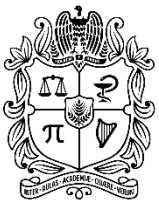

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Endovascular treatment versus standard management for cerebral vasospasm in aneurysmal subarachnoid haemorrhage

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The only thing I knew how to do was to keep on keeping on.

Bob Dylan

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I thank the Diagnostic Imaging Department of the *Universidad Nacional de Colombia*, the *Hospital Universitario Nacional*, the *Fundación Hospital de la Misericordia,* and all of the institutions that supported me during my residency.

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Resumen

Pregunta de investigación: en este trabajo se evaluó la efectividad y la seguridad del tratamiento endovascular (i.e. infusión intraarterial de vasodilatador, angioplastia con balón, stent recuperable o terapia combinada) en comparación con el tratamiento estándar para el manejo del vasoespasmo cerebral en adultos con hemorragia subaracnoidea aneurismática.

Antecedentes: aunque el 30% de los pacientes con vasoespasmo cerebral desarrollan isquemia cerebral tardía, actualmente no hay forma de saber que pacientes desarrollarán esta complicación. Existe una amplia gama de opciones terapéuticas y la elección se basa en la experiencia clínica, las preferencias del paciente y los eventos adversos.

Características de los estudios: se realizó búsqueda sistemática de estudios controlados hasta el 2 de mayo de 2020. Se incluyó 26 estudios con 1783 pacientes. Los estudios incluyeron hombres y mujeres mayores de 18 años con diagnóstico clínico y radiológico de hemorragia subaracnoidea aneurismática y vasoespasmo cerebral. Diez estudios (799 pacientes) incluyeron pacientes que recibieron terapia endovascular versus tratamiento médico. La mayoría de los estudios utilizó infusión intraarterial de vasodilatador (i.e. papaverina, nimodipino, nicardipino, colforsina, etc.). Quince estudios (912 pacientes) compararon diferentes modalidades de terapia endovascular entre sí. Un estudio (72 pacientes) incluyó tres brazos de comparación (terapia médica, vasodilatador intraarterial y angioplastia con balón).

Resultados clave: el estado funcional a largo plazo y la mejoría angiográfica sugiere ser superior con vasodilatador intraarterial comparado con tratamiento médico (riesgo de sesgo moderado / serio). No se observó diferencias significativas en los eventos adversos entre la terapia endovascular versus el tratamiento médico (riesgo de sesgo moderado / serio).

Calidad de la evidencia: los resultados deben interpretarse con cautela: riesgo de sesgo, imprecisión, inconsistencia y heterogeneidad.

Palabras clave: Vasoespasmo Intracraneal; Procedimientos endovasculares; Hemorragia subaracnoidea**.**

Abstract

Review question: in this review we assessed the effectiveness and safety of endovascular therapy (i.e. intra-arterial vasodilator infusion, balloon angioplasty, stent or combined therapy) compared to standard management for treatment of cerebral vasospasm in adults with aneurysmal subarachnoid haemorrhage.

Background: although 30% of patients with cerebral vasospasm develop delayed cerebral ischaemia, currently there is no way to know whether a patient would have this complication. There are a wide range of treatment options and the choice is based on the experience of the clinicians, patient preferences and adverse effects.

Trial characteristics: we searched the available literature up to 2 May 2020 and included 26 controlled studies with 1783 patients. The studies included both men and women aged over 18 years with clinical diagnosis and radiological diagnosis of aneurysmal subarachnoid haemorrhage and cerebral vasospasm. Ten studies (799 patients) included people that had been treated with endovascular treatment and compared with medical therapy. In most studies, people received intra-arterial vasodilatory infusion (i.e. papaverine, nimodipine, nicardipine, colforsin). Fifteen studies compared endovascular therapy against each other technique (912 participants). One study (72 patients) included three arms (medical therapy, intra-arterial vasodilator infusion and balloon angioplasty).

Key results: long-term functional status and angiographic improvement suggest superiority with intra-arterial vasodilator compared to medical treatment (moderate / serous risk of bias). We found no difference on adverse events rate between endovascular therapy and medical treatment (moderate / serous risk of bias).

Quality of evidence: results should be interpreted with cautio because the risk of bias, imprecision, inconsistency and heterogeneity.

Keywords: Vasospasm Intracranial; Endovascular Procedures; Subarachnoid haemorrhage**.**

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Abreviations list

Abreviation	Term
SAH	Subarachnoid haemorrhage
TCD	Transcranial doppler
CT	Computed tomography
DSA	Digitl substraction angiography
CTA	Computed tomography angiography
CTP	Computed tomography perfusion
IAVI	Intra-arteria vasodilator infusion
TBA	Percutaneous transluminal balloon angioplasty
cAMP	Cyclic adenosin monophosphate
MRI	Magnetic resonance imaging
MRA	Magnetic resonance angiography
GOS	Glasgow outcome scale
mRS	Modified Rankin scale
GOSE	Glasgow outcome scale extended
ITT	Intention to treat analysis
SD	Standard deviation
OR	Odds ratio
CI	Confidence interval
MD	Mean difference
SMD	Standardized mean difference
MLCK	Myosin light-chain kinase enzyme

1. Background

1.1 Description of the condition

Subarachnoid haemorrhage (SAH) is a medical emergency consisting of bleeding into the subarachnoid space and — in some cases — the parenchyma or ventricular space, or both (1). Sometimes this bleeding is caused by trauma, however it is usually caused by the rupture of a brain aneurysm, and is a major cause of haemorrhagic stroke (2).

Worldwide, aneurysmal SAH occurs in nearly 600,000 people per year(3). Its incidence varies by geographic region: for example, it has been reported that Kuwait and Japan have an annual incidence of 1.4 and 24.8 cases per 100,000 people/ year, respectively, which suggests that aneurysmal SAH may have a genetic component (4). The condition is more frequent in women (the ratio of women to men is 1.3:1), and the risk of developing it increases with age, with the average age of onset being 50 years (5,6).

The mortality rate of aneurysmal SAH is high; however, in high- income countries it decreased from 55% in 1978 to 35% in 2006; this has been partly attributed to the development of better health systems, as well as progress made in intensive care treatments (3,7). The burden of haemorrhagic stroke resulting from aneurysmal SAH is higher than the burden of ischaemic stroke, because it affects a younger age group with longer life expectancy (3).

Brain damage resulting from a ruptured intracranial aneurysm occurs in two stages. The first phase is a transient cerebral ischaemia caused by a sudden increase of intracranial pressure that alters perfusion, while the second is associated with an uncontrolled systemic response that affects multiple organs (3). Complications of aneurysmal SAH include cerebral vasospasm, hydrocephalus, and re-bleeding. Cerebral vasospasm is a

phenomenon defined as the reversible narrowing of the intracranial vessels; it usually occurs between four and 14 days after aneurysmal SAH takes place. Up to 90% of patients with aneurysmal SAH develop cerebral vasospasm, which may lead to cerebral ischaemia in 10% to 45% of cases (8,9).

Cerebral vasospasm can be detected using transcranial Doppler (TCD), computed tomography (CT), or digital subtraction angiography (DSA). Some clinical practice guidelines recommend performing a CT angiography or a brain perfusion image (or both) for its detection, despite the risks associated with using ionising radiation in these patients (10). In a meta-analysis that included 17 studies, TCD was recommended due to its predictive capability and versatility (11). However, DSA continues to be the gold standard for the diagnosis of this condition; it also allows immediate endovascular treatment (10). CT multimodality techniques for detecting cerebral vasospasm include computed tomography angiography (CTA) and computed tomography perfusion (CTP) imaging. CTA is a fast, non-invasive, and accurate imaging test performed to identify brain vessels narrowing. Likewise, CTP aids in the evaluation of tissue perfusion, for it can help predict cases in which patients require further treatment due to the presence of a prolonged mean transit time (12,13).

Prophylaxis for patients with cerebral vasospasm as a result of aneurysmal SAH has been attempted. For example, oral nimodipine has been proven to be an effective neuroprotector. Other pharmacological therapies that have been tested for treating this condition include fasudil, corticosteroids, magnesium sulphate, and others; however, none of these treatments has shown clinical significance (10). Additionally, a randomised trial of endovascular prophylaxis through balloon angioplasty for preventing cerebral vasospasm reported no clear benefit of this therapy (14). Intra-arterial vasodilator infusion (IAVI) is another prophylactic strategy for this condition, however there are no studies assessing its use.

Treatment of cerebral vasospasm includes one or more of the following: pharmacological management, percutaneous transluminal balloon angioplasty (TBA) and IAVI. Although endovascular treatment is controversial, it is used for the management of patients in which other medical treatments have failed, and those at high risk of developing ischaemia according to the Lindegaard ratio (i.e. mean middle cerebral artery flow velocity divided by

mean ipsilateral extracranial internal carotid artery flow velocity), which is obtained through transcranial Doppler (15).

1.2 Description of the intervention

At present, there are three different types of endovascular treatment for cerebral vasospasm: 1) IAVI, 2) percutaneous transluminal balloon angioplasty (TBA), and 3) retrievable self- expandable stents (10).

Intra-arterial vasodilator infusion is performed under general anaesthesia or conscious sedation. After obtaining vascular access, a catheter is inserted in the affected area; then a vasodilator agent (e.g. papaverine, milrinone, or calcium channel blockers including verapamil, nicardipine, and nimodipine) is administered through the catheter. The continuous infusion may last a few minutes and can be repeated several times during the same procedure; in addition, this procedure can be performed again in case of recurrence (15). IAVI is indicated for the management of a diffuse cerebral vasospasm affecting distal blood vessels, since it makes it possible to treat multiple cerebral vascular territories at the same time.

On the other hand, TBA consists of mechanical vasodilation using compliant or non-compliant balloon catheters that are inflated at the affected site for a few seconds. Like IAVI, it is performed under general anaesthesia or conscious sedation and after peripheral vascular access is achieved. Its use is limited to proximal blood vessels (i.e. the intracranial internal carotid artery, proximal anterior cerebral artery (A1 or A2 segment), proximal stem of the middle cerebral artery (M1 or M2), and vertebrobasilar territory), and focal cerebral vasospasm (16). To give an example, a super-selective endovascular approach through a non- compliant balloon catheter was effective in treating patients with focal cerebral vasospasm affecting the M1 segment of the middle cerebral artery (16).

The use of retrievable self-expandable stents is a recent endovascular technique still in development for this condition. Bhogal has reported a low morbidity rate and a vasodilation effect duration greater than 24 hours using this technique (17).

1.3 How the intervention might work

1.3.1 Pharmacological interventions

One of the objectives of cerebral vasospasm treatment is to achieve vasodilation of brain blood vessels by relaxing the vascular smooth muscle of artery walls. Smooth muscle contraction requires calcium in the intracellular compartment to form a complex with calmodulin that allows the activation of the myosin light-chain kinase (MLCK) enzyme. Nevertheless, calcium channel blockers (i.e. nimodipine, nicardipine, and verapamil) reduce calcium input into the cell through L-type calcium channels, inhibiting muscle contraction. MLCK also inhibits muscle contraction, as it is inhibited directly by fasudil, which, in turn, is a rho-kinase inhibitor that promotes vasodilatation by this route (18).

Muscle contraction is also inhibited by increased concentration of cyclic adenosine monophosphate (cAMP). Milrinone, papaverine, and colforsin increase intracellular cAMP levels by inhibiting phosphodiesterases selectively (milrinone), non- selectively (papaverine), or by acting as a direct activator of adenylate cyclase (colforsin) (18).

Regarding the safety of vasodilators for treating cerebral vasospasm, a study on the complications associated with intra-arterial administration of nimodipine in patients with this condition described that 3% of these patients had new cerebral infarcts secondary to thromboembolic events (19). Other complications related to continuous IAVI therapy include anticoagulant-associated intracranial haemorrhage, severe hypotension episodes, and infection (20).

1.3.2 Mechanical interventions

The internal diameter of affected vessels may change when using intraluminal devices, such as intraluminal balloons or stents. Balloon catheters can be compliant and non-compliant, depending on the capacity to change their diameter according to the insufflation pressure. When using both types there is a risk of causing arterial dissection or the rupture of the blood vessel: with compliant balloons, this is due to the lack of regulation of the final diameter, which leads to rupture of the vessel by overdistension; and with non-compliant balloons, it is due to their high radial force (21).

Few cases of arterial dissection or embolic occlusion have been reported with the use of TBA (22). Furthermore, a randomised controlled trial assessing the efficacy and safety of prophylactic TBA described a 5% complication rate associated with this procedure, consisting of arterial perforation caused by the guidewire and arterial rupture during balloon inflation (14).

1.4 Why it is important to do this review

The importance of identifying effective treatments for cerebral vasospasm secondary to aneurysmal SAH lies in the consequences derived from the care needs of these patients. In this sense, one key aspect is the burden of this disease, since the economic burden is 30% higher when treating people with cerebral vasospasm compared to the management of patients without this condition (23). Furthermore, cerebral vasospasm is associated with a longer hospital stay (up to 25% longer) and with a higher frequency of readmission within 12 weeks following the initial hospital discharge (24). According to Macdonald, this might explain why only a small proportion of patients with severe cerebral vasospasm (10%) are completely independent after 12 weeks of hospitalisation, in comparison to those without cerebral vasospasm secondary to aneurysmal SAH (49%) (24).

Currently, there is no consensus on endovascular management of cerebral vasospasm in patients with aneurysmal SAH. In fact, studies evaluating the efficacy and safety of medical and endovascular therapies for this condition describe mixed outcomes; some state that these therapies offer some benefits (25,26); while others report no benefits at all (27,28). For example, the reported efficacy of IAVI varies significantly in several studies. A meta-analysis of 44 studies on IAVI for treating cerebral vasospasm found that angiographic improvement was achieved in 33% to 100% of patients, and neurological response improvement was observed in 12% to 100% of patients (29). The quality of evidence provided in these studies also needs to be assessed.

This review aims to synthesize the findings from the studies on this topic, and assess the quality of the evidence they provide. The results will be relevant to decision-makers and the healthcare staff who treat these patients.

2. Methods

The aim of this investigation was to evaluate the efficacy and safety of endovascular treatment compared to standard treatment for cerebral vasospasm in patients with aneurysmal subarachnoid haemorrhage.

2.1 Criteria for considering studies for this review

2.1.1 Types of studies

We included published and unpublished randomised controlled trials and non-randomised controlled trials, irrespective of their language.

2.1.2 Types of participants

Adults (over 18 years of age) with aneurysmal subarachnoid haemorrhage (SAH), who had a previous aneurysm secured through coiling or clipping, and who subsequently developed cerebral vasospasm.

Patients were defined as having SAH if they have symptoms compatible with this condition, along with intracranial bleeding confirmed by means of computed tomography (CT), magnetic resonance imaging (MRI), or the detection of xanthochromia in the cerebrospinal fluid. Likewise, the presence of the aneurysm must have been confirmed through digital subtraction angiography (DSA), computed tomography angiography (CTA) or magnetic resonance angiography (MRA).

Cerebral vasospasm was defined according to the following criteria (30,31):

- Angiographic evidence of cerebral vasospasm, detected by DSA, CTA, or MRA. Cerebral vasospasm was considered to be present within the fourth and 21st day after the occurrence of aneurysmal SAH, when the angiogram shows focal or generalised narrowing of cerebral arteries (as reported by each trialist).
- Neurological deterioration associated with radiological cerebral vasospasm that is not explained by other causes (i.e. not caused by seizures, hydrocephalus, metabolic disorders, re-bleeding, or aneurysm occlusion procedures). Neurological deficit includes aphasia, hemiparesis, apraxia, neglect, and decreased level of consciousness.
- We also considered studies including patients with rapid and severe increased blood flow velocities, obtained through transcranial Doppler (TCD).
- No evidence, based on CT or MRI studies, of new cerebral infarction as a result of the procedure performed to treat the aneurysm.

As the definition of cerebral vasospasm varies among studies, we also accepted the definitions used by each author or group of authors if these are appropriately described.

2.1.3 Types of interventions

We included trials comparing endovascular treatment plus standard care versus standard care alone. Endovascular therapies may have included the following interventions.

- Intra-arterial vasodilator infusion (IAVI). We included any vasodilator drug used, regardless of the dose or administration protocol, if it is properly described (i.e. one single session, repetitive sessions, or continuous infusion through microcatheters).
- Percutaneous transluminal balloon angioplasty (TBA), regardless of the number of sessions.
- Retrievable self-expandable stents.

The indication for treatment of cerebral vasospasm had to be clearly described in each study (i.e. parameters considered for the indication of the intervention and how frequently it was measured). The indication could be based on the severity or progression of the condition (i.e. TCD indices and the degree of the narrowing of the blood vessels observed

in the CTA or the DSA). In patients with a confirmed diagnosis, indication for treatment includes neurological deterioration or changes in multimodality neuromonitoring parameters (e.g. continuous electroencephalography, brain tissue oxygen monitoring, cerebral microdialysis, etc.)

2.1.4 Types of outcome measures

Primary outcome

Long-term unfavourable outcome after three months of follow-up — defined as death, vegetative state, or severe disability — as assessed either with the Glasgow Outcome Scale (GOS), modified Rankin Scale (mRS), or Glasgow Outcome Scale Extended (GOS-E) (see Appendix 1).

Secondary outcomes

- Death from any cause during the follow-up.
- Short-term unfavourable outcome (within six months after the aneurysmal SAH): death, vegetative state, or severe disability, as assessed either with the GOS, mRS, or GOS-E.
- Cerebral infarction: CT or MRI detection of cerebral infarction within six weeks of aneurysmal SAH, not evidenced on early CT/MRI scan (24 to 48 hours after occlusion of aneurysm) and not explained by causes other than cerebral vasospasm (e.g. ventricular catheter, intraparenchymal hematoma, etc.)
- Treatment complications: any serious adverse event associated with the drug or procedure used within 24 hours after performing the intervention to treat cerebral vasospasm.
- Angiographic improvement of cerebral vasospasm.
- Procedure-related costs
- Length of hospital stay
- Quality of life assessed using a validated scale at the end of follow-up.

2.2 Search methods for identification of studies

We searched for trials in all languages and arrange for the translation of relevant articles where necessary.

2.2.1 Electronic searches

We searched the following electronic databases:

- MEDLINE (from 1948) (Appendix 2)
- Embase (from 1980) (Appendix 2)

We developed the MEDLINE search strategy with the help of the Cochrane Stroke Group Information Specialist (Appendix 2) and adapted it for the other database.

2.2.2 Searching other resources

We screened the reference lists of included studies and relevant reviews to identify further studies for potential inclusion in the review. Also, we contacted authors for missing information.

2.3 Data collection and analysis

2.3.1 Selection of studies

Two review authors (LCSD and FNE) independently screened the titles and abstracts of the references obtained as a result of our searching activities and exclude obviously irrelevant reports. We retrieved the full-text articles for the remaining references and two review authors (LCSD and OAE) independently screened the full-text articles and identified studies for inclusion, and identified and recorded reasons for excluding ineligible studies. We resolved any disagreements through discussion or, if required, we consulted a third person (TK). We collated multiple reports of the same study so that each study, not each

reference, is the unit of interest in the review. We recorded the selection process and complete a PRISMA flow diagram (32).

2.3.2 Data extraction and management

Two review authors (LCSD and CFGA) independently extracted data from included studies, and recorded data on standard extraction forms created in Microsoft Excel. We extracted the following data.

• Methods: study design, randomisation method, allocation concealment method, blinding methods.
• Participants: sample size, age, sex, number of patients originally allocated to each treatment group, diagnostic criteria used for aneurysmal SAH and cerebral vasospasm, number of patients in each intervention group.
• Intervention: type of intervention and randomisation, type of anaesthesia, microsurgical clipping technique, endovascular coiling technique, endovascular technique used for the treatment of cerebral vasospasm (i.e. TBA, IAVI).
• Outcomes: number of patients in each group with outcomes, including death, neurological deficits, and unfavourable outcome; withdrawals and adverse effects; length of follow-up.
• Other data: publication year, funding sources, intention- to-treat (ITT) analysis; any additional important information.

If the two review authors had any disagreements on data extraction, the full review team discussed the disagreements and make a final decision. We contacted the original study authors for key information when absent in the full text. For dichotomous data, we extracted the number of participants experiencing the event and the total number of participants in each arm of the trial. For continuous data, we extracted the mean value and standard deviation (SD) for the changes in each arm of the trial, along with the total number in each group.

2.3.3 Assessment of risk of bias in included studies

Two review authors (LCSD y CFGA) independently assessed risk of bias for each study using the ROBINS-I tool for non-randomised controlled studies, and for each randomised

controlled trials using the criteria outlines in the Cochrane Handbook for Systematic Reviews of Interventions (33). We resolved any disagreements by discussion or by involving another author (ALC).

Assessment of risk of bias in randomised controlled trials

Studies that were classified as randomised controlled clinical trials were evaluated using the criteria described in the Cochrane Handbook for Systematic Reviews of Interventions (33). Two authors (LCSD and CFGA) independently assessed the risk of bias for each study, disagreements were resolved by discussion or involving another author (ALC). We assessed the risk of bias according to the following domains:

- Random sequence generation;
- Allocation concealment;
- Blinding of participants and personnel;
- Blinding of outcome assessment;
- Incomplete outcome data;
- Selective outcome reporting;
- Other bias.

We judged the risk of bias for each domain to be high, low or unclear. We provided information from the study report, together with a justification for our judgement, in the 'Risk of bias' tables.

Assessment of risk of bias in non-randomised studies

Studies that were classified as non-randomised controlled studies were evaluated with the ROBINS-I instrument (34). Two authors (LCSD and CFGA) independently assessed the risk of bias for each study, disagreements were resolved by discussion or involving another author (ALC). The risk of bias was assessed taking into account the following domains:

- Bias due to confounding;
- Bias in selection of participants into the study;
- Bias in classification of interventions;
- Bias due to deviations from intended interventions;
- Bias due to missing data;

• Bias in measurement of outcomes;
• Bias in selection of the reported result.

The risk of bias was rated for each domain as low, moderate, serious, critical, or no information. Information from the report, along with the rationale for the rating, was provided in the 'Risk of bias' tables.

2.3.4 Measures of treatment effect

For dichotomous data, odds ratios (OR) with 95% confidence intervals (CI) were estimated. For continuous data, mean difference (MD) was used if results were measured in the same way between studies. Standardized mean difference (SMD) was used to combine studies that measured the same outcome but used different methods. The use of a fixed effects model was considered in the case of meta-analysis.

When available, non-randomised studies reported adjusted effect estimates (for example, adjusted odds ratios from logistic regression analysis), these were preferable to analyzes based on summary statistics, as they generally reduce the impact of confounders. Therefore, the adjusted effect estimates that were reported by the authors of each study and the variables used for their adjustment were recorded.

2.3.5 Unit of analysis issues

We consider each participant as the unit of analysis. If any non-typical design was found (i.e. cluster or crossover randomised trials), we considered applying the Cochrane Handbook recommendations for systematic reviews of interventions (35).

In those studies, reporting multiple measurements of outcomes within a single time period (i.e. long-term unfavourable outcome, short-term unfavourable outcome, and quality of life), we included the longest follow-up inside each period. To assess the effect of this procedure on the estimation of the effect, we considered doing a sensitivity analysis dividing the long-term follow-up in the following intervals: three to six, six to 12 months, 12 to 24 months, and over 24 months (35).

2.3.6 Dealing with missing data

Attempts were made to contact study authors to obtain incomplete or missing information that was not mentioned in the abstract or full text article. We performed an intention-to-treat analysis for each outcome included in the protocol. In the event of incomplete or missing information, we perform a best and worst-case scenario analysis, such as a sensitivity analysis, in accordance with the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (36).

2.3.7 Assessment of heterogeneity

We assessed heterogeneity in study design and population. We considered to use the I2 statistic to measure heterogeneity among the trials in each analysis. An I2 value 60% or greater would be considered to indicate moderate to substantial heterogeneity, and we would try to explain possible sources of heterogeneity by subgroup analysis or meta-regression (36).

2.3.8 Assessment of reporting bias

We considered to use funnel plots to assess the risk of reporting bias only if we find more than 10 studies. We would interpret these graphs according to the guidance in the Cochrane Handbook for Systematic Review of Interventions (36).

2.3.9 Data synthesis

Where we considered studies to be sufficiently similar, we would conduct a meta-analysis by pooling the appropriate data using Review Manager 5 (37). We would use a random-effects model if we identified significant heterogeneity.

2.3.10 Subgroup analysis and investigation of heterogeneity

In the case of data synthesis, we would perform these analyses for all outcomes according to the following subgroups:

- Risk groups for cerebral vasospasm, assessed using the Fisher's scale (38), see Appendix 1.
- Patients with poor-grade aneurysmal SAH (Hunt & Hess grade 4 and 5, World Federation of Neurosurgical Societies (WFNS) grade 4 and 5) compared to non-poor-grade aneurysmal SAH patients (39), see Appendix 1.

2.3.11 Sensitivity analysis

In the case of data synthesis when we find six or more studies included in a single analysis, we would conduct a sensitivity analysis to assess the effect of the risk of bias on the results of the meta-analysis. We would re-analyse data after excluding:

- trials within adequate or unclear allocation concealment;
- trials with unclear or no blinding of outcome assessment;
- trials in which the description of the intervention is uncertain;
- trials with other biases or where the presence of bias is uncertain;
- non-randomised studies with risk of bias defined as serious or critical.

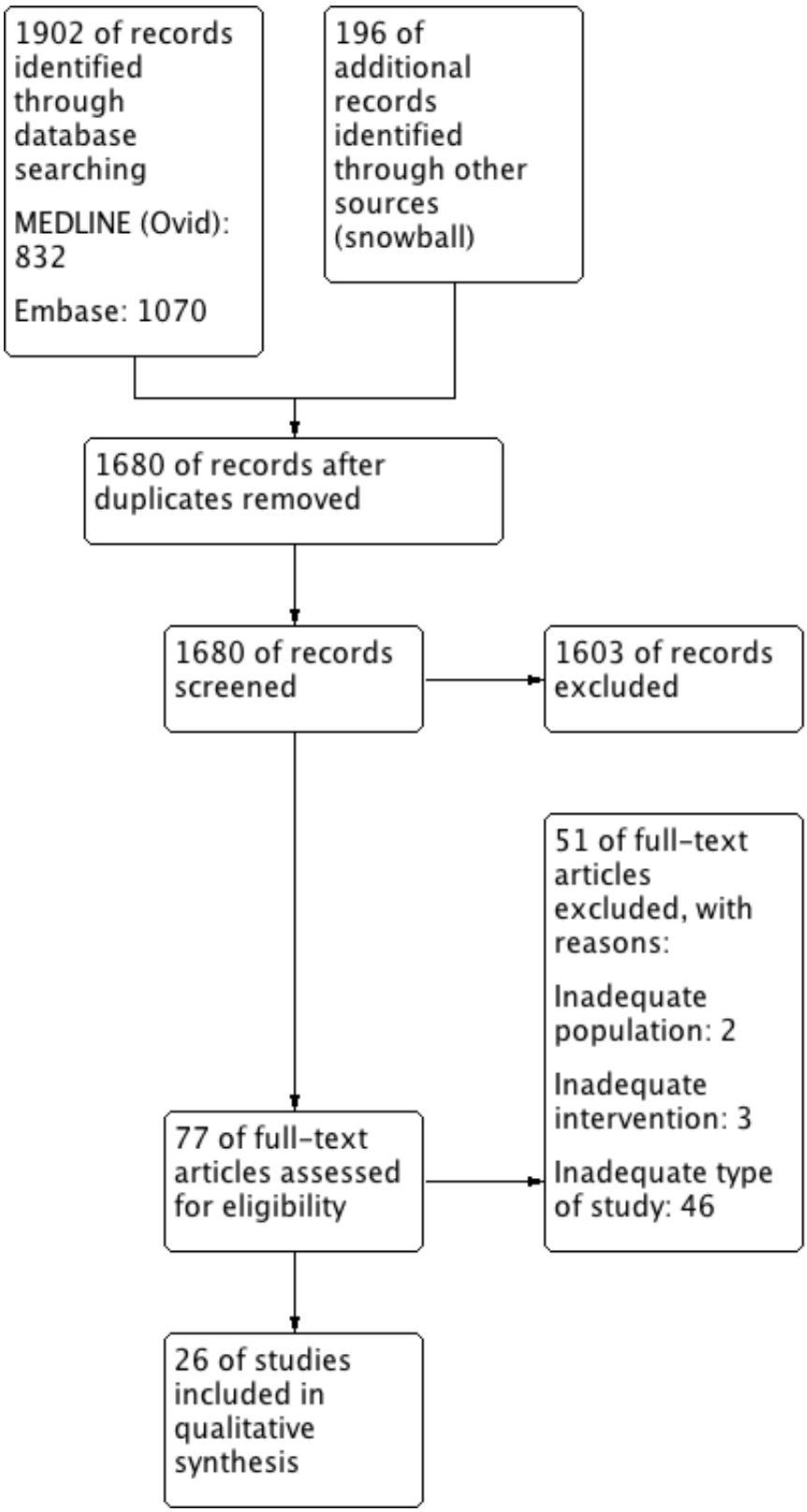
3. Results

3.1 Description of studies

3.1.1 Results of the search

In total, 2098 references were retrieved and 1680 were assessed after eliminating duplicates. Of these, 77 full text articles were initially analyzed and considered probable studies to be included. Finally, 26 published studies met the inclusion criteria (21,40–64).

Figure 3-1: Flow diagram (PRISMA).



Source: Own elaboration.

3.1.2 Included studies

The 26 included studies involved a total of 1854 participants. Sample size ranged between 12 and 231 participants. These studies were conducted in Germany (45,46,58), Australia (49), Austria (43), Canada (53,54,59,62), South Korea (48), the United States (21,41,47,52–54,56,59,61,63,64), France (60), India (42), Japan (44,50,55,57), Mexico (40) and Switzerland (51). Three studies were multicenter trials (53,54,59), one study used a randomised method to assign the intervention and was conducted prospectively (55), and the remaining studies were retrospective. All included studies were written in English.

Population

The included studies recruited men and women over the age of 18. The most common diagnostic method used to confirm the presence of aneurysmal subarachnoid haemorrhage (SAH) was computed tomography in six studies (40,41,49,56,61,63), followed by lumbar puncture in three (41,56,63), and magnetic resonance imaging in two (56,61), 20 studies did not report the SAH diagnostic strategy utilized (21,42–48,50–55,57–60,62,64)[1].

Clinical severity was established using the Hunt-Hess scale (65) and the World Federation of Neurosurgical Societies grading system (66). Thus, poor clinical condition was considered when scores defined grade III to V on the Hunt-Hess scale, or 4 and 5 on the World Federation of Societies of Neurosurgery scale (67,68) (Appendix 1). The frequency of poor clinical condition was between 17% and 87%.

The Fisher scale was used to evaluate the risk of vasospasm, with a classification frequency as follows: grade I, 2-8%; grade II, 10-42%; grade III, 19-66%; and grade IV, 19-93%.

[1] Some studies used multiple diagnostic tests for SAH (41,56,61,63).

Interventions

Intra-arterial vasodilators*:*

The vasodilators evaluated were colforsin (57), fasudil (50), milrinone (60,62), nicardipine (47,48,61), nimodipine (40,42,45,46,51,58), papaverine (41,43–45,49,52–55,57,59,63,64), magnesium sulphate (47), and verapamil (41,47,49,56).

The dose of colforsin used was 3mg diluted in 100 mL of saline solution (57). Intra-arterial fasudil at an infusion rate of 3 mg/min was utilized selectively and non-selectively (50). When milrinone was used, the intra-arterial dose was between 8 and 24mg (60). Nicardipine was used at a dose between 1 and 15mg as monotherapy (61) and between 2 and 3mg in combination with angioplasty and stent placement (48) .

Similarly, the doses of nimodipine used were between 0.2mg and 6mg (40,42,45,46,51,58). Finally, the concentration of papaverine was between 0.1 and 2% (55); the most frequent total dose used was 300mg (45,63,64) but, in this case, it was between 40 and 600mg (43–45,63,64).

Balloon angioplasty:

The most frequently used type of balloon was compliant (21,40,47,49,52). Only one study compared the use of compliant balloon with non-compliant balloon (21), while the remaining studies did not report the type of balloon used (41,43,44,46,51,53,56,59,62,63).

Stent:

Additionally, one study reported the use of retrievable stents in combination with intra-arterial vasodilator infusion (48).

Comparisons

Endovascular versus medical treatment:

Eleven studies used medical treatment as a control group and eight of them compared it with intra-arterial vasodilator infusion (42,44,50,54,58,60–62), one with balloon angioplasty (44)[2], and three with intra-arterial vasodilator infusion plus balloon angioplasty (47,49,53).

[2] The study by Katoh et al. (44) included two comparisons.

Intra-arterial vasodilator infusion versus balloon angioplasty:
Seven studies compared intra-arterial vasodilator infusion with balloon angioplasty (40,44,52,56,59,63,64).

Intra-arterial vasodilator infusion versus another intra-arterial vasodilator:
Two studies compared vasodilators. One of them compared papaverine vs. nimodipine (45) and the other compared papaverine vs. colforsin (57).

Intra-arterial vasodilator infusion versus combination therapy (IAVI + TBA):
Three studies compared intra-arterial vasodilator infusion with intra-arterial vasodilator infusion plus percutaneous transluminal balloon angioplasty (41,43,46).

Balloon angioplasty versus combination therapy (IAVI + TBA):
One study compared balloon angioplasty with combined endovascular therapy (IAVI + TBA) (56).

Compliant balloon angioplasty versus non-compliant balloon angioplasty:
One study compared the use compliant balloon angioplasty with non-compliant (21).

Comparison between sequences of vasodilator infusion while stent retriever therapy:
One study evaluated nicardipine infusion associated with the use of a recoverable stent, comparing the sequence of application of the vasodilator (before using the stent vs. after using the stent) (48).

Comparison between different doses of the same intra-arterial vasodilator:
One study (55) randomly compared three different intra-arterial papaverine concentrations, one group received 0.2% papaverine, the second group 0.4% papaverine, and the third group received 0.8-2%.

Comparison between different number of endovascular therapy sessions:
Finally, one study compared the number of sessions carried out using intra-arterial vasodilator infusion plus balloon angioplasty (51). One group received 1 to 2 sessions vs. the other group that received 3 to 6 sessions of combination therapy, as described above.

Outcomes

The included studies reported at least one primary outcome pre-specified in this review. However, there were some differences in the reporting and definition of results between studies.

Unfavourable outcome was assessed using the modified Rankin Scale (mRS) and the Glasgow Outcome Score (GOS). Thirteen studies reported unfavourable outcomes at hospital discharge (21,41,42,44,45,50,52,56–58,61), and nine studies reported the outcome after three months or more of follow-up (40,42,49,51,53,54,58,60,63).

Mortality during follow-up was reported in 14 studies (40,44,45,47–51,53,54,58,60,61,63). The appearance of ischaemic lesions during follow-up tomography or magnetic resonance was described in 11 studies (21,40,43,45,50,51,53,54,57,58,61).

The included studies also reported improvement of neurological symptoms after treatment, improvement after treatment with angiography, hospital stay, and adverse events. No data on costs associated with the treatments, nor on quality of life during follow-up, were obtained.

Length of follow-up

Participants were monitored for 3 months (42,43,53,54) or 12 months (47,51,60).

3.1.1 Risk of bias in the included randomised trials

The assessment of risk of bias in the randomised trials analyzed is summarized in Table 3-1, including the only article that used a randomised method for intervention allocation (55). The methods were barely described, so the evaluation of multiple domains was not possible.

Table 3-1: Assessment of the risk of bias in the study by Sawada *et al.* (55)

Item	Assessment	Support for assessment
Random sequence generation (selection bias)	Unclear risk	The researchers did not describe the strategy used for generating the sequence: "*The assignment of patients into these three groups was performed at random*."
Allocation concealment (selection bias)	Unclear risk	There was not enough information to judge this item.
Blinding of participants and personnel (performance bias)	Low risk of bias	The impact of participant and staff blinding was considered to be of little relevance to the outcomes assessed in the study.
Blinding of outcome assessment (detection bias)	Unclear risk	It did not specify whether evaluators were blinded.
Incomplete outcome data (attrition bias)	Unclear risk	No losses were reported during follow-up.
Selective reporting (reporting bias)	Unclear risk	There was no access to the protocol for assessment.
Other sources of bias	Low risk	No additional issues

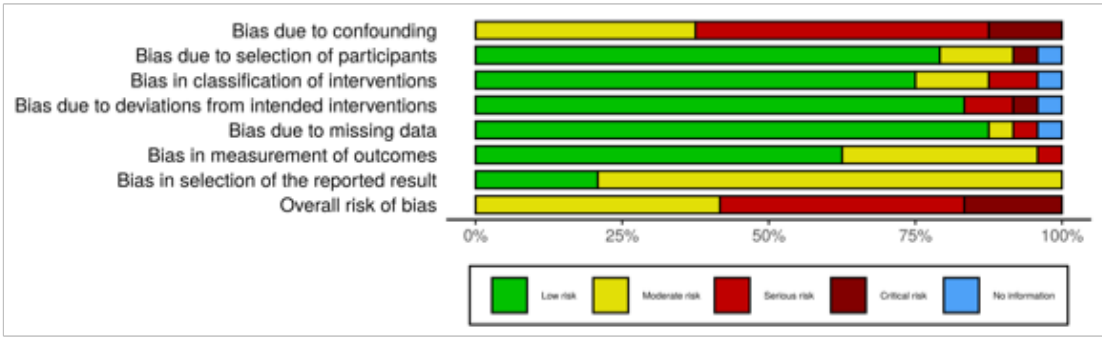
3.1.2 Risk of bias in the included non-randomised trials

The assessment of the risk of bias of non-randomised trials is summarized in Figures 3-2 and 3-3. Furthermore, additional details of the studies included are provided in the Characteristics of Included Studies tables (Appendix 3).

Figure 3-2: Risk of bias assessment in non-randomised studies using the ROBINS-I tool.

Source: Own elaboration.

Figure 3-3: Summary of risk of bias assessments in non-randomised trials using the ROBINS-I tool.



Source: Own elaboration.

Bias due to confounding

All included studies had some degree of risk of confounding; therefore, no study was rated as low risk of bias. Nine studies (44,46,47,53,54,56–59) were rated as moderate risk of bias, three studies used historical cohorts as control group (47,57,58), five studies used multivariate analysis to assess the effect of covariates on outcomes (47,54,56,57,59), and three studies nested the population recruited in a controlled clinical experiment and performed a paired-control analysis (53,54,59). Finally, two studies clearly defined the selection criteria for the comparison groups with an adequate balance of covariates at baseline (44,46).

Twelve studies were rated as having serious risk of bias, of which seven did not clearly present the criteria to allocate participants to the intervention groups (21,40,43,48,50,61,62). On the other hand, five studies used different criteria between the two comparison groups (42,45,52,60,61), and eight did not use multivariate analysis methods to control for confounding factors (40,45,48,52,60–63).

The remaining three studies were at critical risk of bias (41,49,51), and used inclusion criteria related to the outcome; patients were allocated to the intervention groups according to the severity of the disease. Furthermore, the statistical methods used were insufficient to control the risk of bias.

Bias due to selection of participants into the study

One study (41) changed the intervention to which the patients were allocated based on the angiographic response after its performance, which generated a critical risk of bias. In addition, three studies (51,58,61) modified the intervention groups according to the response obtained during treatment, which led to a moderate risk of bias. One study (62) no proporcionó suficiente información para establecer el riesgo de sesgo. did not provide sufficient information to establish risk of bias. The remaining 19 studies had no problems in the selection criteria of subjects; therefore, the risk of selection bias was low for this domain (21,40,42–50,52–54,56,57,59,60,63).

Bias in classification of interventions

Two studies (41,42) were rated at risk of serious bias. Frontera et al. allocated the participants to the intervention groups during the process, making unclear how the control groups were defined. Goel et al. did not provide a clear definition of the control group.

Three studies (40,50,61) included findings in angiography as an intervention allocation criterion and were, therefore, considered at risk of moderate bias. One study (62) did not provide sufficient information to assess risk of bias. The remaining studies, on the other hand, provided an adequate definition of the interventions and were considered at low risk of bias for this domain (21,43–49,51–54,56–60,63,64).

Bias due to deviations from intended interventions

Two studies (41,43) made changes in intervention allocation during follow-up according to responses or development of new symptoms. This circumstance was classified as a risk of serious bias.

Elliot et al. changed the intervention groups systematically and asymmetrically. The criteria for receiving a second therapy were different between the groups; this was assessed as a risk of critical bias (63). One study did not provide sufficient information to establish risk of bias (62). The remaining studies showed a low risk of bias for this domain (21,40,42,44–54,56–61).

Bias due to missing data

Three studies were rated as no low risk of bias. In one of them was rated at moderate risk of bias (43), the authors reported a significant number of losses; however, it did not have a significant effect on the balance of the groups. The second study was rated at serious risk of bias (60), excluded all cases with missing data and did not analyze the excluded population. The third study (62) did not provide sufficient information to establish risk of bias. The remaining studies showed a low risk of bias for this domain (21,40–42,44–54,56–59,61,63,64).

Bias in measurement of outcomes

In Kerz et al., outcomes were assessed by the same person who administered the intervention; therefore, it was rated as a risk of serious bias (45). In eight studies (42,46–48,50,56,57,63), although the evaluator was a third party, it probably knew the type of intervention administered to the patient, so risk of bias was considered moderate. The remaining studies showed a low risk of bias for this domain (21,40,41,43,44,49,51–54,58–62,64).

Bias in selection of the reported result

19 studies had a potential source of bias related to the selective reporting of outcomes, as the protocol of the studies could not be verified (21,41–52,56–58,60,62,63). The remaining studies showed a low risk of bias for this domain (40,53,54,59,61,64).

Overall Risk of Bias judgement

A total of 24 studies were assessed using the ROBINS-I instrument. We did not evaluate one study (64) because it did not report any one of the outcomes of interest in this review. Ten studies (42%) showed a moderate risk of bias (44,46–48,53,54,56–59), ten studies (42%) were rated as a risk of serious bias (21,40,42,43,45,50,52,60–62), and four studies (16%) were rated as a risk of critical bias (41,49,51,63).

The confounding bias domain had the largest number of qualified studies at risk of serious-critical bias. The selective outcome reporting domain showed a high frequency of studies rated as moderate risk of bias. The domains with the most studies at low risk of bias were bias due to selection of participants, bias in classification of interventions, bias due to deviations from intended interventions, and bias due to missing data.

3.2 Effect of Interventions

3.2.1 Intra-arterial vasodilators versus medical therapy

Eight studies involving 479 patients compared intra-arterial vasodilator infusions with standard medical therapy (42,44,50,54,58,60–62). Those studies contributed data for some outcomes.

Long-term unfavourable outcome

The information obtained corresponded to the results of four studies (42,54,58,60). Intra-arterial vasodilator infusion was associated with an unfavourable outcome at three to twelve months in between 24% and 55% of the cases, compared with medical therapy, which is estimated at between 23% and 90%. Only the Bele et al. study showed statistically significant differences in this outcome (OR 0.1, CI 95% 0.02-0.52), the results of the multivariate logistic regression did not show any statistically significant association. The other three studies showed no significant differences, neither they reported any significant association on multivariate analysis for this outcome.

Short-term unfavourable outcome

The information obtained corresponded to the results of four studies (42,44,50,58). Intra-arterial vasodilator infusion showed unfavourable outcomes between 50% to 100% of the cases during patient discharge, compared with figures between 48% and 90% in medical therapy. No study showed a statistically significant difference in this outcome. No study reported multivariate analysis for this outcome.

Mortality

The information obtained corresponded to the results of five studies (44,50,58,60,61). Intra-arterial vasodilator infusion had 0% to 44% mortality rates during follow-up, compared with medical therapy, which showed mortality between 3% and 35%. No study showed a statistically significant difference in this outcome. No study reported multivariate analysis for this outcome.

Cerebral infarction

The information obtained corresponded to the results of four (50,54,58,61). Intra-arterial vasodilator infusion was involved in between 9% to 85% of delayed cerebral infarctions as per computerized tomography during follow-up, compared with medical therapy, which was between 0% and 80%. Two studies showed statistically significant differences, Bele et al. showed an OR 0.25 (95% CI 0.07-0.95) and Besheli et al. showed an OR 22.8 (95% CI 1.05-4.93); the remaining studies did not show statistically significant differences. No study reported multivariate analysis for this outcome.

Neurological deficit improvement

La información obtenida correspondió a los resultados de un estudio (42). Intra-arterial vasodilator infusion was associated with improvement after the treatment of neurological deficit in 72%, as compared with medical therapy that showed 43% (a difference without statistical significance). This study did not report any multivariate analysis for this outcome.

Angiographic improvement of cerebral vasospasm

The information obtained corresponded to the results of one study (62). Intra-arterial vasodilator infusion showed angiographic improvement in 90% of cases compared with 11% ($p<0.0001$) of angiographic improvement in the medical treatment group, with an estimated OR 75 (CI 95% 25-216). This study did not report any multivariate analysis for this outcome.

Length of hospital stay

The information obtained corresponded to the results of one study (61). Intra-arterial vasodilator infusion showed an 18-day stay in ICU compared with the medical treatment group with a 12.2-day stay period ($p<0.001$). This study did not report any multivariate analysis for this outcome.

Adverse events

La información obtenida correspondió a los resultados de tres estudios (50,58,60). Intra-arterial vasodilator infusion showed 10% to 50% adverse events compared with medical treatment, which showed between 0% and 46% adverse events. No study showed a statistically significant difference for this outcome. No study reported multivariate analysis for this outcome.

3.2.2 Balloon angioplasty versus medical therapy

One study with 52 patients compared balloon angioplasty versus standard medical therapy (44). Data were not obtained for any of the outcomes.

Short-term unfavourable outcome

Balloon angioplasty showed unfavourable outcome at hospital discharge in 50% of the cases compared with 48% of medical therapy. The difference was not statistically significant (44). This study did not report any multivariate analysis for this outcome.

Mortality

Balloon angioplasty showed 0% mortality compared with 12% mortality of medical therapy. The difference was not statistically significant (44). This study did not report any multivariate analysis for this outcome.

3.2.3 Intra-arterial vasodilator plus balloon angioplasty versus medical therapy

Three studies involving 347 patients compared intra-arterial vasodilator infusion plus balloon angioplasty with standard medical therapy (47,49,53). Those studies contributed data for some outcomes.

Long-term unfavourable outcome

The information obtained corresponded to the results of two studies (49,53). Intra-arterial vasodilator infusion plus balloon angioplasty showed unfavourable outcomes at three months in between 6% and 47% of the cases, compared with 17% and 40% in medical therapy. No study showed a statistically significant difference in this outcome. These studies did not report any multivariate analysis for this outcome.

Short-term unfavourable outcome

The information obtained corresponded to the results of two studies (47,49). Intra-arterial vasodilator infusion plus balloon angioplasty showed between 33% and 53% unfavourable outcomes during patient discharge compared with 45% of medical therapy. No study showed a statistically significant difference in this outcome. Khatri et al. reported the result

of the multivariate analysis adjusted for age, severity and type of aneurysm treatment, without statistically significant association.

Mortality

The information obtained corresponded to the results of two studies (47,49). Intra-arterial vasodilator infusion plus balloon angioplasty showed mortality rates between 0% to 23% during follow-up, compared with medical therapy, which showed between 3% and 32%. No study showed a statistically significant difference in this outcome. Khatri et al. reported the result of the multivariate analysis adjusted for age, severity and type of aneurysm treatment, without statistically significant association.

Length of hospital stay

The information obtained corresponded to the results of two studies (47,49). The length of hospital stay in cases treated with intra-arterial vasodilator infusion plus balloon angioplasty was between 15 and 27 days, compared with a length of hospital stay between 17 and 22 days in the control group. Differences were not statistically significant. These studies did not report any multivariate analysis for this outcome.

Mortimer et al. (49) reported a stay in the intensive care unit in the vasodilator infusion group of 20 days and 12 days in the control group, a MD of 7.9 days was estimated (95% CI 6.49-9.31, $p<0.0001$). These studies did not report multivariate analysis for this outcome.

Adverse events

The frequency of adverse events was reported in one study (49). Intra-arterial vasodilator infusion plus balloon angioplasty showed a 6% frequency of adverse events, compared with no adverse events of medical treatment ($p=0.21$). No statistical significance was shown. This study did not report any multivariate analysis for this outcome.

3.2.4 Intra-arterial vasodilator versus balloon angioplasty

Seven studies involving 280 patients compared intra-arterial vasodilator infusion with balloon angioplasty (40,44,52,56,59,63,64). Those studies contributed data for some outcomes.

Long-term unfavourable outcome

One study reported long-term unfavourable outcomes (40). Intra-arterial vasodilator infusion was associated with 23% of unfavourable outcomes at 12 months, compared with 38% of balloon angioplasty. Intra-arterial vasodilator infusion was associated with 45% of unfavourable outcomes at 3 months, compared with 50% of balloon angioplasty. The difference was not statistically significant. This study did not report any multivariate analysis for this outcome.

Short-term unfavourable outcome

The information obtained corresponded to the results of four studies (44,52,56,63). Intra-arterial vasodilator infusion showed between 38% and 85% unfavourable outcomes during patient discharge compared with 33% to 73% of balloon angioplasty. No study showed a statistically significant difference in this outcome.

Sokolowski et al. (56) reported the result of the multivariate analysis for an unfavourable outcome at discharge, the regression model included age, history of cigarette smoking, arterial hypertension, severity on admission and presence of symptoms, they reported a non-significant difference between the two groups; the remaining studies did not show statistically significant differences in this outcome, nor did they report the results of multivariate analysis.

Mortality

The information obtained corresponded to the results of three studies (40,44,63). Intra-arterial vasodilator infusion showed 0% to 25% mortality, compared with balloon angioplasty, which showed between 0% and 38% mortality. No study showed statistically significant differences. These studies did not report any multivariate analysis for this outcome.

Cerebral infarction

One study reported delayed infarction on control tomography (40). Intra-arterial vasodilator infusion was observed in 95% of cerebral infarction cases during CT, compared with 100% of balloon angioplasty. The difference was not statistically significant. This study did not report any multivariate analysis for this outcome.

Neurological deficit improvement

These data comes from the results of three studies (44,52,59). Intra-arterial vasodilator infusion showed 25% to 50% neurological deficit improvement, compared with balloon angioplasty, which showed improvements between 29% and 58%. No study showed a statistically significant difference for this outcome. These studies did not report any multivariate analysis for this outcome. Coenen et al. reported the result of the multivariate analysis that did not show significant differences between the two groups, the rest of the studies did not report multivariate analysis for this outcome.

Improvement of angiographic vasospasm

Two studies reported improvement of angiographic vasospasm between 93% and 100% of patients receiving intra-arterial vasodilator infusion and 100% of patients receiving balloon angioplasty (56,63). There was no statistical significance. These studies did not report any multivariate analysis for this outcome.

Adverse events

Two studies reported the frequency of serious adverse events (44,63). Intra-arterial vasodilator infusion had no serious complications compared with balloon angioplasty with one adverse event (2.5%). There was no statistical significance. This study did not report any multivariate analysis for this outcome.

3.2.5 Intra-arterial vasodilator versus intra-arterial vasodilator plus balloon angioplasty

Five studies involving 388 patients compared intra-arterial vasodilator infusion (IAVI) versus combined endovascular therapy with IAVI plus balloon angioplasty (TBA) (41,43,46,52,56). Those studies contributed data for some outcomes.

Short-term unfavourable outcome

Three studies assessed unfavourable outcomes at the time of patient discharge (41,52,56). The proportion of 38% to 80% adverse outcomes was found in the group that received combined endovascular therapy (IAIV + TBA) versus the group that received intra-arterial

vasodilator infusion that was 40% to 85% (52,56). Frontera y col. (41) reported a binary logistic regression model with an OR 0.6 (95%CI 0.2–1.7, p=0.351).

Cerebral infarction

One study reported the frequency of delayed cerebral infarction during control tomography (43). Intra-arterial vasodilator infusion had a frequency of 25.5% in delayed cerebral infarctions observed through computerized tomography during follow-up, compared with 36% in patients that received combined endovascular therapy (IAVI + TBA); this is not a statistically significant difference. This study reported multivariate analysis for this outcome, without evidence of a statistically significant association (the variables included were the clinical severity of SAH, days of treatment, severity of vasospasm, and number of interventions).

Neurological deficit improvement

One study reported the frequency of neurological recovery after treatment (52). Intra-arterial vasodilator infusion showed a neurological recovery frequency of 45%, compared with combined endovascular therapy (IAVI + TBA), which was 62% (difference without statistical significance). This study did not report multivariate analysis for this outcome.

Improvement of angiographic vasospasm

The information obtained corresponded to the results of three studies (41,43,56). Intra-arterial vasodilator infusion showed angiographic improvements in 30% to 93% of patients, compared with 50% to 100% of angiographic improvements in the combined endovascular therapy group (IAVI + TBA). Differences were not statistically significant. These studies did not report any multivariate analysis for this outcome.

Adverse events

The information obtained corresponded to the results of one study (46). Intra-arterial vasodilator infusion showed a frequency of 0% of adverse events compared with adverse events of 19% in patients that received combined endovascular therapy (IAVI + TBA). No study showed a statistically significant difference for this outcome. These studies did not report any multivariate analysis for this outcome.

3.2.6 Balloon angioplasty versus intra-arterial vasodilator plus balloon angioplasty

Dos estudios que incluyeron 75 pacientes comparó la angioplastia con balón versus la terapia endovascular combinada (IAVI + TBA) (52,56). Data were not obtained for any of the outcomes.

Short-term unfavourable outcome

Balloon angioplasty was associated with unfavourable outcomes at discharge between 42% to 73% of patients, compared with 39% to 80% of combined endovascular therapy (IAVI + TBA). The difference was not statistically significant (52,56). Only Sokolowski et al. reported a multivariate analysis, it did not show any significant association (56).

Neurological deficit improvement

Balloon angioplasty showed neurological recovery in 50% of the patients, compared with combined endovascular therapy (IAVI + TBA), which was 62%. There was no statistical significance (52). This study did not report multivariate analysis for this outcome.

Improvement of angiographic vasospasm

Balloon angioplasty showed improvement of angiographic vasospasm in 100% of patients, compared with 100% of combined endovascular therapy (IAVI + TBA). There was no statistically significant differences (56). This study did not report any multivariate analysis for this outcome.

Adverse events

Neither balloon angioplasty nor combined endovascular therapy (IAVI + TBA) showed serious adverse events (56). No adverse events were identified.

3.2.7 Intra-arterial vasodilator versus intra-arterial vasodilator

Three studies involving 117 patients compared two or more regimes of intra-arterial vasodilator infusion (45,55,57). One study compared three different concentrations of papaverine (55), one study compared nimodipine versus papaverine (45)), and one study

compared papaverine versus colforsin (57). Those studies contributed data for some outcomes.

Short-term unfavourable outcome

The information obtained corresponded to the results of two studies (45,57). In Kerz et al., intra-arterial infusion of papaverine showed an unfavourable outcome at discharge in 47% of patients, compared with 33% ($p>0.05$) of intra-arterial infusion of nimodipine, without any statistical significance (45). However, Suzuki et al. reported unfavourable outcomes at the discharge in 34% of patients receiving intra-arterial infusion of colforsin, compared with 66% of papaverine infusion ($p=0.032$). The difference was not statistically significant (57). Also, Suzuki et al. reported the results of the multivariate analysis (included age, sex, clinical severity, surgery) that reported OR 5.61 (95% CI 1.54-20.43).

Mortality

The information obtained corresponded to the results of two studies (45,57). In Kerz et al., the intra-arterial infusion of papaverine showed 0% mortality, compared with 33% ($p< 0.05$) of intra-arterial infusion of nimodipine, showing significant statistical differences (45). In Suzuki et al., the intra-arterial infusion of colforsin showed an unfavourable outcome at discharge in 0% of patients, compared with 15% ($p>0.05$) of intra-arterial infusion of papaverine, without any statistical significance (57). These studies did not report any multivariate analysis for this outcome.

Cerebral infarction

Two studies assessed the presence of delayed cerebral infarction during control brain imaging (45,57). The intra-arterial colforsin infusion group showed a cerebral infarction rate of 62%, compared with 85% of the papaverine infusion group ($p=0.039$) (57). The difference was not statistically significant. This study did not report any multivariate analysis for this outcome.

The group of intra-arterial infusion of nimodipine showed a frequency of cerebral infarction of 67%, compared to the infusion of papaverine that was 53% ($p = 0.71$), the difference was not statistically significant (45); this study did not report multivariate analysis for this outcome.

Neurological deficit improvement

The information obtained corresponded to the results of one study (55). Intra-arterial infusion of papaverine was administered continuously at 3 different concentrations: 0.1-0.2%, 0.4% and 0.8-2%. The first group showed an improvement of 21% in neurological symptoms; the second, 44%, and the third, 6%. A statistically significant difference was found with the second group, which had greater improvement in neurological symptoms, compared with the third group. This study did not report any multivariate analysis for this outcome.

Angiographic improvement of cerebral vasospasm

The information obtained corresponded to the results of two studies (45,55). In Kerz et al., intra-arterial infusion of papaverine showed 60% of angiographic improvement compared with 33% of intra-arterial infusion of nimodipine ($p< 0.01$). Outcomes showed statistically significant differences (45).

In Sawada et al., intra-arterial papaverine infusion was administered continuously at 3 different concentrations: 0.1-0.2%, 0.4% and 0.8-2%. The first group showed 47% of angiographic improvement; the second, 80%, and the third, 20%. Infusion at 0.4% concentration showed to be statistically higher than the other two groups. These studies did not report any multivariate analysis for this outcome (55).

Length of hospital stay

The information obtained corresponded to the results of one study (45). Intra-arterial infusion of papaverine showed an average length of hospital stay of 28.3 $\pm$ to 13.2 days compared with 26.2$\pm$11 days in the nimodipine infusion group. There were no statistically significant differences. This study did not report any multivariate analysis for this outcome.

Adverse events

The information obtained corresponded to the results of two studies (55,57). Intra-arterial infusions of papaverine and colforsin did not show any serious adverse event (57).

In Sawada et al., intra-arterial papaverine was administered continuously at 3 different concentrations: 0.1-0.2%, 0.4% and 0.8-2%. 7% of the patients in the first group, 6% in the

second, and 44% in the third group developed adverse events. The 0.82% concentration infusion group showed that the number of adverse events with statistical significance was higher than in the other two groups. These studies did not report any multivariate analysis for this outcome (55).

3.2.8 Compliant balloon angioplasty versus non-compliant balloon angioplasty versus non-compliant balloon angioplasty

One study involving 30 patients compared compliant balloon angioplasty versus non-compliant balloon angioplasty (21). No data was obtained for all outcomes.

Short-term unfavourable outcome

Compliant balloon angioplasty showed a short-term unfavourable outcome rate of 60%, compared with non-compliant balloon angioplasty, which was 25% (p = 0.1); without statistical significance. This study did not report multivariate analysis for this outcome.

Mortality

Compliant balloon angioplasty showed a mortality of 20%, compared with non-compliant balloon angioplasty, which was 20% (p = 1); without statistical significance. This study did not report multivariate analysis for this outcome.

Cerebral infarction

Compliant balloon angioplasty was associated with 21% of delayed cerebral infarctions during follow-up compared with 10% of non-compliant balloon angioplasty (p=0.21). There were no statistically significant differences. This study reported the result of the multivariate analysis for this outcome: OR 1.7 95% CI (0.51-5.8, p = 0.39).

Adverse events

There were no serious adverse events from compliant balloon angioplasty or non-compliant balloon angioplasty in the study.

3.2.9 Number of intra-arterial vasodilators plus balloon angioplasty sessions

One study involving 83 patients compared 1-2 sessions versus 3-6 sessions of intra-arterial vasodilator treatment for vasospasm (51). No data was obtained for all outcomes.

Long-term unfavourable outcome

Treatments administered in 1-2 sessions showed unfavourable outcomes at last follow-up (mean 11 ± 6.3 months) in 40% of cases, compared with 42% of 3-6 sessions ($p>0.05$) (51). There were not statistically significant differences. This study did not report any multivariate analysis for this outcome.

Short-term unfavourable outcome

Treatments administered in 1-2 sessions showed unfavourable outcomes in 69% of patients when discharged, compared with 84% of 3-6 sessions ($p>0.05$) (51). There were not statistically significant differences. This study did not report any multivariate analysis for this outcome.

Mortality

The rate of cerebral infarction in treatments administered in 1-2 sessions 1 was 35% infarction during control tomography, compared with 55% of 3-6 sessions ($p>0.05$) (51). There were not statistically significant differences. This study did not report any multivariate analysis for this outcome.

Cerebral infarction

The rate of cerebral infarction in treatments administered in 1-2 sessions 1 was 35% infarction during control tomography, compared with 55% of 3-6 sessions ($p>0.05$) (51). There were not statistically significant differences. This study did not report any multivariate analysis for this outcome.

Adverse events

The frequency of adverse events was 2% in the 1-2-session treatment group, compared with the 16% (p>0.05) of 3-6-session group (51). There were not statistically significant differences. This study did not report any multivariate analysis for this outcome.

3.2.10 Stent retriever plus intra-arterial vasodilator

One study in 12 patients compared treatment using a stent retriever. One of the groups received 3-5 mg of nicardipine intra-arterially followed by angioplasty with retrievable stent, while the other group received angioplasty with retrievable stent prior to the administration of nicardipine (48). Information on all the outcomes was not available.

Short-term unfavourable outcome

Administration of nicardipine before stent placement showed an unfavourable outcome of 40% compared to stent placement before administering nicardipine, which was 29%. The difference was not statistically significant (48). This study did not report multivariate analysis for this outcome.

Mortality

No mortality events occurred or were reported in the study (48).

Neurologic deficit improvement

Nicardipine before placing a retrievable stent showed neurological improvement in 60% of the cases, compared to the use of the retrievable stent prior to the administration of nicardipine which was 85.7%. The difference was not statistically significant (48). This study did not report any multivariate analysis for this outcome.

Improvement of angiographic vasospasm

Nicardipine before placing the retrievable stent showed angiographic improvement in 71% of the sample, compared to the use of the retrievable stent prior to nicardipine administration which was 82%. The difference was not statistically significant (48). This study did not report any multivariate analysis for this outcome.

Adverse events

Nicardipine before placing the retrievable stent was associated with adverse events in 20% of patients (events), compared to the use of the retrievable stent prior to nicardipine administration in 29% of them. The difference was not statistically significant (48). This study did not report any multivariate analysis for this outcome.

4. Discussion

4.1 Summary of main results

Twenty-six studies (1783 participants) met the inclusion criteria. Of these, 25 were non-randomised controlled studies and one was a randomised controlled clinical trial. Furthermore, 11 studies compared some type of endovascular treatment with conventional medical therapy and the other 15 compared different endovascular treatments with each other.

Eleven studies (871 participants) addressed the use of endovascular treatment and medical therapy. Seven of these studies compared endovascular treatment to intra-arterial vasodilator infusion (IAVI), three compared it to combination therapy (IAVI + TBA), and one study compared three groups (medical therapy vs. IAVI vs. TBA).

When comparing the use of intra-arterial vasodilator infusion (IAVI) to medical therapy, statistically significant evidence was found in favor of IAVI over medical therapy. The frequency of unfavourable outcomes at 3 months was lower in patients who received IAVI (52% vs. 90%, p=0.01), and angiographic improvement was higher in patients who received IAVI (90% vs. 10%, p<0.001). However, intensive care unit stay was longer in the IAVI group (18 days vs. 12.2 days, p<0.001). No statistically significant differences were found regarding the other outcomes reported in the studies that compared endovascular therapy (IAVI, TBA, or IAVI + TBA) to medical therapy. The risk of bias in these studies was moderate-serious.

Seven studies (280 patients) compared intra-arterial infusion of vasodilators (IAVI) to balloon angioplasty (TBA). Outcomes included mortality, delayed cerebral infarction on brain imaging, neurologic/angiographic improvement, unfavourable outcome at discharge,

unfavourable outcome in the long-term, and adverse events. None of the studies demonstrated statistically significant differences for or against the interventions evaluated. The risk of bias was moderate-critical.

On the other hand, five studies (388 patients) compared combined therapy (IVIA + TBA) to the administration of these interventions separately, no statistically significant differences. The risk of bias was moderate-serious-critical.

Three studies (117 patients) compared different intra-arterial vasodilators with each other; one of them was randomised. In the first study, papaverine had lower mortality compared with nimodipine (0% vs. 33%, $p<0.05$), as well as higher angiographic response (60% vs. 33%, $p<0.01$). The second compared colforsin with papaverine, demonstrating lower frequency of delayed cerebral infarction when colforsin was used (62% vs. 85%, $p=0.039$) and lower frequency of unfavourable outcome in the colforsin group (34% vs. 66%, $p=0.032$).

The third study randomly compared three different concentrations of papaverine: the 0.4% concentration had a higher percentage of neurological improvement compared to the 0.8-2% concentration (44% vs. 6%, $p<0.02$), while angiographic improvement was higher in the treatment with papaverine at 0.4% compared to the concentrations 0.1-0.2% and 0.8-2% ($p<0.05$); finally, adverse events were more frequent in the group that received papaverine with a concentration of 0.8-2% ($p<0.005$) compared to the concentrations 0.1-0.2% and 0.4%. The risk of bias was moderate-serious in the non-randomised trials and unclear in the randomised trial.

Three studies (125 patients) evaluated the types of balloon angioplasty, the number of combination therapy sessions (TBA + IAVI), and stent retriever therapy. The first study compared compliant versus non-compliant balloon angioplasty without finding any statistically significant associations. The second study compared the number of sessions of combined endovascular therapy (TBA + IAVI), 1-2 sessions vs. 3-6 sessions, without finding any significant differences. The third study compared different sequences of stent therapy; one group received vasodilator before retrievable stent placement and the other group received management with a retrievable stent prior to the administration of the vasodilator without finding significant differences. The risk of bias was moderate-critical.

Finally, the results on the safety of endovascular therapy did not show an increase in adverse events in any of the comparison groups, except for the increased risk of complications at high concentrations of papaverine compared to lower concentrations.

Adverse events reported in patients receiving intra-arterial vasodilator infusion included embolic/spastic vascular occlusion, hemodynamic instability, cardiac arrhythmia, endocranial hypertension, and transient focal neurologic deficit.

Lastly, adverse events observed in balloon angioplasty included re-bleeding of the brain aneurysm, hardware rupture, and arterial occlusion. No significant differences in this regard were found in the comparison groups.

4.2 Overall completeness and applicability of evidence

Although a comprehensive search was conducted to retrieve all published and unpublished studies, this systematic review included studies with moderate-critical risk of bias, thus the confidence in the effect estimate is low. In addition, in many cases, data were incomplete, and some important clinical outcomes were not reported. For example, most of the included studies did not assess long-term functional status, which accounts for the overall impact of the intervention, while no studies assessed quality of life or costs associated with care. Furthermore, the definition of some outcomes (e.g., angiographic improvement) had great variability among studies.

The applicability of the evidence in the target population (patients with cerebral vasospasm secondary to aneurysmal subarachnoid haemorrhage) is limited since the studies retrieved had substantial degree of heterogeneity in their clinical contexts, case definitions, and methodological designs.

The interventions discussed in this review should be implemented with caution in certain clinical settings; however, they require trained personnel, local or general anesthesia,

appropriate biomedical devices, diagnostic imaging equipment, and infrastructure to enable the execution of endovascular therapy.

4.3 Quality of the evidence

Non-randomised controlled studies were assessed for risk of bias using the ROBINS-I instrument as low (0%), moderate (42%), serious (42%), and critical (16%). The risk of bias of the randomised controlled clinical trial was unclear according to the Cochrane Collaboration tool. Therefore, confidence in the effect estimation was very low, and the actual effect is likely to be substantially different. Confidence is very low due to study limitations (lack of control for confounding factors, selection bias, lack of blinding for outcome assessment, and risk of bias from selective reporting), and because some imprecise results were documented (few patients and events). It was not possible to assess the risk of reporting bias as there were very few studies included in each comparison.

4.4 Potential biases in the review process

There were concerns about reporting bias, as this was a possibility due to the limited number of studies for each comparison. Another major limitation of this systematic review is measurement bias, especially in the studies in which the authors evaluated the outcomes subjectively. Finally, although a comprehensive search was conducted, not all studies reported results for most outcomes of clinical relevance; moreover, the differences reported as significant in this review originated from a few studies, with a high number of imprecise results. Therefore, these results should be interpreted with caution.

5. Conclusions

5.1 Implications for practice

Due to the risk of bias, imprecision, and heterogeneity of many of the outcomes assessed in this review, the positive and negative effects of endovascular therapy compared to medical therapy should be considered with caution (Appendix 4). The frequency of adverse events was low and did not seem to be different between medical therapy and endovascular therapy, with moderate to critical risk of bias.

Evidence from some of the results showing that intra-arterial vasodilator infusion is superior to standard treatment, in terms of functional outcome at 3 months and outcome of angiographic vasospasm, is at moderate risk of bias.

When comparing the effects of different vasodilators, papaverine seems to be superior to nimodipine because it has lower mortality rates and higher angiographic improvement rates. Compared to colforsin, papaverine had worse functional outcome at discharge and higher frequency of cerebral infarction during follow-up. The quality of evidence from studies evaluating multiple vasodilators had a moderate to serious risk of bias.

The comparison of different endovascular therapy options shows no significant difference between intra-arterial vasodilator infusion and balloon angioplasty, with moderate to critical risk of bias.

5.2 Implications for research

High-quality controlled clinical trials regarding treatment are needed for patients with cerebral vasospasm secondary to subarachnoid haemorrhage, particularly comparing

endovascular therapy to standard treatment. Further research should focus on avoiding risk of bias, especially in relation to the allocation and selection of intervention groups, the failure to comply with the intention-to-treat principle, and selective reporting. Those studies should report major clinical outcomes such as functional outcome in the long-term, adverse events, the need for additional interventions, patient satisfaction with the treatment administered, cost-effectiveness of the intervention, among others.

A. Appendix 1: Classification and scales

Glasgow Outcome Scale (GOS)

Unfavourable outcome: categories 1, 2 or 3 (67,68).

Table 5-1: Glasgow Outcome Scale.

Category	Definition
1. Death	Severe injury or death without recovery of consciousness
2. Persistent vegetative state	Severe damage with prolonged state of unresponsiveness and a lack of higher mental functions
3. Severe disability	Severe injury with permanent need for help with daily living
4. Moderate disability	No need for assistance in everyday life, employment is possible but may require special equipment
5. Low disability	Light damage with minor neurological and psychological deficits

Glasgow Outcome Scale Extended (GOS-E)

Unfavourable outcome: categories 1, 2, 3 or 4 (67,68).

Table 5-2: Glasgow Outcome Scale Extended.

Category	Definition
1. Death	
2. Vegetative state	Condition of unawareness with reflex responses only, but with periods of spontaneous eye opening
3. Low severe disability	Person who is dependent for daily support for mental or physical disability, usually a combination of both. If the person cannot be left alone for more than 8 hours at home, it is low level of severe disability
4. Upper severe disability	Person who is dependent for daily support for mental or physical disability, usually a combination of both. If the person can be left alone for more than 8 hours at home, it is upper level of severe disability
5. Low moderate disability	Person has some disability such as aphasia, hemiparesis or epilepsy and/or deficits of memory or personality but is able to look after him/herself. Person is independent at home but dependent outside. If unable to return to work, even with special arrangements, it is low level of moderate disability
6. Upper moderate disability	Person has some disability such as aphasia, hemiparesis or epilepsy and/or deficits of memory or personality, but is able to look after him/herself. Person is independent at home, but dependent outside. If able to return to work with special arrangements, it is upper level of moderate disability
7. Low good recovery	Resumption of normal life with the capacity to work even if pre-injury status has not been achieved. Some people have minor neurological or psychological deficits. If these deficits are disabling, then it is lower level of good recovery
8. Upper good recovery	Resumption of normal life with the capacity to work even if pre-injury status has not been achieved. Some people have minor neurological or psychological deficits. If these deficits are not disabling, then it is upper level of good recovery

Modified Rankin Scale (mRS)

Unfavourable outcome: categories 4, 5 o 6 (69)

Table 5-3: Modified Rankin Scale.

Category	Definition
0	No symptoms at all
1	No significant disability and able to carry out all duties
2	Slight disability. Unable to carry out some previous activities but able to look after own affairs without assistance
3	Moderate disability. Requiring some help but able to walk without assistance
4	Moderately severe disability. Unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability. Bedridden, incontinent and requiring constant nursing care and attention
6	Death

Fisher's Scale

Assessed with CT (38)

Table 5-4: Fisher's Scale.

Category	Definition
Grade I	no subarachnoid (SAH) or intraventricular haemorrhage (IVH) detected
Grade II	diffuse thin (<1 mm) SAH, no clots
Grade III	localized clots and/or layers of blood >1 mm in thickness, no IVH
Grade IV	diffuse or no SAH, ICH or IVH present

Hunt & Hess Scale

Assessed at beginning (39).

Table 5-5: Hunt & Hess Scale.

Category	Definition
Grade 0	Unruptured aneurysm
Grade 1	Mild Headache, Alert and Oriented, Minimal (if any) Nuchal Rigidity
Grade 2	Full Nuchal Rigidity, Moderate-Severe Headache, Alert and Oriented, No Neuro Deficit (Besides CN Palsy)
Grade 3	Lethargy or Confusion, Mild Focal Neurological Deficits
Grade 4	Stuporous, More Severe Focal Deficit
Grade 5	Comatose, showing signs of severe neurological impairment (ex: posturing)

World Federation of Neurosurgical Societies Scale

Assessed at beginning (39).

Table 5-6: World Federation of Neurosurgical Societies Scale.

Category	Definition	
	Glasgow Coma Scale	**Motor Deficit**
Grade I	15 points	Not
Grade II	13-14 points	Not
Grade III	13-14 points	Yes
Grade IV	7-12 points	Yes / Not
Grade V	3-7 points	Yes / Not

B. Appendix 2: Search strategy

MEDLINE (R) <1946 to April Week 4 2020>

1 exp subarachnoid hemorrhage/ (21096)

2 ((subarachnoid$ or arachnoidal$) adj3 (h?emorrhag$ or h?ematoma or bleed$ or blood)).tw. (22733)

3 1 or 2 (28017)

4 vasospasm, intracranial/ (3187)

5 (((brain or cerebr$ or intracranial) adj3 spasm) or vasospasm or angiospasm or vasoconstriction).tw. (35169)

6 4 or 5 (35586)

7 3 and 6 (5629)

8 endovascular procedures/ (18125)

9 vascular surgical procedures/ (30901)

10 ((((blood adj3 vessel) or vascular) adj3 (repair or reconstruct$ or surg$)) or angiosurgery).tw. (20252)

11 (endovasc$ adj3 (procedure or surg$ or treatment$ or repair)).tw. (23548)

12 angioplasty/ or angioplasty, balloon/ or stents/ or dilatation/ (92556)

13 (((balloon or transluminal) adj3 angioplasty) or (artery adj3 dilatation) or stent$ or dilat$).tw. (217849)

14 exp vasodilator agents/ or exp phosphodiesterase inhibitors/ or dantrolene/ (457814)

15 (vasodilat$ or (vasoactive adj3 antagon$) or vasorelaxant$ or IAVI).tw. (64752)

16 (calcium adj3 (inhib$ or antagon$ or block$)).tw. (42814)

17 (acetylcholine or adenosine or adrenomedullin or alprostadil or amiodarone or amlodipine or amrinone or bencyclane or bepridil or betahistine or bradykinin or carvedilol or celiprolol or chromonar or cilostazol or colforsin or cromakalim or cyclandelate or dantrolene or diazoxide or dihydroergocristine or dihydroergocryptine or dilazep or diltiazem or dipyridamole or dyphylline or enoximone or ergoloid mesylates or erythritol or

erythrityl tetranitrate or fasudil or felodipine or fenoldopam or flunarizine or hexobendine or hydralazine or iloprost or isosorbide dinitrate or isoxsuprine or isradipine or kallidin or khellin or lidoflazine or mibefradil or milrinone or minoxidil or molsidomine or moxisylyte or nafronyl or nebivolol or niacin or nicardipine or nicergoline or nicorandil or nifedipine or nimodipine or nisoldipine or nitrendipine or nitroglycerin or nitroprusside or nonachlazine or nylidrin or oxprenolol or oxyfedrine or papaverine or pentaerythritol tetranitrate or pentoxifylline or perhexiline or phenoxybenzamine or pinacidil or pindolol or polymethyl methacrylate or prenylamine or propranolol or sildenafil citrate or simendan or sodium azide or suloctidil or tadalafil or theobromine or theophylline or thiouracil or tolazoline or trapidil or trimetazidine or vardenafil dihydrochloride or verapamil or vincamine or xanthinol niacinate).tw. (369118)

18 or/8-17 (942566)

19 7 and 18 (1911)

20 exp subarachnoid hemorrhage/dt [Drug Therapy] (1403)

21 brain vasospasm/dt [Drug Therapy] (0)

22 20 or 21 (1403)

23 19 or 22 (3003)

24 randomized controlled trial.pt. (504191)

25 controlled clinical trial.pt. (93615)

26 randomized.ab. (411665)

27 placebo.ab. (187040)

28 randomly.ab. (282000)

29 trial.ab. (430105)

30 groups.ab. (1745117)

31 or/24-30 (2543514)

32 23 and 31 (832)

Embase

No.	Query	Results	Date
#35.	#23 AND #34	1,070	2 May 2020
#34.	#24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33	2,424,089	2 May 2020
#33.	assign*:ab,ti OR allocat*:ab,ti	532,031	2 May 2020
#32.	trial:ti	302,767	2 May 2020
#31.	placebo*:ab,ti OR sham:ab,ti	419,690	2 May 2020

#30. (cross-over:ab,ti OR cross:ab,ti) AND over:ab,ti OR crossover:ab,ti	205,644	2 May 2020
#29. ((singl* OR doubl* OR tripl* OR trebl*) NEAR/5 (blind* OR mask*)):ab,ti	241,866	2 May 2020
#28. random*:ab,ti OR rct:ab,ti OR rcts:ab,ti	1,532,344	2 May 2020
#27. 'single blind procedure'/de OR 'triple blind procedure'/de	38,794	2 May 2020
#26. 'double blind procedure'/de	171,671	2 May 2020
#25. 'crossover procedure'/de	62,681	2 May 2020
#24. 'randomized controlled trial'/de OR 'randomized controlled trial (topic)'/de	773,780	2 May 2020
#23. #19 OR #22	5,846	2 May 2020
#22. #20 OR #21	3,608	2 May 2020
#21. 'brain vasospasm'/dd_dt	1,715	2 May 2020
#20. 'subarachnoid hemorrhage'/exp/dd_dt	2,220	2 May 2020
#19. #7 AND #18	3,528	2 May 2020
#18. #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17	1,280,987	2 May 2020
#17. ((acetylcholine:ab,ti OR adenosine:ab,ti OR adrenomedullin:ab,ti OR alprostadil:ab,ti OR amiodarone:ab,ti OR amlodipine:ab,ti OR amrinone:ab,ti OR bencyclane:ab,ti OR bepridil:ab,ti OR betahistine:ab,ti OR bradykinin:ab,ti OR carvedilol:ab,ti OR celiprolol:ab,ti OR chromonar:ab,ti OR cilostazol:ab,ti OR colforsin:ab,ti OR cromakalim:ab,ti OR cyclandelate:ab,ti OR dantrolene:ab,ti OR diazoxide:ab,ti OR dihydroergocristine:ab,ti OR dihydroergocryptine:ab,ti OR dilazep:ab,ti OR diltiazem:ab,ti OR dipyridamole:ab,ti OR dyphylline:ab,ti OR enoximone:ab,ti OR ergoloid:ab,ti) AND mesylates:ab,ti OR erythritol:ab,ti OR (erythrityl:ab,ti AND tetranitrate:ab,ti) OR fasudil:ab,ti OR felodipine:ab,ti OR fenoldopam:ab,ti OR flunarizine:ab,ti OR hexobendine:ab,ti OR hydralazine:ab,ti OR iloprost:ab,ti OR (isosorbide:ab,ti AND dinitrate:ab,ti) OR isoxsuprine:ab,ti OR isradipine:ab,ti OR kallidin:ab,ti OR khellin:ab,ti OR lidoflazine:ab,ti OR mibefradil:ab,ti OR milrinone:ab,ti OR minoxidil:ab,ti OR molsidomine:ab,ti OR moxisylyte:ab,ti OR nafronyl:ab,ti OR nebivolol:ab,ti OR niacin:ab,ti OR nicardipine:ab,ti OR nicergoline:ab,ti OR nicorandil:ab,ti OR nifedipine:ab,ti OR nimodipine:ab,ti OR nisoldipine:ab,ti OR nitrendipine:ab,ti	106,057	2 May 2020

OR nitroglycerin:ab,ti OR nitroprusside:ab,ti OR nonachlazine:ab,ti OR nylidrin:ab,ti OR oxprenolol:ab,ti OR oxyfedrine:ab,ti OR papaverine:ab,ti OR (pentaerythritol:ab,ti AND tetranitrate:ab,ti) OR pentoxifylline:ab,ti OR perhexiline:ab,ti OR phenoxybenzamine:ab,ti OR pinacidil:ab,ti OR pindolol:ab,ti OR polymethyl:ab,ti) AND methacrylate:ab,ti OR prenylamine:ab,ti OR propranolol:ab,ti OR (sildenafil:ab,ti AND citrate:ab,ti) OR simendan:ab,ti OR (sodium:ab,ti AND azide:ab,ti) OR suloctidil:ab,ti OR tadalafil:ab,ti OR theobromine:ab,ti OR theophylline:ab,ti OR thiouracil:ab,ti OR tolazoline:ab,ti OR trapidil:ab,ti OR trimetazidine:ab,ti OR (vardenafil:ab,ti AND dihydrochloride:ab,ti) OR verapamil:ab,ti OR vincamine:ab,ti OR (xanthinol:ab,ti AND niacinate:ab,ti)		
#16. (calcium NEAR/3 (inhib* OR antagon* OR block*)):ab,ti	57,277	2 May 2020
#15. vasodilat*:ab,ti OR ((vasoactive NEAR/3 antagon*):ab,ti) OR vasorelaxant*:ab,ti OR iavi:ab,ti	90,384	2 May 2020
#14. 'vasodilator agent'/exp OR 'phosphodiesterase inhibitor'/exp OR 'dantrolene'/de	672,712	2 May 2020
#13. (((balloon OR transluminal) NEAR/3 angioplasty):ab,ti) OR ((artery NEAR/3 dilatation):ab,ti) OR stent*:ab,ti OR dilat*:ab,ti	380,471	2 May 2020
#12. 'angioplasty'/de OR 'percutaneous transluminal angioplasty'/de OR 'stent'/de OR 'dilatation'/de	144,562	2 May 2020
#11. (endovasc* NEAR/3 (procedure OR surg* OR treatment* OR repair)):ab,ti	41,300	2 May 2020
#10. ((blood OR vessel OR vascular) NEAR/3 (repair OR reconstruct* OR surg*)):ab,ti	57,211	2 May 2020
#9. 'vascular surgery'/de OR angiosurgery:ab,ti	38,468	2 May 2020
#8. 'endovascular surgery'/de	24,569	2 May 2020
#7. #3 AND #6	9,170	2 May 2020
#6. #4 OR #5	50,537	2 May 2020
#5. (((brain OR cerebr* OR intracranial) NEAR/3 spasm):ab,ti) OR vasospasm:ab,ti OR	48,579	2 May 2020

	angiospasm:ab,ti OR vasoconstriction:ab,ti		
#4.	'brain vasospasm'/de	7,168	2 May 2020
#3.	#1 OR #2	48,960	2 May 2020
#2.	((subarachnoid* OR arachnoidal*) NEAR/3 (h$emorrhag* OR h$ematoma OR bleed* OR blood)):ab,ti	34,493	2 May 2020
#1.	'subarachnoid hemorrhage'/exp	44,038	2 May 2020

C. Appendix 3: Characteristics of studies

Table 5-7: Summary of included studies.

Study	Long term unfavourable	Short term unfavourable	Mortality	Infarction	Neuro recovery	Angio improvement	Hospital stay	Adverse events	Exposure	Control	Sample	Bias
Aburto 2012	x		x	x					TAB	IAV	30	Serious
Andereggen 2017	x		x	x				x	IAV + TAB #	IAV + TAB #	83	Critical
Bele 2015	x	x	x	x				x	IAV	MED	41	Moderate
Besheli 2017		x	x	x					IAV	MED	115	Serious
Coenen 1998					x				IAV	TAB	69	Moderate
Crespy 2018	x		x					x	IAV	MED	101	Serious
Elayoubi 2013						x			IAV	MED	18	Serious
Elliott 1998		x	x			x		x	IAV	TAB	52	Critical
Elsayed 2006									IAV	TAB	22	-
Frontera 2011		x				x			IAV	IAV + TAB	92	Critical
Goel 2016	x	x			x				IAV	MED	53	Serious
Hosmann 2018				x		x			IAV	IAV + TAB	77	Serious

Katoh 1999		x	x		x			x	TAB / IAV	MED	72	Moderate
Kerz 2012		x	x	x		x	x		IAV	IAV	30	Serious
Kerz 2016								x	IAV	IAV + TAB	47	Moderate
Khatri 2011		x	x				x		IAV + TAB	MED	146	Moderate
Kwon 2018		x	x		x	x		x	IAV + Stent	Stent + IAV	12	Moderate
Miley 2011		x		x				x	TABc	TABnc	30	Serious
Mortimer 2014	x	x	x				x	x	IAV + TAB	MED	80	Critical
Nakamura 2013		x	x	x				x	IAV	MED	31	Serious
Oskouian 2002		x			x				IAV	TAB / IAV +TAB	45	Serious
Polin 1998	x			x					IAV	MED	93	Moderate
Polin 2000	x								IAV + TAB	MED	121	Moderate
Sokolowski 2017		x				x			TAB	IAV + TAB / IAV	159	Moderate
Suzuki 2012		x	x	x				x	IAV	IAV	133	Moderate
Sawada 2012					x	x		x	IAV	IAV	31	Unclear

Table 5-8: Risk of bias in non-randomised studies.

Study	D1	D2	D3	D4	D5	D6	D7	Overall
Aburto 2012	Serious	Low	Moderate	Low	Low	Low	Low	Serious
Andereggen 2017	Critical	Moderate	Low	Low	Low	Low	Moderate	Critical
Bele 2015	Moderate	Moderate	Low	Low	Low	Low	Moderate	Moderate
Besheli 2017	Serious	Moderate	Moderate	Low	Low	Low	Low	Serious
Coenen 1998	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Crespy 2018	Serious	Low	Low	Low	Serious	Low	Moderate	Serious
Elayoubi 2013	Serious	No information	No information	No information	No information	Low	Moderate	Serious
Elliott 1998	Serious	Low	Low	Critical	Low	Moderate	Moderate	Critical
Frontera 2011	Critical	Critical	Serious	Serious	Low	Low	Moderate	Critical
Goel 2016	Serious	Low	Serious	Low	Low	Moderate	Moderate	Serious
Hosmann 2018	Serious	Low	Low	Serious	Moderate	Low	Moderate	Serious
Katoh 1999	Moderate	Low	Low	Low	Low	Low	Moderate	Moderate
Kerz 2012	Serious	Low	Low	Low	Low	Serious	Moderate	Serious
Kerz 2016	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate
Khatri 2011	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate
Kwon 2018	Serious	Low	Low	Low	Low	Moderate	Moderate	Moderate
Miley 2011	Serious	Low	Low	Low	Low	Low	Moderate	Serious
Mortimer 2014	Critical	Low	Low	Low	Low	Low	Moderate	Critical
Nakamura 2013	Serious	Low	Moderate	Low	Low	Moderate	Moderate	Serious
Oskouian 2002	Serious	Low	Low	Low	Low	Low	Moderate	Serious
Polin 1998	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Polin 2000	Moderate	Low	Low	Low	Low	Low	Low	Moderate
Sokolowski 2017	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate
Suzuki 2012	Moderate	Low	Low	Low	Low	Moderate	Moderate	Moderate

Tabla 5-9: Description of interventions.

Study	Description of the intervention	Description of the comparator
Aburto 2012	Nimodipine diluted in saline (solution up to 0.200 mg), dose 1200 mg	Compliant balloon, no anticoagulation
Andereggen 2017	1-2 Sessions Nimodipine 2.5 mg per blood vessel. Balloon does not specify type or anticoagulation	3-6 sessions Nimodipine 2.5 mg per vessel, balloon: does not specify type or anticoagulation
Bele 2015	Continuous infusion Nimodipine 0.5-1.2 mg / h + heparin, according to response by multimodal therapy + Triple H therapy	Triple H therapy according to response by DTC, PBTO2, CBF
Besheli 2017	Nicardipine 1-15mg +- Milrinone 5-15mg	Triple H Therapy + Oral Nimodipine
Coenen 1998	Intra-arterial papaverine, does not refer dose, was administered 15 hours after symptoms	Balloon angioplasty at 21 hours after symptoms, does not refer if anticoagulated or the type of balloon
Crespy 2018	Milrinone IA 8-24 mg + Milrinone 1 mcg / kg / min 14 days + Mechanical angioplasty if two IAVI options fail	Milrinone 1 mcg / kg / min + - boluses 8 mg 7 Days + - angioplasty or IAVI according to clinical criteria
Elayoubi 2013	Milrinone IA + - balloon angioplasty	Patient with or without vasospasm who did not receive milrinone
Elliott 1998	IA Papaverine 300 mg per blood vessel, no anticoagulation	Low pressure angioplasty balloon, anticoagulation
Frontera 2011	Silica Commodore Balloon Posterior to IAVI	Papaverine (13 ptes) 75 mg initial dose max 300 mg per territory; Verapamil (46 ptes) initial dose 5 mg max 30 mg per vascular territory
Goel 2016	Nimodipine IA 1-3 mg max 6 mg	Oral nimodipine + PAS 150-150
Hosmann 2018	Papaverine IA, mean dose 252 +- 191 mg	Papaverine + TBA, does not specify the type of balloon, they only used this therapy in case of severe vasospasm
Katoh 1999	Papaverine IA 40-160 mg	Hypertensive hypervolemic hemodilution
Katoh 1999	Silicone Balloon	Hypertensive hypervolemic hemodilution
Katoh 1999	Papaverine IA 40-160 mg	Silicone balloon
Kerz 2012	Papaverine IA 300-600 mg	Nimodipine IA 1-1.5mg
Kerz 2016	Nimodipine IA 1.5 mg per territory, 2.5 mg dose per patient	Balloon that does not over-inflate
Khatri 2011	Compliant / non-compliant balloon angioplasty + - vasodilator (nicardipine, verapamil, magnesium sulfate)	Hypervolemic hypertension
Kwon 2018	Nicardipine IA 2-3 mg, followed by Stent Retriever, with heparin	Stent Retriever, followed by Nicardipine IA 2-3 mg, with heparin
Miley 2011	Compliant balloon, heparin	Non-compliant balloon, heparin
Mortimer 2014	Compliant balloon, heparin or IAVI (Verapamil 10-15 mg or Papaverine)	Nimodipine IV 20 mcg / kg / h, PAS 140-160, hydration
Nakamura 2013	Fasudil 30mg, 3mg / min selective	Fasudil IV + Edarabon IV
Oskouian 2002	Papaverine IA 0.3% 60-360 mg	Low pressure compliant balloon

Polin 1998	Papaverine 90mg / 100mL up to 300mg / 100ml	Same dose of tirilizad + nimodipine 60 mg oral
Polin 2000	Balloon angioplasty + - IAVI papaverine	Same dose of tirilizad + nimodipine 60 mg oral
Sokolowski 2017	IA Papaverine Verapamil	Angioplasty + heparin
Sokolowski 2017	Angioplasty + heparin	Combined endovascular therapy
Suzuki 2012	1 mL papaverine 4% diluted in 19 mL of SSN at a rate of 2 mg / min	4 mg colforsin diluted in 100mL Saline, infused a 0.15 mg / min

Table 5-10: Description of outcomes.

Study	Outcome	Description
Aburto 2012	Long term unfavourable	1 year.
Aburto 2012	Long term unfavourable	3 moths.
Aburto 2012	Mortality	1 year.
Aburto 2012	Cerebral ifarction	Doesn´t specify time of infarction assessment, nor the evaluators, nor the blinding.
Andereggen 2017	Long term unfavourable	Last follow up 11 +- 6.3, range 2-22 months, mRS 3-6.
Andereggen 2017	Mortality	Last follow up 11 +- 6.3, range 2-22 months, mRS 6.
Andereggen 2017	Cerebral ifarction	At discharge, doesn´t specify who assessed, nor blinding.
Andereggen 2017	Adverse events	Related to procedures, arterial dissections: 1 event in the intervention group and 5 in the control group (1 nneded stent), 1 event of pseudoaneurysm in the puncture site.
Bele 2015	Long term unfavourable	GOS at 6 months.
Bele 2015	Short term unfavourable	At discharge, GOS (unfavourable was defined as 1-3).
Bele 2015	Mortality	6 months.
Bele 2015	Cerebral ifarction	CT at discharge, independent neuroradiologist .
Bele 2015	Adverse events	Related with the procedura, 1 case of vascular oclusion (revascularization), 1 embolic/sastic oclusion, general complications as pneumonia or heart failure. No cases of sepsia, no bleeding related with heparin.
Besheli 2017	Short term unfavourable	Median of GOS score.
Besheli 2017	Mortality	During hospital stay.
Besheli 2017	Cerebral ifarction	During hospital stay.
Coenen 1998	Neurological deficit improvement	Assessment by using mGCS at day 1 and 4, doesn't specify whether it was blind or independent.
Crespy 2018	Long term unfavourable	mRS at 1 year – phone call with patient, family or physician.
Crespy 2018	Mortality	Aparently at 1 year.
Crespy 2018	Adverse events	Included: vasopresor treatment, cardiac arritmia, hypokalemia, hemodinamic instability, cardiac schock.
Elayoubi 2013	Angiographic vasospasm improvement	8 radiologist assessed arterial diameter by all the evaluators.
Elliott 1998	Short term unfavourable	Unfavourable = severely disabled, vegetative, or dead.
Elliott 1998	Angiographic vasospasm improvement	At the time of initial treatment.

Elliott 1998	Adverse events	Re-bleeding.
Frontera 2011	Short term unfavourable	Hospital discharge disposition was dichotomized as poor (expired, discharged to a nursing home or subacute care facility) vs. good (discharged to home, an acute rehabilitation facility, or home with a health aide).
Goel 2016	Long term unfavourable	GOS and modified Rankin Scale at discharge and at 3 months. The outcome was divided into two groups: favourable (GOS 4–5, modified Rankin scale 0–3) and unfavourable (GOS 1–3, modified Rankin scale 4–5).
Goel 2016	Short term unfavourable	GOS and modified Rankin Scale at discharge and at 3 months. The outcome was divided into two groups: favourable (GOS 4–5, modified Rankin scale 0–3) and unfavourable (GOS 1–3, modified Rankin scale 4–5).
Goel 2016	Neurological deficit improvement	The clinical status was assessed every few hours in either group.
Hosmann 2018	Cerebral ifarction	CT at 10 days post-treatment, blind evaluators, by vascular territories.
Hosmann 2018	Angiographic vasospasm improvement	Positive if blood vessel dilatation by territory, when improved more than one category
Katoh 1999	Short term unfavourable	Glasgow Outcome Scale
Katoh 1999	Short term unfavourable	Glasgow Outcome Scale
Katoh 1999	Adverse events	Serious and transitory adverse events: in the case of papaverine were altered state of consciousness 36%, blood pressure elevation 14%, decerebration posture 7%, conjugate gaze deviation 7%, tachycardia 7%, sweating 7%, nausea 7%
Katoh 1999	Short term unfavourable	Glasgow Outcome Scale
Kerz 2012	Short term unfavourable	Glasgow Outcome Scale
Kerz 2012	Mortality	During hospital stay
Kerz 2012	Cerebral ifarction	CT 4-14 days posterior of bleeding, two blind assessors
Kerz 2012	Angiographic vasospasm improvement	Assessment of six main blood vessels, improvement for each vessel
Kerz 2016	Adverse events	Arterial oclusion, arterial disection, cerebral infarction
Khatri 2011	Short term unfavourable	at discharge, mRS, one blind assessor
Khatri 2011	Mortality	1 year follow up
Kwon 2018	Short term unfavourable	mRS at discharge
Kwon 2018	Neurological deficit improvement	Doesn’t specify
Kwon 2018	Angiographic vasospasm improvement	DSA at 24 hours, doesn’t specify if blind or independent
Kwon 2018	Adverse events	None of the complicated caused a permanent deficit. Complications included blood vessel rupture or oclusion.
Miley 2011	Cerebral ifarction	CT, one blind assessor.
Miley 2011	Short term unfavourable	Discharge, mRS.
Miley 2011	Mortality	Any cause mortality.

Miley 2011	Adverse events	Blood vessel rupture, arterial dissection.
Mortimer 2014	Long term unfavourable	GOS, mRS, blind independent assessors, at 3 months.
Mortimer 2014	Short term unfavourable	GOS, mRS, blind independent assessors.
Mortimer 2014	Adverse events	Thrombo-embolic event.
Nakamura 2013	Short term unfavourable	Glasgow Outcome Scale.
Nakamura 2013	Cerebral ifarction	CT.
Nakamura 2013	Adverse events	Seizures.
Nakamura 2013	Short term unfavourable	Glasgow Outcome Scale.
Nakamura 2013	Cerebral ifarction	CT.
Nakamura 2013	Adverse events	Seizures.
Oskouian 2002	Short term unfavourable	Glasgow Outcome Scale.
Oskouian 2002	Short term unfavourable	Glasgow Outcome Scale.
Oskouian 2002	Short term unfavourable	Glasgow Outcome Scale.
Polin 1998	Long term unfavourable	GOS at 3 months, one blind assessors.
Polin 1998	Cerebral ifarction	CT , blind evaluators.
Polin 2000	Long term unfavourable	GOS at 3 moths, blind assessors.
Sokolowski 2017	Short term unfavourable	mRS at discharge, poor outcome was defined as 3-6.
Sokolowski 2017	Angiographic vasospasm improvement	Reperfusion was defined as narrowing improvement over 50% of stenosis.
Sokolowski 2017	Short term unfavourable	mRS at discharge, poor outcome was defined as 3-6.
Sokolowski 2017	Angiographic vasospasm improvement	Reperfusion was defined as narrowing improvement over 50% of stenosis.
Sokolowski 2017	Short term unfavourable	mRS at discharge, poor outcome was defined as 3-6.
Sokolowski 2017	Angiographic vasospasm improvement	Reperfusion was defined as narrowing improvement over 50% of stenosis.
Suzuki 2012	Short term unfavourable	mRS at discharge.
Suzuki 2012	Cerebral ifarction	MRI.
Suzuki 2012	Mortality	At discharge.

Tabla 5-11: Effect of interventions.

Study	Outcome	Intervention	Description	Control	Description	N Exp	N Cont	Event Exp	Event Cont	P	OR DM	Value	CI Inf	CI Sup	Author's report
Aburto 2012	Long term unfavourable	IAVI	Nimodipine	TAB		22	8	5	3	0,64	OR	0,49	0,06	4,38	
Aburto 2012	Long term unfavourable	IAVI	Nimodipine	TAB		22	8	10	4	1,00	OR	0,83	0,12	5,79	
Aburto 2012	Mortality	IAVI	Nimodipine	TAB		22	8	3	3	0,30	OR	0,26	0,03	2,71	
Aburto 2012	Cerebral ifarction	IAVI	Nimodipine	TAB		22	8	21	8	1,00	OR	1,20	0,02	26,20	
Andereggen 2017	Long term unfavourable	IAVI+TAB	1-2 Sesions	IAVI+TAB	3-6 sesions	52	31	21	13	1,00	OR	0,94	0,35	2,56	
Andereggen 2017	Mortality	IAVI+TAB	1-2 Sesions	IAVI+TAB	3-6 sesions	52	31	7	9	0,09	OR	0,38	0,11	1,34	
Andereggen 2017	Cerebral ifarction	IAVI+TAB	1-2 Sesions	IAVI+TAB	3-6 sesions	49	31	18	17	0,16	OR	0,48	0,17	1,31	OR 1.28 IC 95% (0.66–2.46) P=.469
Andereggen 2017	Adverse events	IAVI+TAB	1-2 Sesions	IAVI+TAB	3-6 sesions	51	31	1	5	0,03	OR	0,10	0,00	1,01	
Bele 2015	Long term unfavourable	IAVI	Nimodipine	Medical		21	20	5	15	0,00	OR	0,10	0,02	0,52	
Bele 2015	Short term unfavourable	IAVI	Nimodipine	Medical		21	20	16	18	0,41	OR	0,36	0,03	2,61	
Bele 2015	Mortality	IAVI	Nimodipine	Medical		21	20	2	7	0,05	OR	0,20	0,02	1,30	
Bele 2015	Cerebral ifarction	IAVI	Nimodipine	Medical		21	20	9	15	0,04	OR	0,25	0,07	0,95	
Bele 2015	Adverse events	IAVI	Nimodipine	Medical		21	20	2	0	0,26	OR	5,26	0,24	116,57	
Besheli 2017	Short term unfavourable	IAVI	Nicardipine +- Milrinone	Medical		22	93	mean 2,6	mean 1	0,00	DM	1,60	na	na	P<0.001
Besheli 2017	Mortality	IAVI	Nicardipine +- Milrinone	Medical		22	93	0	3	1,00	OR	0,57	0,03	11,53	
Besheli 2017	Cerebral ifarction	IAVI	Nicardipine +- Milrinone	Medical		22	93	2	0	0,04	OR	22,80	1,05	493,11	
Besheli 2017	ICU stay	IAVI	Nicardipine +- Milrinone	Medical		22	93	18	12.2	0,00	DM	5,80			P<0.001
Coenen 1998	Neurological deficit improvement	IAVI	Papaverine	TAB		31	38	12	11	0,45	OR	1,55	0,57	4,24	P=0,.2578
Crespy 2018	Long term unfavourable	IAVI	Milrinone	Medical		24	77	8	18	0,42	OR	1,64	0,60	4,45	
Crespy 2018	Mortality	IAVI	Milrinone	Medical		24	77	4	2	0,03	OR	7,50	1,28	43,93	

Crespy 2018	Adverse events	IAVI	Milrinone	Medical		24	77	12	35	0,34	OR	1,20	0,48	3,00	
Elayoubi 2013	Angiographic vasospasm improvement	IAVI	Milrinone	Medical		72	72	65	8	0,00	OR	74,29	25,44	216,89	
Elliott 1998	Short term unfavourable	IAVI	Papaverine	TAB		13	39	5	13	0,75	OR	1,25	0,34	4,59	
Elliott 1998	Mortality	IAVI	Papaverine	TAB		13	39	0	1	1,00	OR	0,95	0,04	24,77	
Elliott 1998	Angiographic vasospasm improvement	IAVI	Papaverine	TAB		13	39	13	39	1,00	OR	1,00	na	na	
Elliott 1998	Adverse events	IAVI	Papaverine	TAB		13	39	0	1	1,00	OR	0,95	0,04	24,77	
Frontera 2011	Short term unfavourable	IAVI + TAB		IAVI	Papaverine	33	59				OR				OR 0.6, 95% CI 0.2–1.7, P = 0.351
Frontera 2011	Angiographic vasospasm improvement	IAVI + TAB		IAVI	Papaverine	33	59	33	52	0,05	OR	9,57	0,53	173,14	
Goel 2016	Long term unfavourable	IAVI	Nimodipine	Medical		36	13	13	6	0,53	OR	0,66	0,18	2,38	
Goel 2016	Short term unfavourable	IAVI	Nimodipine	Medical		39	14	28	10	1,00	OR	1,02	0,26	3,94	
Goel 2016	Neurological deficit improvement	IAVI	Nimodipine	Medical		39	14	28	6	0,10	OR	3,39	0,96	12,06	
Hosmann 2018	Cerebral ifarction	IAVI	Papaverine	IAVI+TAB		63	14	16	5	0,51	OR	0,61	0,18	2,10	
Hosmann 2018	Mejoría angiográfica	IAVI	Papaverine	IAVI+TAB		63	14	19	7	0,21	OR	0,43	0,13	1,40	
Katoh 1999	Short term unfavourable	IAVI	Papaverine	Medical		4	40	4	19	0,11	OR	9,92	0,50	196,41	
Katoh 1999	Mortality	IAVI	Papaverine	Medical		4	40	1	5	0,46	OR	2,33	0,20	27,03	
Katoh 1999	Short term unfavourable	TAB		Medical		12	40	6	19	1,00	OR	1,11	0,30	4,02	
Katoh 1999	Mortality	TAB		Medical		12	40	0	5	0,58	OR	0,26	0,01	5,01	
Katoh 1999	Neurological deficit improvement	IAVI	Papaverine	TAB		4	12	1	7	0,57	OR	0,24	0,02	3,01	
Katoh 1999	Adverse events	IAVI	Papaverine	TAB		4	12	0	0	1,00	OR	1,00	na	na	
Katoh 1999	Short term unfavourable	IAVI	Papaverine	TAB		4	12	4	6	0,23	OR	9,00	0,40	203,30	
Katoh 1999	Mortality	IAVI	Papaverine	TAB		4	12	1	0	0,25	OR	10,71	0,35	325,25	

Kerz 2012	Short term unfavourable	IAVI	Papaverine	IAVI	Nimodipine	15	15	7	5	0,71	OR	1,75	0,40	7,66	
Kerz 2012	Mortality	IAVI	Papaverine	IAVI	Nimodipine	15	15	0	5	0,04	OR	0,10	0,01	0,,65	
Kerz 2012	Cerebral infarction	IAVI	Papaverine	IAVI	Nimodipine	15	15	8	10	0,71	OR	0,58	0,14	2,46	
Kerz 2012	Angiographic vasospasm improvement	IAVI	Papaverine	IAVI	Nimodipine	138	210	83	69	0,00	OR	3,22	2,09	4,94	
Kerz 2012	Hospital stay	IAVI	Papaverine	IAVI	Nimodipine	15	15	28,3 +- 13,2	26,2 +- 11		DM	2,10	-6,60	10,80	
Kerz 2016	Adverse events	IAVI	Nimodipine	IAVI+TAB		26	21	0	4	0,03	OR	0,09	0,01	0,70	
Khatri 2011	Short term unfavourable	IAVI + TAB		Medical		57	89	19	40	0,17	OR	0,62	0,32	1,22	OR 0,61 IC 95% 0,27-1,39
Khatri 2011	Mortality	IAVI + TAB		Medical		57	89	13	28	0,35	OR	0,65	0,31	1,37	OR 0,63 IC 95% 0,25-1,55
Khatri 2011	Hospital stay	IAVI + TAB		Medical		57	89	15	17	na	na	na	na	na	P=0,32
Kwon 2018	Short term unfavourable	IAVI + Stent	Nicardipine	Stent + IAVI	Nicardipine	5	7	2	2	1,00	OR	1,60	0,16	16,48	
Kwon 2018	Mortality	IAVI + Stent	Nicardipine	Stent + IAVI	Nicardipine	5	7	0	0	na	na	na	na	na	
Kwon 2018	Neurological deficit improvement	IAVI + Stent	Nicardipine	Stent + IAVI	Nicardipine	5	7	3	6	0,52	OR	0,28	0,02	3,60	
Kwon 2018	Mejoría angiográfica	IAVI + Stent	Nicardipine	Stent + IAVI	Nicardipine	14	39	10	32	0,45	OR	0,53	0,12	2,36	
Kwon 2018	Adverse events	IAVI + Stent	Nicardipine	Stent + IAVI	Nicardipine	5	7	1	2	1,00	OR	0,66	0,05	8,32	
Miley 2011	Cerebral ifarction	TAB		TAB		34	51	7	5	0,21	OR	2,41	0,70	8,31	OR 1.7 IC 95% (0.51-5.8) P=.39
Miley 2011	Short term unfavourable	TAB		TAB		10	20	6	5	0,11	OR	4,29	0,91	20,20	
Miley 2011	Mortality	TAB		TAB		10	20	2	4	1,00	OR	1,00	0,15	6,46	
Miley 2011	Adverse events	TAB		TAB		10	20	0	0	na	na	na	a	na	
Mortimer 2014	Long term unfavourable	IAVI + TAB		Medical		17	63	1	11	0,44	OR	0,41	0,09	1,81	
Mortimer 2014	Short term unfavourable	IAVI + TAB		Medical		17	63	9	28	0,59	OR	1,40	0,48	4,08	
Mortimer 2014	Mortality	IAVI + TAB		Medical		17	63	0	2	1,00	OR	0,28	0,01	8,36	
Mortimer 2014	Hospital stay	IAVI + TAB		Medical		17	63	27,1 +- 3,6	21,5 +- 3,4	na	DM	5,60	3,69	7,51	P=0.392

Mortimer 2014	ICU stay	IAVI + TAB		Medical		17	63	20,2 +- 2,7	12,3 +- 2,4	na	DM	7,90	6,49	9,31	P<0.0001
Mortimer 2014	Adverse events	IAVI + TAB		Medical		17	63	1	0	0,21	OR	110,60	0,92	13320,66	
Nakamura 2013	Short term unfavourable	IAVI	Fasudil	Medical		10	11	5	8	0,39	OR	0,40	0,07	2,23	
Nakamura 2013	Mortality	IAVI	Fasudil	Medical		10	11	0	3	0,21	OR	0,12	0,01	1,31	
Nakamura 2013	Cerebral ifarction	IAVI	Fasudil	Medical		10	10	6	8	0,63	OR	0,40	0,06	2,61	
Nakamura 2013	Adverse events	IAVI	Fasudil	Medical		10	11	1	0	0,48	OR	8,17	0,16	413,39	
Nakamura 2013	Short term unfavourable	IAVI	Fasudil	Medical		9	11	7	8	1,00	OR	1,29	0,18	9,38	
Nakamura 2013	Mortality	IAVI	Fasudil	Medical		9	11	4	3	0,64	OR	2,05	0,34	12,39	
Nakamura 2013	Cerebral ifarction	IAVI	Fasudil	Medical		10	10	6	8	0,63	OR	0,40	0,06	2,61	
Nakamura 2013	Adverse events	IAVI	Fasudil	Medical		10	11	3	0	0,09	OR	10,31	0,95	112,35	
Oskouian 2002	Short term unfavourable	IAVI	Papaverine	TAB		12	20	5	8	1,00	OR	1,07	0,25	4,49	
Oskouian 2002	Neurological deficit improvement	IAVI	Papaverine	TAB		12	20	6	9	1,00	OR	1,21	0,30	4,98	
Oskouian 2002	Short term unfavourable	IAVI	Papaverine	IAVI+TAB		20	13	8	5	1,00	OR	1,06	0,26	4,35	
Oskouian 2002	Neurological deficit improvement	IAVI	Papaverine	IAVI+TAB		20	13	9	8	0,48	OR	0,53	0,13	2,08	
Oskouian 2002	Short term unfavourable outcome	TAB		IAVI+TAB		12	13	5	5	1,00	OR	1,14	0,24	5,46	
Oskouian 2002	Neurological deficit improvement	TAB		IAVI+TAB		12	13	6	8	0,70	OR	0,64	0,14	3,00	
Polin 1998	Long term unfavourable	IAVI	Papaverine	Medical		31	62	17	27	0,38	OR	1,57	0,66	3,69	
Polin 1998	Cerebral ifarction	IAVI	Papaverine	Medical		20	54	17	41	0,53	OR	1,70	0,49	5,85	
Polin 2000	Long term unfavourable	TAB +- IAVI		Medical		38	83	18	33	0,44	OR	1,36	0,63	2,96	
Sokolowski 2017	Short term unfavourable	IAVI	Papaverine Verapamil	TAB		100	11	85	8	0,38	OR	2,45	0,46	13,15	P=0.429

Sokolowski 2017	Angiographic vasospasm improvement	IAVI	Papaverine Verapamil	TAB		56	11	52	11	1,00	OR	0,29	0,02	4,28	
Sokolowski 2017	Short term unfavourable	TAB		IAVI+TAB		11	39	8	31	0,69	OR	0,68	0,14	3,36	P=0.429
Sokolowski 2017	Angiographic vasospasm improvement	TAB		IAVI+TAB		11	35	11	35	na	na	na	na	na	P=1
Sokolowski 2017	Short term unfavourable	IAVI		IAVI+TAB		100	39	85	31	0,32	OR	1,49	0,55	4,01	P=0.429
Sokolowski 2017	Angiographic vasospasm improvement	IAVI		IAVI+TAB		56	35	52	35	0,29	OR	0,19	0,02	1,44	
Suzuki 2012	Short term unfavourable	IAVI	Papaverine	IAVI	Colforsin	27	29	18	10	0,03	OR	3,54	1,25	10,01	P=0.032 Good functional outcome Colforsin vs PPV OR 5.61 (IC 95% 1.54-20.43)
Suzuki 2012	Cerebral ifarction	IAVI	Papaverine	IAVI	Colforsin	27	29	23	18	0,05	OR	3,18	0,98	10,29	P=0.039
Suzuki 2012	Adverse events	IAVI	Papaverine	IAVI	Colforsin	27	29	0	0	na	na	na	na	na	
Suzuki 2012	Mortality	IAVI	Papaverine	IAVI	Colforsin	27	29	4	0	0,05	OR	8,27	1,19	67,41	

D. Appendix 4: Summary of findings table (GRADE)

Question: endovascular treatment compared to standard management for cerebral vasospasm in patients with aneurysmal subarachnoid haemorrhage.

Comparison: endovascular treatment versus standard management.

Bibliography: (42,44,62,47,49,50,53,54,58,60,61).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endovascular treatment	Standard management	Relative (95% CI)	Absolute (95% CI)		
Long term unfavorable outcome (follow up: range 3 months to 12 months; assessed with: GOS, mRS)												
6	observational studies	very serious	serious	not serious	serious		62/167 (37.1%)	110/318 (34.6%)	not estimable		-	CRITICAL
Mortality												
7	observational studies	very serious	serious	not serious	serious		24/176 (13.6%)	50/393 (12.7%)	not estimable		-	CRITICAL
Short term unfavorable outcome (at discharge; assessed with: GOS, mRS)												
6	observational studies	very serious	serious	not serious	serious		94/169 (55.6%)	123/237 (51.9%)	not estimable		-	CRITICAL
Cerebral infarction on brain imaging (delayed)												
4	observational studies	serious	serious	not serious	serious		40/83 (48.2%)	64/177 (36.2%)	not estimable		-	CRITICAL

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Endovascular treatment	Standard management	Relative (95% CI)	Absolute (95% CI)		
Adverse events												
4	observational studies	very serious	not serious	not serious	very serious		19/82 (23.2%)	35/171 (20.5%)	not estimable		-	CRITICAL
Angiographic improvement												
1	observational studies	serious	not serious	not serious	not serious		65/72 (90.3%)	8/72 (11.1%)	not estimable		-	CRITICAL

CI: Confidence interval; **GOS**: Glasgow outcome scale; **mRS**: modified Rankin scale.

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