents, that is, without any other embolization devices for aneurysmal sac filling.\textsuperscript{36} These are self-expandable and flexible stents consisting of a mesh of braided microfilaments with significantly lower porosity than that of conventional stents (65–70% compared with 88–91%). The special design of these stents promotes aneurysm thrombosis and theoretically permits blood flow through the branches or perforating arteries arising from the artery covered by the stent.\textsuperscript{37} Because of this profile, Pipeline and Silk stents are particularly useful for the treatment of aneurysms that are otherwise difficult to treat, such as microaneurysms\textsuperscript{37} and large, giant, fusiform or wide-necked aneurysms\textsuperscript{38}. However, their indications have not been accurately established yet.\textsuperscript{31}

Since the series published so far in the literature are scarce and their results are heterogeneous from one series to another,\textsuperscript{31} the safety of these novel devices is difficult to determine, especially when it comes to delayed aneurysm rupture, thromboembolic complications and potential occlusion or stenosis of the branches covered by the stent. The procedure itself, however, seems to pose a lower risk than conventional embolization techniques. As a matter of fact, a number of authors\textsuperscript{36,37} argue that one of the major advantages of these stents is that aneurysm catheterization and coiling are not necessary. This means a simplification of the technique and a reduced risk of intraoperative rupture (Fig. 7).

As regards the efficacy of Pipeline and Silk stents, preliminary results are promising; particularly taking into account the aneurysms treated with these stents are usually complex. Unlike aneurysms that are treated with coiling or surgical clipping, thrombosis induced by Pipeline and Silk
Figure 3  Incidental wide-necked aneurysm at the origin of the left P1 segment. (A) Preoperative digital subtraction angiogram (DSA) in the working projection. The bell-shaped configuration of the aneurysm (arrow) is unfavorable to perform conventional embolization since the coils would protrude into the parent artery. (B) Deployed stent in the parent artery covering the aneurysm neck (arrows). (C) Angiography without subtraction in the working projection. Stent deployed in the parent artery (arrows) and coils inside the sac (arrowhead). In this case, it was necessary to introduce the microcatheter into the sac (not shown) through the stent mesh. (D) DSA at the end of the procedure with good angiographic outcome.

stents does not commonly occur immediately, but normally over some weeks or months. Current data reveal that complete occlusion of the aneurysm only occur in 10–16% of cases immediately after the procedure, whereas the rate amounts to 49–95% at six-month follow-up arteriography.31 Therefore, the operator should be aware that the expected angiographic findings at the conclusion of the procedure differ from those yielded by conventional techniques for endosaccular occlusion. These latter techniques seek to achieve complete aneurysmal occlusion, whereas the new devices often cause slower contrast flow and residual filling within the sac that should not be regarded as treatment failure. Misinterpreting these findings may lead to unnecessary therapies (placement of several stents, coiling) that may increase the risk of short- and medium-term complications.36

Figure 4  Incidental aneurysm at the tip of the basilar artery. (A) 3D reconstruction demonstrates a wide-necked aneurysm at the tip of the basilar artery that involves the origin of both posterior cerebral arteries (PCAs). To ensure their patency, a stent was deployed in each of the PCAs placing the proximal end of both devices in the basilar artery. (B) Digital subtraction angiogram (DSA) in the working projection demonstrates the first stent deployed in the right PCA (arrows) and the microguidewire inside the basilar artery prior to implantation of the second stent (arrowhead). Note a previously embolized right carotid aneurysm (asterisk). (C and D) Angiograms with and without digital subtraction, respectively, show complete deployment of the two stents and optimal flow through them (arrows). (E) 3D image acquired by rotational angiography shows the configuration of the two stents deployed. (F) The sac is catheterized through one of stent interstices (not shown), and is gradually filled with coils to achieve complete aneurysmal occlusion (asterisk). (G) DSA obtained at the end of the procedure demonstrates an accurate V-shaped sealing of the aneurysm neck and the morphologic reconstruction of both PCAs.
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Figure 5  Aneurysm in the distal internal carotid artery (ICA) with symptoms caused by compression of the III pair of cranial nerves treated with covered balloon-expandable stents for coronary arteries. (A) Initial digital subtraction angiogram (DSA). In the absence of branches in the artery segment involved, a covered coronary stent is used to occlude the aneurysm. (B) Digital artery map shows the covered stent deployed in the ICA (arrows). (C) DSA after conclusion of the procedure. Excluded aneurysm with adequate anatomic reconstruction of the parent artery. A change in the ICA morphology can also be observed, the ICA seems to be stretched due to the stiffness of the stent (arrows). Precisely, lack of flexibility and poor navigability are the main limitations of this type of stent. (D) Follow-up CT-angiogram six months after the procedure. Excluded aneurysm with patent stent and free of stenosis areas (arrows).

Figure 6  Incidental aneurysm in the anterior communicating artery (ACoA) treated with a non-covered balloon-expandable stent for intracranial use. (A) Digital subtraction angiogram (DSA) of the left carotid artery in the anterior-posterior projection demonstrating the ACoA aneurysm (arrow). (B and C) Angiograms without subtraction during the procedure. Balloon inflation in the anterior cerebral artery (ACA) (thin arrows) to achieve complete deployment of the stent (thick arrow). Coils observed inside a previously treated right carotid artery aneurysm (asterisk). (D) Final DSA. The change in the hemodynamic pattern induced by the stent facilitated complete sealing of the aneurysm without requiring coiling (arrow).
Onyx® embolization

Onyx® (eV3-MTI, Irvine, CA, USA) is a nonadhesive liquid embolic agent made of biocompatible ethylene vinyl alcohol (EVOH) copolymer dissolved in dimethyl sulfoxide (DMSO). When it comes into contact with an aqueous solution (blood in this case), Onyx precipitates and forms an initially soft cast, with a peripheral spongy outer layer and a semiliquid centre. The material solidifies completely 10 min after injection.

The viscosity of Onyx increases exponentially with EVOH concentration. Onyx 18, which is used for embolization of arteriovenous malformations, contains 6% EVOH and has a viscosity of 18 centipoise (water viscosity is one centipoise). In contrast, Onyx HD-500, a highly viscous variant specifically designed for cerebral aneurysm embolization, has 20% EVOH and 500-centipoise viscosity.

In all cases, Onyx embolization involves placement of a remodeling balloon covering the aneurysm neck. A sealing test before the procedure is required to determine whether the balloon is satisfactorily occluding the neck. The test involves the injection of contrast material into the sac while the balloon is inflated to check for absence of leakage to the parent artery or adjacent side branches; the test is then considered positive. Patients with negative sealing test should not be treated with Onyx.

Even though it has been applied in the treatment of small aneurysms, Onyx embolization was initially proposed as an alternative method for the treatment of large, giant or wide-necked aneurysms. According to the results of the multicentre and prospective CAMEO study, Onyx can induce durable aneurysm occlusion in patients with these types of aneurysms, which are always difficult to treat. In fact, other endovascular techniques yield worse results and surgery is associated with significant morbidity. Again, according to the CAMEO study, the clinical outcome and complication rate with Onyx would be comparable to conventional embolization of this type of aneurysm, and the complete occlusion rate reported (79%) is significantly higher than that reported with conventional techniques (59%).

Several series have reported good angiographic outcomes with Onyx, outcomes that are basically found to be due to
two factors. First, Onyx provides full filling (100%) of the sac (coiling rarely provides a filling rate higher than 30%). Second, angiographic images with Onyx are more easily subtracted than coil images, which facilitates the treatment when part of the aneurysm overlaps the parent artery in the working projection.40

Another typical advantage of the Onyx treatment is its lower recanalization rate compared with conventional embolization. There are so far no reports of compaction of the embolic agent, which is the most common form of recanalization after endovascular treatment with coils.40 Nevertheless, the nonadhesive nature of Onyx may give rise to a type of recanalization located between the Onyx cast and the vessel wall, which is difficult to treat and results from incomplete neck sealing.39,40 To minimize the risk of appearance, a number of strategies have been developed,39-41 being the stent-assisted combined technique the one with the best outcomes.41 In fact, some authors argue that optimal parent artery reconstruction and prolonged occlusion of large or giant aneurysms treated with Onyx necessarily involves the placement of a stent that covers the aneurysm neck (Fig. 8).

The major disadvantage of cerebral aneurysm embolization with Onyx is that it involves a higher technical complexity than conventional endovascular treatment.39,40 After the injection, the embolic agent tends to keep advancing through the artery, and unlike coils, it cannot be retrieved if it is placed in an undesired position. For this reason, and taking into account that part of it can travel from the aneurysm sac to the parent artery, embolic material is not recommended in those cases involving perforating arteries in the neck or in its vicinity.40 In addition, if the arteries are tortuous or the aneurysm is located in a curve, advancement and placement of the protecting balloon, indispensable for the treatment, may be difficult or impossible.40,41 The development of new devices, such as the Quick Stop syringe, which allows nearly immediate stopping of the injection, and the new generations of remodeling balloons, more suitable for distal navigation and longer for better neck protection, have simplified the technique and facilitated its application in routine practice.39,41

Since the CAMEO study reports on a significant number of cases of delayed occlusion of the parent artery after Onyx treatment, administration of anticoagulants and/or antiplatelets is recommended whenever this embolization technique is used. Treatment guidelines vary according to whether or not endoprosthesis has been used and whether Onyx remnants stay in the parent artery.41

Double microcatheter embolization

Another technique for endovascular management of aneurysms with unfavorable configuration (large aneurysms, wide-necked aneurysms, and aneurysms with branches arising from the neck) is double microcatheter embolization. This technique involves the introduction of two microcatheters in the sac that deploy two coils beside each other. This is a stable side-by-side configuration that forms a lattice through the aneurysmal neck for deployment of subsequent coils.43,44
The main advantage of this technique is that it does not require double femoral puncture or devices additional to those used in conventional embolization. Thus, a single 6F guiding catheter is sufficient to contain the two microcatheters. In addition, its small gauge size allows this device to be used for the treatment of distal aneurysms and even of vessel elongation.44

Baxter et al.43 described double microcatheter embolization as a rescue technique in those cases in which placement of the first coil causes endosaccular instability (a too small coil helix and risk of distal migration) or space compromise in the parent artery (a too large coil helix and coils in the lumen). More recently, several authors44,45 have used this technique as an initial procedure for the treatment of complex aneurysms.

The aneurysmal sac is divided into two imaginary parts that are filled with the first and second coils, respectively. Several centimeters of each coil are deployed alternatively or the coils are completely deployed on a consecutive basis. In any case, the coils are not delivered until both of them are completely deployed and endosaccular stability is secured. Once the initial coil helix is formed, the free aneurysmal space is filled with smaller coils using the two microcatheters (Fig. 9).

The authors of the largest series of patients treated with double microcatheterization that has been published to date44 regard this technique as a simple technical variant of conventional embolization without a higher rate of complications than that of single-microcatheter treatment.

**Extrasaccular embolization**

As with large and giant aneurysms, the management of cerebral microaneurysms (those with a sac ≤3 mm in diameter) is difficult both with an endovascular and open surgical approaches.

Neurosurgical techniques remain the modality of choice to treat cerebral microaneurysms in many centers because of their high rate of rupture during conventional endovascular procedures. However, clipping such small aneurysms may be impossible due to the low dome-to-neck ratio. Other types of intervention, such as trapping (proximal and distal to the aneurysm), may cause serious neurological sequelae because they involve the occlusion of the main arteries or of potential pathways of collateral circulation.46 Because of these limitations and considering that on many occasions the clinical condition of the patient does not allow a neurosurgical approach, several authors have proposed alternative endovascular techniques.37,47,48

One of these techniques is extrasaccular embolization, which involves stabilization of the microcatheter in the microaneurysm neck using a remodeling balloon, deploying the coil outside the sac, and introducing it by inflating the balloon (Fig. 10). This procedure prevents the microcatheter from invading the sac, and minimizes the risk of rupture.49

The number of patients with cerebral microaneurysms treated with an endovascular approach remains low, so further research is needed to assess the long-term outcomes of this type of procedure.
Conclusions

The great advances made in recent years in interventional neuroradiology applied to the treatment of cerebral aneurysms have broadened the indications for the management of aneurysms with unfavorable size and configuration, which have traditionally been treated surgically.

The continuous development of new techniques and materials offers a significantly wider range of therapeutic possibilities. At the same time, the personnel involved in the treatment of patients with cerebral aneurysms are required to constantly update their knowledge and reach a high degree of specialization.

In the lack of clinical trials that assess systematically the outcomes of new procedures, each case needs to be evaluated on an individual basis in a multidisciplinary session in order to provide each patient with the safest and most effective therapeutic option available at a particular time for each specific case.

Authorship

1. Responsible for the integrity of the study: AMM.
2. Conception of the study: AMM, EMQ and AGG.
3. Design of the study: AMM and EMQ.
4. Acquisition of data: AMM, EMQ, AGG, PVV and ASA.
5. Analysis and interpretation of data: AMM, EMQ, AGG, PVV and ASA.
6. Statistical analysis: N/A.
7. Bibliographic search: AMM, EMQ, AGG and PVV.
8. Writing of the paper: AMM, EMQ and PVV.
9. Critical review with intellectually relevant contributions: AMM, EMQ, AGG, PVV and ASA.

Conflicts of interest

The authors declare not having any conflicts of interest.

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