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**ΔΙΑΚΡΑΤΙΚΟ ΜΕΤΑΠΤΥΧΙΑΚΟ ΠΡΟΓΡΑΜΜΑ ΣΠΟΥΔΩΝ:
ΕΝΔΑΓΓΕΙΑΚΕΣ ΤΕΧΝΙΚΕΣ**

**ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ
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ΜΙΛΑΝΟΥ-BICOCCA**

ΔΙΠΛΩΜΑΤΙΚΗ ΕΡΓΑΣΙΑ

ΘΕΜΑ:

Stent assisted coiling of unruptured intracranial aneurysms with wide neck

**ΜΕΤΑΠΤ. ΦΟΙΤΗΤΗΣ:
ΠΑΠΑΔΟΠΟΥΛΟΣ ΦΙΛΙΠΠΟΣ**

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ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ

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«Ενδαγγειακές Τεχνικές»

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Η Τριμελής Εξεταστική Επιτροπή η οποία ορίσθηκε από την ΓΣΕΣ της Ιατρικής Σχολής του Παν. Αθηνών Συνεδρίαση της 13ης Ιανουαρίου 2010 για την αξιολόγηση και εξέταση τ... υποψηφίου κ... ...., συνεδρίασε σήμερα ___/____/2019

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Στην ψηφοφορία για την βαθμολογία ο υποψήφιος έλαβε για τον βαθμό «ΑΡΙΣΤΑ» ψήφους...................., για τον βαθμό «ΛΙΑΝ ΚΑΛΩΣ» ψήφους .... και για τον βαθμό «ΚΑΛΩΣ» ψήφους .... Κατά συνέπεια, απονέμεται ο βαθμός «.....................».

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CONTENTS

1. INTRODUCTION

Incidence of cerebral aneurysms is difficult to be estimated. Range of autopsy prevalence of aneurysms is 0,2-7,9%.Recent studies indicate prevalence of 5%. Ratio of ruptured: unruptured (incidental) aneurysm is 5:3 to 5:6 (rough estimate is 1:1, i.e. 50% of these aneurysms rupture. Only 2% of aneurysms present during childhood.

Reported rates of intraoperative rupture (IAR) range from almost 18% in the cooperative study (1963-1978) to 40% in more recent studies. Morbidity and mortality for patients experiencing significant IAR is approximately 30-35% (vs10% in absence of this complication), although may primarily affects outcome when it occurs during induction of anesthesia or opening of dura.

The exact pathophysiology of the development of aneurysms is still controversial. In contrast to extracranial blood vessels, there is less elastic in the tunica media and adventitia of cerebral blood vessels, the media has less muscle, the adventitia is thinner, and the internal elastic lamina is more prominent. This together with the fact that large cerebral blood vessels lie within the subarachnoid space with little supporting connective tissue may predispose to the development of aneurysms. Aneurysms tend to arise in areas where there is a curve in the parent artery, in the angle between it and a significant branching artery and point in the direction that the parent artery would have continued had the curve not been present. [1]

The etiology of aneurysms may be:

- congenital predisposition (e,g. defect in the muscular layer of the arterial wall, referred to as a medial gap)
- atherosclerotic or hypertensive: presumed etiology of most saccular aneurysms, probably interacts with congenital predisposition described above
- embolic: as in atrial myxoma
- infectious (so called mycotic aneurysms)
- traumatic
- associated with other conditions: autosomal dominant kidney disease, fibromuscular dysplasia (FMD) (prevalence of aneurysms is 7% in renal FMD, 21% in aortocranial FMD), AVM including moyamoya disease, connective tissue disorders: Ehlers-Danlos type iv (deficient collagen type iii,

Marfans'syndrome, familiar intracranial aneurysm syndrome (2 or more relatives, third degree or closer), coarctation of aorta, Osler-Weber-Rendu syndrome, atherosclerosis, bacterial endocarditis.[1]

Location

- Saccular aneurysms, berry aneurysms are usually located on major named cerebral arteries at the apex of branch points which is the site of maximum hemodynamic stress in a vessel.
- More peripheral aneurysms do occur, but tend to be associated with infection (mycotic aneurysms) or trauma.
- Fusiform aneurysms are more common in the vertebrobasilar system.
- Dissecting aneurysms should be categorized with arterial dissection.

Saccular aneurysms location:

❖ 85-95% in carotid system, with the following 3 most common locations:

  i) Anterior communication artery (AcoA) (single most common) 30% [ACoA and Anterior cerebral artery (ACA) are more common in males].

  ii) P-comm 25% (posterior communication artery).

  iii) Middle cerebral artery (MCA) 20%.

  iv) 5-15% in posterior circulation (vertebrobasilar).

    a) 10% on basilar artery (BA): basilar bifurcation, basilar tip, is the most common, followed by BA-SCA (superior cerebellar artery), BA-VA (vertebral artery) junction, AICA (anterior inferior cerebellar artery).

    b) 5% on vertebral artery: VA-PICA (posterior inferior cerebellar artery) junction is the most common.

  v) 20-30% of aneurysms patients have multiple aneurysms. [1]

Presentation of aneurysms [1]

Major rupture is the most frequent presentation

1) Most commonly produces subarachnoid hemorrhage (SAH), which may be accompanied by:

2) Intracerebral hemorrhage: occurs in 20-40% (more common with aneurysms distal to the circle of Willis, e.g MCA aneurysms).

3) Intraventricular hemorrhage: occurs in 13-28% (64% mortality).

- a-comm (anterior communication) aneurysm tends to rupture through the lamina terminalis into the anterior 3rd or lateral ventricles.
- distal basilar artery or carotid terminus aneurysms: may rupture through the floor of the 3rd ventricle.
- distal PICA aneurysms may rupture directly into 4th ventricle through the foramen of Luscka.

4) Mass effect (giant aneurysms compress brain stem producing hemiparesis and cranial neuropathies, a Pcom (posterior communication) or basilar aneurysm causes non-pupil-sparing third nerve palsy, ophthalmic artery aneurysms may compress optic nerve causing visual loss or visual loss is caused due to chiasmal syndromes due to a-comm, basilar apex and ophthalmic aneurysms, intracavernous or supraclinoid aneurysms may cause facial pain syndromes in the ophthalmic or maxillary nerve distribution that may mimic trigeminal neuralgia, endocrine disturbance due to pituitary gland or stalk compression from intra or suprasellar aneurysms).

5) Minor hemorrhage.

6) Small infarcts or transient ischemia due to distal embolization.

7) Seizures.

8) Headache without hemorrhage (has been attributed to aneurysmal expansion, thrombosis, or intramural bleeding, all without rupture), present for>2weeks: unilateral retro-orbital or periorbital, diffuse or bilateral possibly due to mass effect and increased ICP (intracranial cerebral pressure).

9) Incidentally discovered e.g those found on angiography, CT OR MRI obtained for other reasons.

Incidentally or unruptured aneurysms [1]

Incidence of unruptured intracranial aneurysms (UIA) is 5-10% of the population.

UIA merit consideration for treatment since the outcome from SAH with or without surgery is poor even under the best of circumstances. About 65% of patients die from the first SAH and even in patients with no neurologic deficit after aneurysm rupture, only 46% fully recover and only 44% return to their former jobs.

Predictors of rupture

1) ***Patients factors:***
   A) History of previous SAH from a separate aneurysm significantly increases the risk of rupture of an UIA.
   B) Patient age (50yr).
   C) Concurrent medical condition.

2) ***Aneurysm characteristics:***
   A) Location: p-comm, vertebrobasilar/posterior cerebral and basilar tip UIAs are more likely to rupture.
   B) Aneurysm size the most important predictor for future rupture.
   C) Morphology.

3) ***Experience of the surgical team and ancillary services available.***

Aneurysm size:

An estimate for UIA rupture is 1% per year. The risk of bleeding in patients with multiple aneurysms is higher (6,8%) than for patients with single aneurysms(2,3%).

Risk for rupture depends on aneurysm diameter. Estimated annual risk of rupture of aneurysms of diameter <10mm is 0,05% (range 0-4%) and is lower than for diameters >10mm which is 1%. For giant (2,5cm) risk is 6%.

Management recommendations based on aneurysm size:

- Aneurysms >10mm: we have to treat.
- Aneurysms with diameter 7-9mm have to be repaired in young and middle-aged patients.
- Aneurysms < 7mm have to be followed with serial angiography.

Diagnosis can be made with Computed Tomography Angiography (CTA), Magnetic Resonance Angiography (MRA) and Digital Subtraction Angiography (DSA), which is the gold standard since it allows the immediate endovascular treatment.

Treatment options for aneurysms

The best treatment for an aneurysm depends on the condition of the patient, the anatomy of the aneurysm, the ability of the surgeon and must be weighed against the natural history of the condition.

Treatment could be surgical placing a clip across the neck of the aneurysm to exclude it from the circulation without occluding normal vessels. Another way to treat an aneurysm could be trapping (effective treatment requires distal and proximal arterial interruption by direct surgical means, ligation or occlusion with a clip) or vascular by-bass to maintain flow distal to trapped segment. [1]

Alternatively, dramatic advances have occurred in endovascular technology and techniques for the treatment of intracranial aneurysms. The introduction of the Guglielmi coil in 1991 has revolutionized the field (Fig.1).Subsequent development of soft and three-dimensional coil technology has expanded the application of the basic coil occlusion technique.

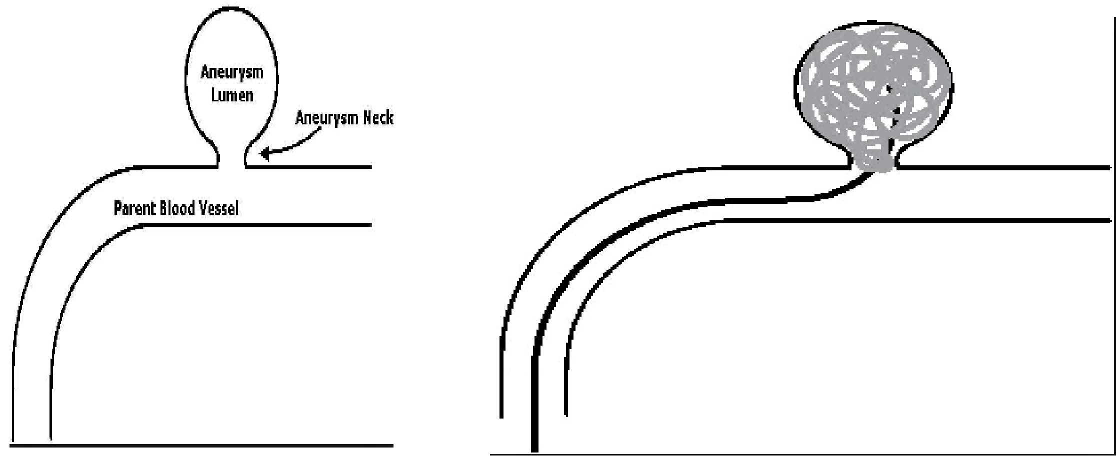

Fig.1 Endovascular treatment of aneurysms with coils

Although endosaccular coiling seems to work best for small to medium-sized aneurysms with narrow necks, successful endovascular treatment of aneurysms with wide necks is now possible because of the addition of balloons and stents to the endovascular armamentarium. The use of stents in conjunction with coils includes the potential for a lower risk for dissection or vessel rupture. The implantation of a stent across the neck area serves a buttress to the coil mass and contributes to changing hemodynamic parameters locally by directing the flow and providing a substrate for endothelization in that area (Fig.2). For example, the approval by the FDA of the

Neuroform microdelivery stent has been greeted with enthusiasm by many practitioners. The availability of a self-expanding stent that can now be placed with reasonable ease in the intracranial vessels is a major advance, and there is no doubt that other similar devices will become available. Given the significant number after coiling especially in large and giant aneurysms with wide necks, other avenues of endovascular treatment were sought. The use of a liquid agent that would be able to obliterate the aneurysm sac completely and seal the neck has significant attractions and has been examined for several years. The liquid non-adhesive embolic agent proposed for this purpose is Onyx. [3,4]

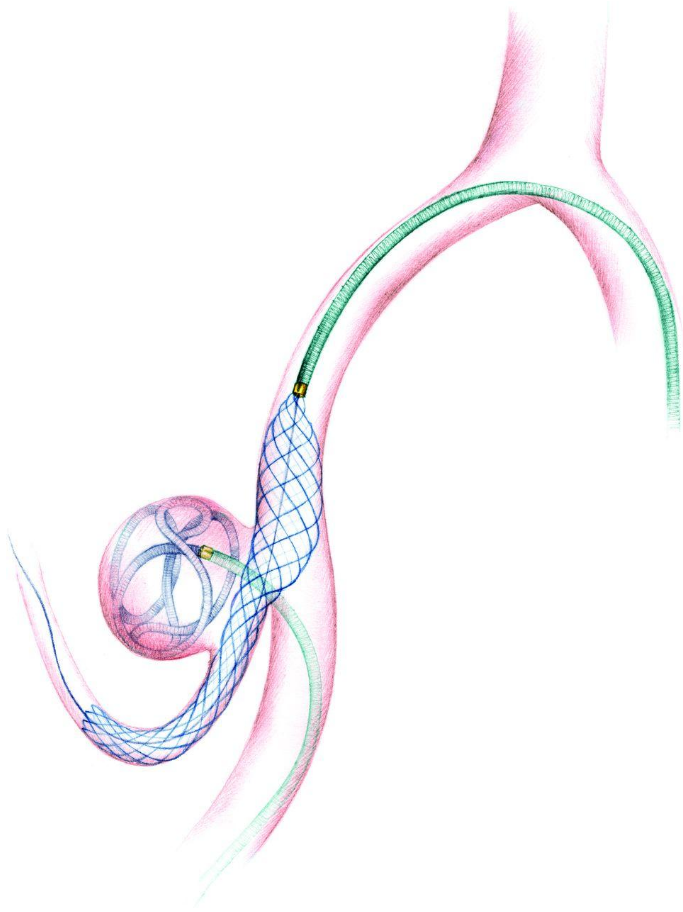

Fig.2Use of stent for coilinga wide neckedaneurysm

Types of coils [2]:

i) The soft coil

ii) The 2D and the 3D coil

iii) The stretch resistant coil

iv) The 360 GDC coil: GDCs are composed of a radio-opaque platinum coil encased in an insulated stainless-steel delivery wire which is less radio-opaque. When a

1Ma electric current passes through the wire, the detachable platinum coil is detached. The coiling technique is based on electrolysis that is used to detach the detachable platinum coil from stainless steel delivery (platinum is not affected by electrolysis) (Fig.3)

v) Bioactive coil (enhances aneurysm healing and decreases recanalization)

vi) HydroCoil is a hybrid hydrogel-platinum coil that can expand up to 11 times its size and has the potential advantage of decreasing the rates of aneurysmal recanalization. Potential complications include delayed hydrocephalus and inflammatory response around the optic nerves.

Fig.3Example of 360°GDC coil

Description of coiling procedure [2,4]:

Under general anesthesia, a sheath is placed in the femoral artery, heparinized saline is infused into the patient and the ICA (internal carotid artery) or VA is catheterized using a soft-tipped 6F catheter. Using the guiding catheter, a diagnostic angiogram is performed and the aneurysm neck is clearly and optimally visualized as well as its relation to adjacent perforating and major arteries. It is particularly important to isolate the aneurysm neck from the parent vessel angiographically so that any coil prolapse into the parent vessel can easily be detected. This often requires the acquisition of multiple oblique views. A coaxial system consisting of a microcatheter and microwire is used to catheterize the aneurysm. The coaxial system and guide catheter are flushed continuously with a solution of saline and heparin to prevent thrombus formation between the two catheters or while the coils are being advanced through the microcatheter. Access to the aneurysm is obtained via the micro-guide wire followed by microcatheter placement. Road mapping is helpful during this part of the procedure. Care is taken to avoid touching the aneurysm wall with tip of the wire or microcatheter. An appropriately sized coil is chosen by matching thee helix radius of the coil to the estimated diameter of the aneurysm. The best choice for the first coil is one that bridges the aneurysm and allows dense homogenous packing of the aneurysm. In principle, the longest coil available to fill as much of the aneurysm sac as possible should be used. The first and the second coils are critical for achieving complete occlusion. The first coil should be placed in a basket-like configuration within the aneurysm. The placement of a second basket coil within the first may provide a more stable configuration for the deposition of subsequent coils. After placement and before detachment of each coil, a control angiogram is obtained with injection of contrast material trough the guide catheter to confirm proper placement of the coil as well as to demonstrate patency of the adjacent arteries. After placement of the initial basket coil or coils, the remaining cavity is filled with smaller diameter coils, which are placed within the loops of the basket to prevent bulging into the parent artery. Coils are deposited until dense packing is achieved or when the aneurysm accepts no more coils. When dense packing is achieved, the microcatheter is removed and a final angiogram assessing aneurysm packing and patency of all vessels is performed. A follow-up DSA or MRA is performed according to local protocols although a 6-month follow-up is the minimum standard.

Wide necked aneurysms (aneurysms with an aspect dome to neck ratio of less than 2 or with a neck size greater than 4mm) can be coiled using balloon assisted techniques or stent assisted coiling (Fig.4).

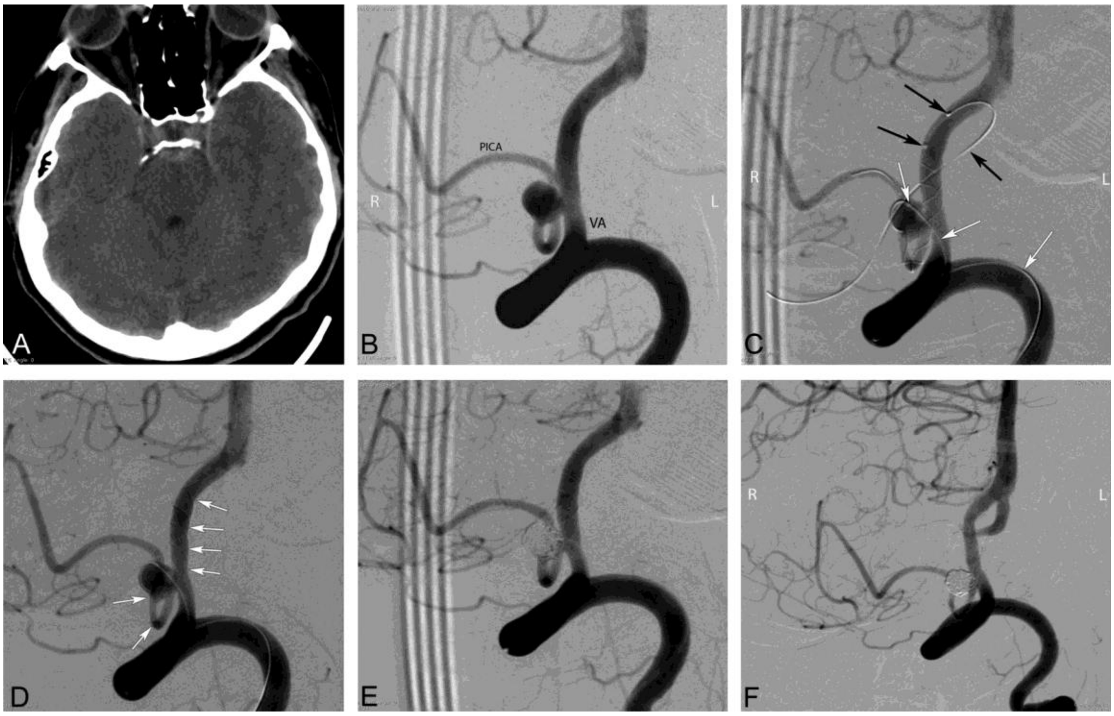

Fig.4 Preprocedural cranial CT and procedural and follow-up angiography images of a 44-year-old female patient with a ruptured PICA aneurysm. **A,** ***Cranial CT image obtained 9 days before the endovascular procedure (5 days following the rupture of aneurysm) shows the subarachnoid hemorrhage in the prepontine cistern.*** **B,** ***DSA image in a right anterior oblique projection reveals a 5-mm wide-neck aneurysm located on the medullary segment of the left PICA.*** **C,** ***DSA images obtained during the procedure show the catheterization of the parent artery for stent placement (*****black arrows*****) from the contralateral (*****right*****) vertebral artery and jailing of the coiling microcatheter (*****white arrows*****) through the ipsilateral (*****left*****) vertebral artery (the small filling defect in the aneurysm sac is a small air bubble introduced by the delivery of coil and trapped between the coil loops).*** **D,** ***DSA image obtained during the procedure shows the successful deployment of a LEO Baby stent (*****arrows*****) into the parent artery (PICA–vertebral artery).*** **E,** ***Immediate postprocedural DSA demonstrates the near-total occlusion of the aneurysm, with minimal filling in the neck.*** **F,** ***Six-month follow-up DSA shows complete occlusion of the aneurysm and a moderate degree of in-stent stenosis.***

Complications [2,4]:

i) Intraprocedural rupture during aneurysm coiling: 2-8%.

ii) Thromboembolic events 3,5-24% (coils and catheters can act as thromboembolism sources.

iii) Coil migration and parent occlusion.

iv) Aneurysm regrowth is 13-20% from incomplete packing.

v) Angiographic vasospasm.

vi) During balloon inflated in case of balloon assisted coiling thromboembolic complications are increased by temporary interruption of blood flow in the parent vessel and intraprocedural rupture increases too due to the increased intra-aneurysmal pressure during balloon inflation. In this case balloon is inflated and hemorrhage is rapidly managed.

vii) In case of stent assisted coiling: A) A neointimal proliferation after stent placement which can result in hemodynamically significant stenosis. B) Occlusion of the perforating arteries may result in ischemia.

Preprocedural medications:

For patients with unruptured and non-acutely ruptured aneurysms scheduled for primary coiling, we routinely administer aspirin for at least 4 days before the procedure. If balloon or stent assisted coiling is anticipated, Clopidogrel is added to the regimen. Intravenous heparin is given just after placement of the introducer sheath, with the aim of obtaining an activated coagulation time in the range of 250 to 300 seconds. For patients with ruptured aneurysms we routinely proceed without administering heparin and antiplatelet agents. If balloon or stent assistance is necessary, we may opt for partially coiling the aneurysm, completing the treatment during the same admission but after the acute phase of rupture has passed (ie. when the patient has recovered neurologically) [4].

1.1 Objective

The aim of this systematically review and meta-analysis was to investigate the clinical outcomes of stent assisted coiling limited to the unruptured intracranial aneurysms with wide neck.We explored the literature in terms of case series, concerning the mortality and the morbidity, the complications, the access and the techniques of the method.

2. METHODS

2.1 Data collection

The meta-analysis was conducted using the Preferred Reporting items for Systematic Reviews and Meta-analysis guidelines. The following medical literature databases were systematically searched: Google Scholar and Pubmed. A snowball process in the reference lists of the eligible articles was performed after retrieval of the relevant articles from search of the databases.

2.2 Search methodology, inclusion and exclusion criteria, and data extraction.

We used the following Medical Subject Headings terms (“stent-assisted coiling intracranial aneurysms wide neck”). We searched for all scientific papers, without gender or language restriction, until January 2019.We investigated studies focusing on stent assisted coiling limited to the unruptured intracranial aneurysms with wide neck for all possible locations. Studies reporting on intracranial aneurysms without wide neck and on ruptured intracranial aneurysms with wide neck were excluded.

Data extracted from eligible studies included the first author’s name, study year, country in which the study was conducted, total number of patients, number of male or female patients, follow-up (months), the mean age of patients, inclusion and exclusion criteria, vascular access (transfemoral), type of anesthesia applied, type of anticoagulation used, type of endograft used and description of complications during follow-up (Table I).

We also extracted the number of patients with outcomes which were described as early and late (Fig. 6-15). Early outcomes were defined as outcomes during the periprocedural period and late ones as those ones happening beyond this period. Periprocedural outcomes included the following: technical success, total obliteration, rupture, neurological events, stroke, and deaths. Postprocedural outcomes included total obliteration, rupture, recanalization rate, deaths, neurological complications, stroke and in stent stenosis.

2.3 Statistical analyses

i) Data synthesis and treatment effects.

The outcome rates in patients with stent assisted coiling in unruptured intracranial aneurysms with wide neck were estimated for each study and reported as the proportion of patients with the corresponding outcome among all patients with stent assisted coiling in UIA with wide neck (Fig.6-15).Values of the concomitant outcomes were subsequently appropriately calculated, expressed as proportions and 95% confidence intervals (CLs) and thereafter transformed into quantities according to the Freeman-Tukey variant of the arcsine square root transformed proportion.The pooled effect estimates were calculated as the back-transformation of the weighted mean of the transformed proportions, using Der Simonian-Laird weights of random effects model and expressed as percentage proportions. One meta-analysis was conducted taking into account all case series.

ii) Heterogeneity and publication bias.

Formal statistical test for heterogeneity using the I^2 test was performed. Publication bias was assesed using the Egger test for small-study effects as well as visual inspection of funnel plots.We used Stata statistical software version 14(StataCorp LP. College Statio, Tex) for the analyses.

3.RESULTS

Study characteristics

We identified 886 potentially eligible studies after a literature search. We excluded a total of 82 duplicate records, as well as 17 articles which referred to in vitro experiments and in vivo ones based on laboratory animals, 76 case reports and 3 articles referred to children. Review of the titles and abstracts evidenced that 201 articles were irrelevant. We also removed 323 articles because they were reviews and not original articles or they did not refer to aneurysms with wide neck. A total of 184 articles were further evaluated. Among them 130 and 28 articles including both of ruptured and unruptured aneurysms with wide neck or only ruptured ones respectively were excluded. Finally, 26 articles were deemed relevant to be included in the systematic review. However, 11 articles were further excluded as they were referred to endovascular treatment of unruptured intracranial aneurysms with wide neck using flow diverters or temporary stent as well as 2 articles because of overlapping population, and eventually 13 articles participated in the meta-analysis corresponding to a total of 976 patients who underwent stent assisted coiling of their unruptured intracranial aneurysms with wide neck (Fig.5).

Baseline study characteristics of the 13 eligible studies included in the systematic review are presented in Table I.The included studies were published from 2005-2017. Among 976 patients included in our systemic review 384 were female (72,6%). For another 447 patients, the gender is not specified. The access vessel was noted in 466 of 976 patients. Among them the device delivery system was advanced transfemorally. Neuroform and Entreprise devices were used in the majority of the patients.The procedure took place under general anesthesia in 460 cases (47,1%), whereas the type of anesthesia was not reported for the remaining patients. The age of the study sample ranged from 18 to 80 years with an average age of 50 years and the median follow-up ranged from 6 months to 2 years. Finally, antiplatelet drugs were routinely administrated during the periprocedural and postprocedural period along with intravenous heparin during procedure (Table I).

3.1 Meta-analysis

Pooled outcomes rates are presented in Figures 6-15. Technical success of the method was 98.43% (95% CI: 95.62-99.95). Technical success was defined as stable device placement and adequate function on computed tomography angiography. Among the other early outcomes, total obliteration-periprocedural was 50.20% (95% CI: 36.09-64.30) and rupture- periprocedural was 0.00% (95% CI: 0.00-0.43) (Fig.6-8).

The pooled rates for total obliteration during follow-up was 63.83% (95% CI: 45.80-80.18) and for overall late rupture was 0.41% (95% CI: 0.00-2.38). However, this figure (0,41%) corresponds to only 4 of 365 patients, whereas the ruptured proportion was not reported for the remaining patients who were followed during postprocedural period. Similarly, pooled in-stent stenosis rate is attributed to only 8 of 261 cases which are referred during follow-up with 1.24% (95% CI: 0.02-3.63) (Fig.9-11).

Finally, total mortality was estimated with a pooled rate of 0.02% (95% CI: 0,00-0,51).Also, overall neurological complications and stroke rates were represented with 4.33% (95% CI: 2.03-7.23) and 3.94% (95% CI: 1.48-7.33) respectively. Regarding recanalization the pooled rate was 7.07% (95% CI: 4.35-10.26) (Fig.12-15).

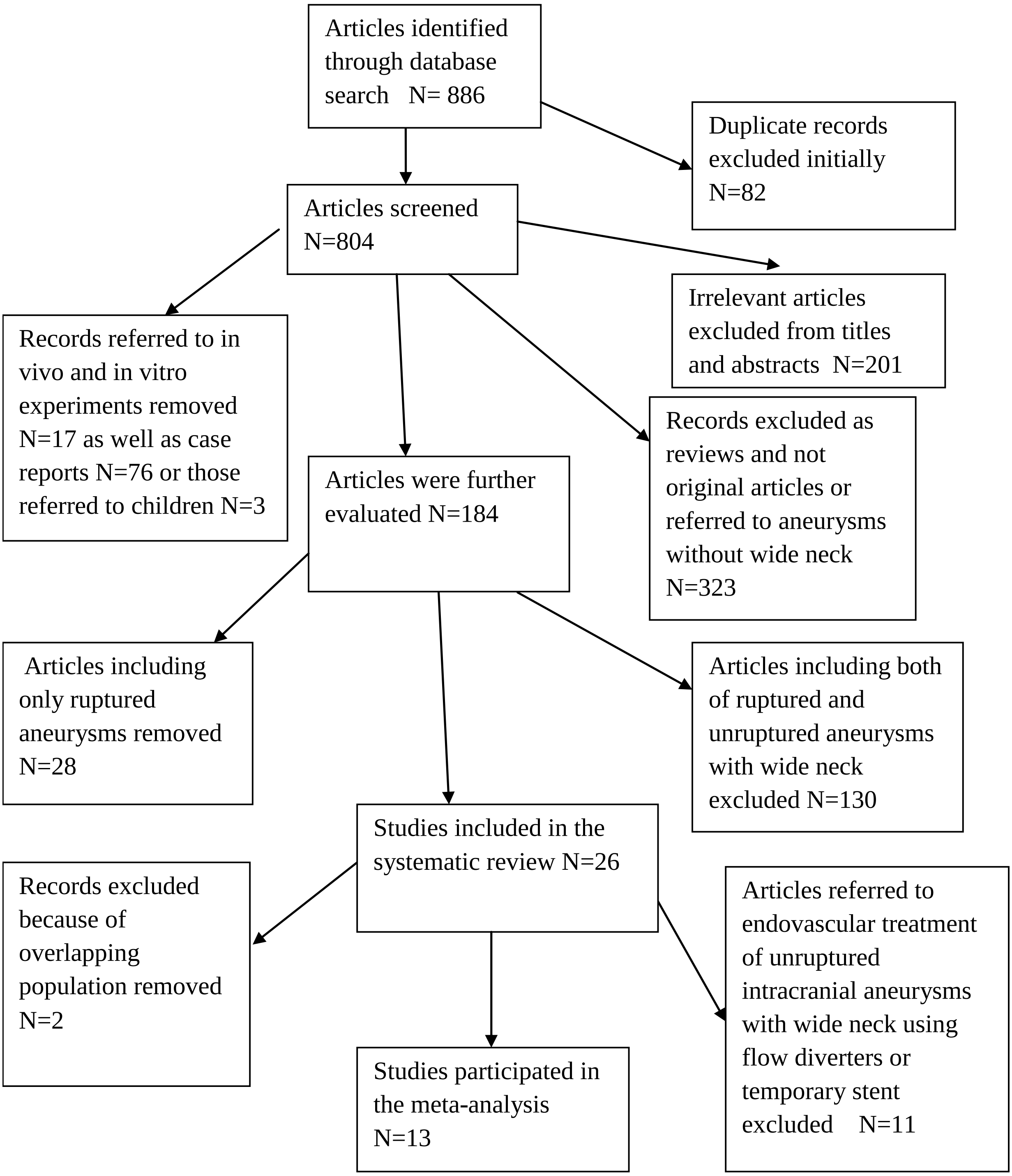

Fig.5 Flow chart of the study selection process for eligible studies in the systematic review and meta-analysis

5. TABLES AND FOREST PLOTS

Table I. Characteristics of case series (N=13) included in the systematic review*(continuing)*

STUDY	STUDY PERIOD	COUNTRY	TOTAL NO OF PATIENTS	MEAN AGE YEARS	GENDERS	DEVICE DELIVERY	GENERAL ANESTHESIA	ANTICO-AGULATION	ENDO-GRAFT USED	FOLLOW UP	ANEURYSM LOCATION	ADDITIONAL TREATMENT	EXCLUDED CRITERIA	INCLUDED CRITERIA
1) Jennifer Frontera 2014	2003-2010 December 2003 until August 2010	USA	116 47 patients underwent SAC* 36 pt coiling 33 pt clipping	55-58	female sac 89% female coil 55%		Yes	aspirin 325mg clopidogrel 75mg 5 days prior to surgery 4000iu heparin intraoperatively redose 1000/h	2003-2006 Neuroform 2007-2010 Entreprise	6 months or 1 year	Supraclinoid ICA Basilar Tip Anterior circulation: 37 SAC Posterior: 9 SAC	Pt with SAC: 7 Pt with COIL: 2 Pt with CLIP: O		UIA with wide neck SAC: 9mm aneurysm size Coil:6,8mm >> Clip: 7,7 mm >>
2)Hwang 2013	2008-2010 November 2008 until December 2010	Korea	116 pt with SAC With 121UIA	55,4 years	Women 87 Men 29	femoral puncture		dual antiplatelet agents 6 months 5 days prior to surgery: aspirin 100mg+clopidogrel75mg 3000iu bolus+1000ui/h during femoral puncture and discontinued after embolization clopidogrel+aspirin for 6 months after surgery	Entreprise	13,4 months with MRA	99aneurysms anterior circulation:81,8% 22 posterior: 18,2% paraclinoid 69pt 57% basilar artery tip 12pt 9,9% pcom 8pt 6,6%	recoiling o,8%	ruptured, fusiform, traumatic or mycotic aneurysms	wide neck UIA Dome to neck<2 or neck > 4mm mean D:7,56+or-4,59mm
3) Hwang 2011	2003-2008 May 2003 Until January 2008	Korea	126UIA 121pt 40pt with SAC	stent group: 56,5+- 10,28 non stent group: 59,4+- 9,83	stent group: male 10 non stent group: male 23		yes	3000IU iv bolus 1000/h antiplatelet medication 5 days prior to procedure	Neuroform Entreprise	2 years	ICA 25pt MCA 2pt ACA 2pt BA 7pt for stent group			UIA, Neck size >4mm dome to neck <1,5 D7,7+-3,06:stent group D 7,5+-2,53:non stent group Neck size: 6,1+-2,36mm: stent group 5,6+-1,82mm: non stent group
4) William E.Thorell 2005		Ohio	7pt			Y-Configuration Dual Stent Assisted Technique		aspirin & clopidogrel 5 days prior to procedure and 3 months after. Aspirin continued for additional 3 months Heparin during procedure and 24h after		DSA 6 months	Basilar Tip			UIA with wide neck

Table I. Characteristics of case series (N=13) included in the systematic review *(continuing)*

STUDY	STUDY PERIOD	COUNTRY	TOTAL NO OF PATIENTS	MEAN AGE YEARS	GENDERS	DEVICE DELIVERY	GENERAL ANESTHESIA	ANTICO-AGULATION	ENDO-GRAFT USED	FOLLOW UP	ANEURYSM LOCATION	ADDITIONAL TREATMENT	EXCLUDED CRITERIA	INCLUDED CRITERIA
5) Wojciech Ponculjsz 2014		Poland MSW hospital	78 pt with SAC			Femoral Approach	Yes	5000IU Heparin iv Bolus Salospir+Clopidogrel 5 days prior to procedure Continued for 3 months followed by salospir only	LVIS stent	6 months CTA OR DSA	59 Anterior circulation 19 Posterior			UIA with wide neck
6) Benjamin Gory 2017	2014-2015 June 2014-October 2015	Europe USA hospital Hospices Civils De Lyon France	19 pt with SAC	63	10 WOMEN 9 MEN		yes	Antiplatelet therapy Salospir+clopidogrel 5 days prior to procedure clopidogrel continued for 3 months salospir for 12 months	PulseRider	6 months				UIA with wide neck Neck size: 5,8mm Dome: 8,8mm
7)ROBERT M STARKE 2014	2006-2012	USA University of Virginia	100pt Dual microcatheter technique (DMT) 160pt SAC	57,9+-1,5 DMT 56,7+-1 SAC		femoral approach		aspirin, plavix 5-7 days prior to treatment heparin bolus clopidogrel or ticlopidin for 3 months aspirin was continued	Entreprise or Neuroform	27+- 18,9 months DSA CTA OR MRA	**SAC:** ACA 4pt ACOM 9pt AICA 1pt anterior choroidal 1pt BA TIP 22pt MCA 10pt		dissecting, fusiform, blister aneurysms	Dome to Neck:<2 Neck d>4mm **SAC:** D:8,2+-4,1mm neck d:4,6+-1,3
8)Benjamin Mine 2014	2004-2012 January 2004-November 20012	Belgium Erasme University	164pt with SAC 183UIA	46	115 women 49 men		yes	5000iu heparin followed by 1500-2500/h aspirin and clopidogrel one day prior to procedure clopidogrel was continued for 1 month while aspirin for 6 months	Entreprise,Leo, Solitaire	in 137 pt mean 26 months DSA: 6, 12 months MRA: 12 months Then MRA for 2 years	MCA 39 ICA 58 ACOM 21 BA 15 VA 9 SCA 5			UIA with wide neck means D:8,4mm

Table I. Characteristics of case series (N=13) included in the systematic review*(continuing)*

STUDY	STUDY PERIOD	COUNTRY	TOTAL NO OF PATIENTS	MEAN AGE YEARS	GENDERS	DEVICE DELIVERY	GENERAL ANESTHESIA	ANTICO-AGULATION	ENDO-GRAFT USED	FOLLOW UP	ANEURYSM LOCATION	ADDITIONAL TREATMENT	EXCLUDED CRITERIA	INCLUDED CRITERIA
9) Arturo Consoli 2014	2004-2012 January 2004- December 2012	Italy Careggi University	268pt 286UIA 117 with stent assisted coiling	56+-10				Salospir, clopidogrel 1 days prior to procedure It was continued for 3 months or 6 months if more than one stent was used aspirin not stopped for pt aged > 50 years	Entreprise or Solitaire	DSA AT 6 months in246 pt	**SAC** 36 ACOM 41 MCA 11 BA 71 ICA Posterior circulation	all recurrences retreated one case two retreatment	Ruptured,dissecting,blister fusiform and those treated with other endovascular techniques size:<3mm 3/286 pt EVT was suspended of difficulty with vascular access	neck >4mm UIA dome to neck rate <1,5
10) David Fiorella 2015	Mach 2012 until November 2012	USA Stony Brook University	31pt with SAC	18-80 average 58,6	23 women			Aspirin, clopidogrel 5 days prior to procedure antiplatelet was continued for 3months iv heparin bolus	LVIS device	6 months	5 posterior circulation the rest anterior			neck> 4mm dome to neck ratio < 2 UIA size: 7,2mm
11) J.C.Gentric 2013	2008-2010 January 2008- April 2010	France	107pt with SAC 107aneurysms	52	Men 33 Women 74	Femoral Approach	Yes	Antiplatelet therapy Clopidogrel via nasogastric tube in 29pt IV Aspirin iv 65pt It was continued for 2 months in 90% mean range was 13,4 weeks for clopidogrel and 32,7 weeks for aspirin	Neuroform	12-18 months	ICA 28% MCA 26,2% PCOM 15%	among 13 residual aneurysms 4 were retreated by additional coiling	Dissecting Fusiform Aneurysms Multiple Aneurysms associated with AVM	Only Neuroform Stent was used UIA with wide neck Dome to neck<2 mean width of aneurysm:6,2mm neck d: 4,5mm
12)I.Saatci 2011			5pt with SAC	44.6	men 2 3 women	bilateral femoral approach	yes	aspirin and clopidogrel one week prior to procedure clopidogrel for 6 months lifelong aspirin	Entreprise, Solitaire	6 months 2pt 2-year control	ACOM			UIA with wide neck 3 aneurysms were small and 2 large>10mm

Table I. Characteristics of case series (N=13) included in the systematic review

STUDY	STUDY PERIOD	COUNTRY	TOTAL NO OF PATIENTS	MEAN AGE YEARS	GENDERS	DEVICE DELIVERY	GENERAL ANESTHESIA	ANTICO-AGULATION	ENDO-GRAFT USED	FOLLOW UP	ANEURYSM LOCATION	ADDITIONAL TREATMENT	EXCLUDED CRITERIA	INCLUDED CRITERIA
13)S.W.Hetts 2014		California San Francisco	361pt UIA AMONG UIA 158pt had wide neck>4mm Among pt with wide neck: 85pt received stent and coil and 73 coil	18-80				antiplatelet use	137pt were treated Neuroform	1 year			ruptured, those with protocol violation, lost to follow up	UIA with wide neck stent-coiled aneurysms had wider neck >4mm vs coiling only and lower dome to neck ratios 1,3 vs 1,8

SAC: Stent Assisted Coiling
ICA: Internal Carotid Artery
MCA: Middle Cerebral Artery
ACA: Anterior Cerebral Artery
Pcom: Posterior Communication Artery
ACOM: Anterior Communication Artery
BA: Basilar Artery
VA: Vertebral Artery
SCA: Superior Cerebellar Artery
AICA: Anterior Inferior Cerebellar Artery
UIA: Unruptured Intracranial Aneurysms
EVT: Endovascular Treatment

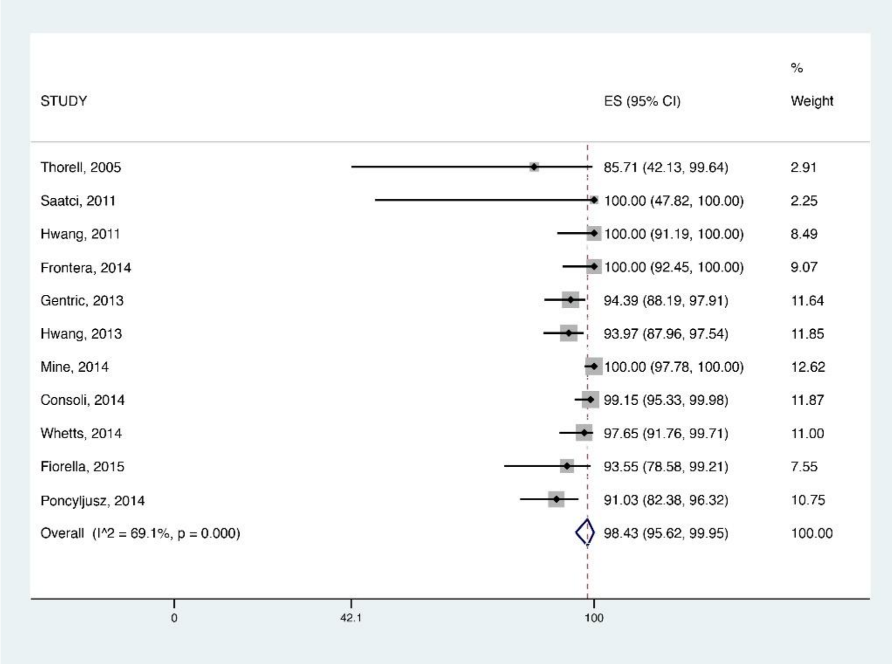

Fig.6 Forest plot presenting the meta-analysis of technical success based on event rates for case series. Event rates in the individual studies are presented as squares with 95% confidence intervals (CLs) presented as extending lines. The pooled event rate with its 95% CI is depicted as a diamond. ES, Effect size.

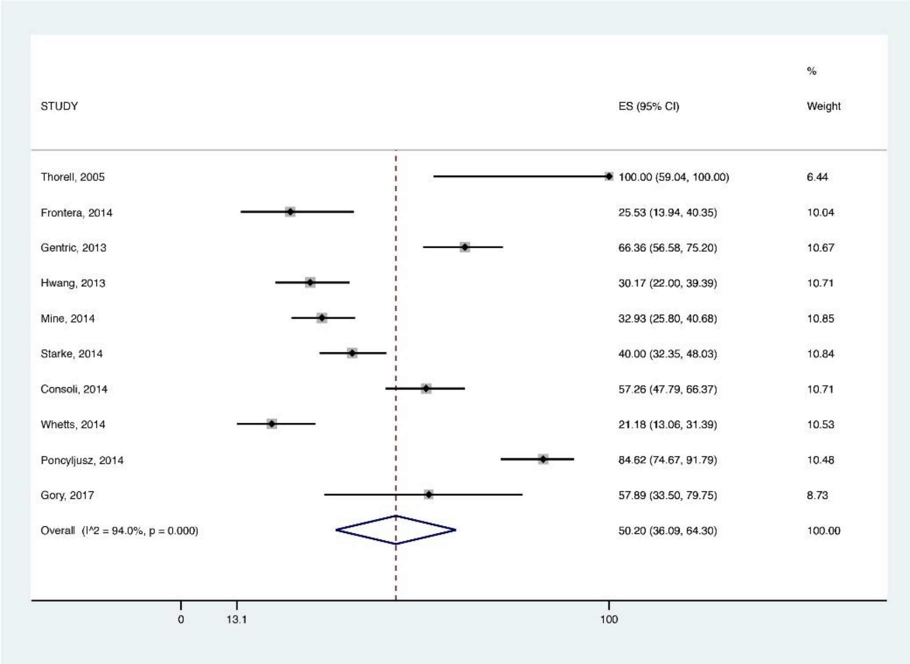

Fig.7 Forest plot presenting the meta-analysis of periprocedural obliteration based on event rates for case series. Event rates in the individual studies are presented as squares with 95% confidence intervals (CLs) presented as extending lines. The pooled event rate with its 95% CI is depicted as a diamond. ES, Effect size.

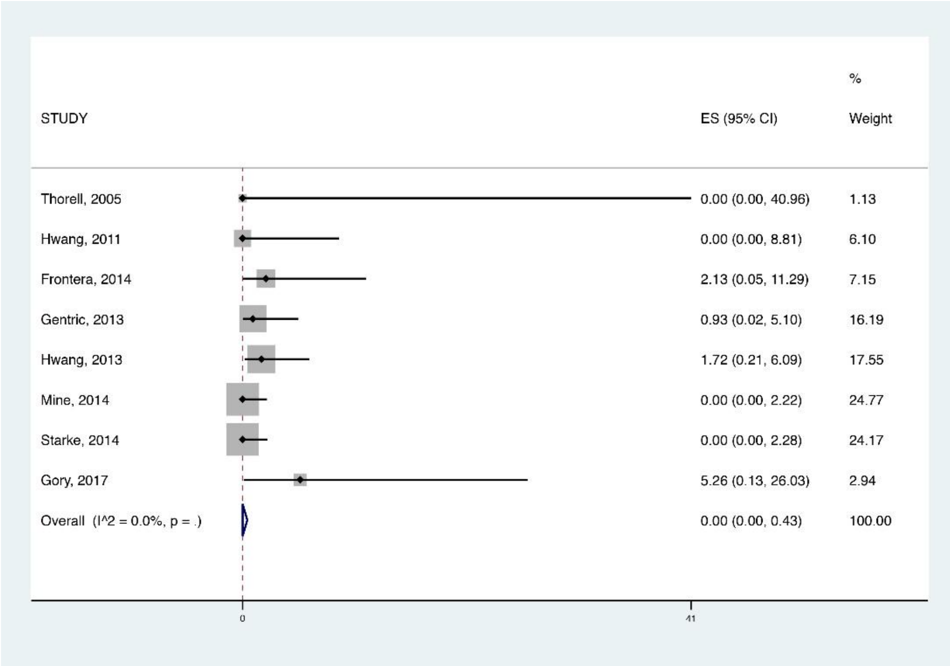

Fig.8 Forest plot presenting the meta-analysis of periprocedural rupture based on event rates for case series. Event rates in the individual studies are presented as squares with 95% confidence intervals (CLs) presented as extending lines. The pooled event rate with its 95% CI is depicted as a diamond. ES, Effect size.

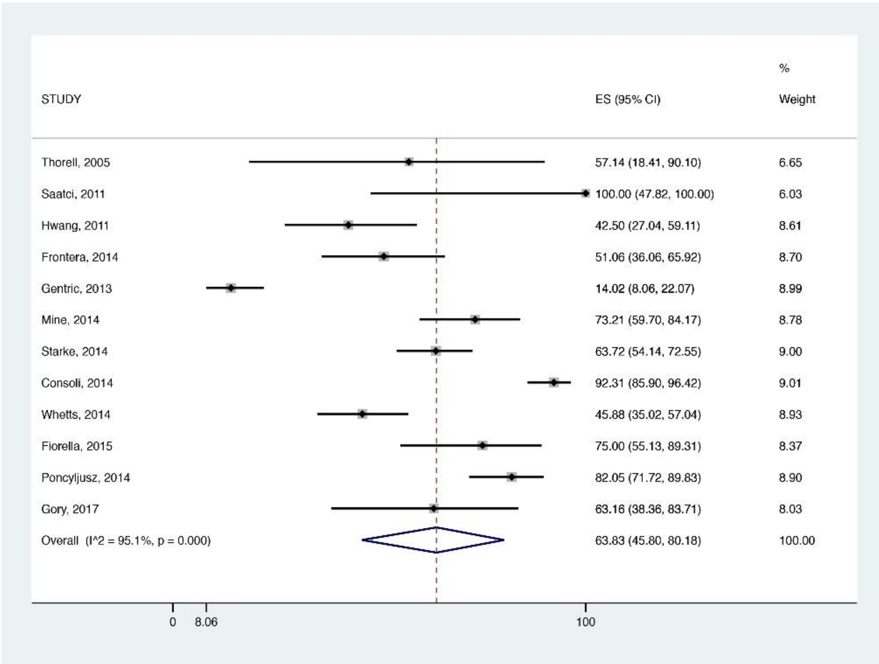

Fig.9 Forest plot presenting the meta-analysis of obliteration during follow up based on event rates for case series. Event rates in the individual studies are presented as squares with 95% confidence intervals (CLs) presented as extending lines. The pooled event rate with its 95% CI is depicted as a diamond. ES, Effect size.

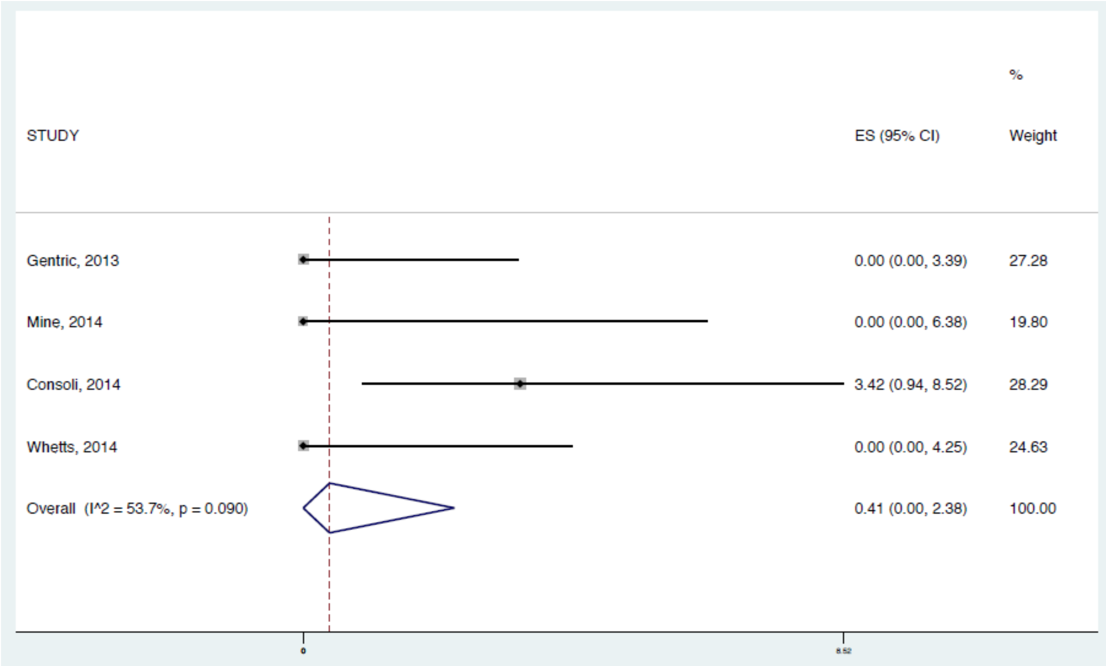

Fig.10 Forest plot presenting the meta-analysis of rupture during follow up based on event rates for case series. Event rates in the individual studies are presented as squares with 95% confidence intervals (CLs) presented as extending lines. The pooled event rate with its 95% CI is depicted as a diamond. ES, Effect size.

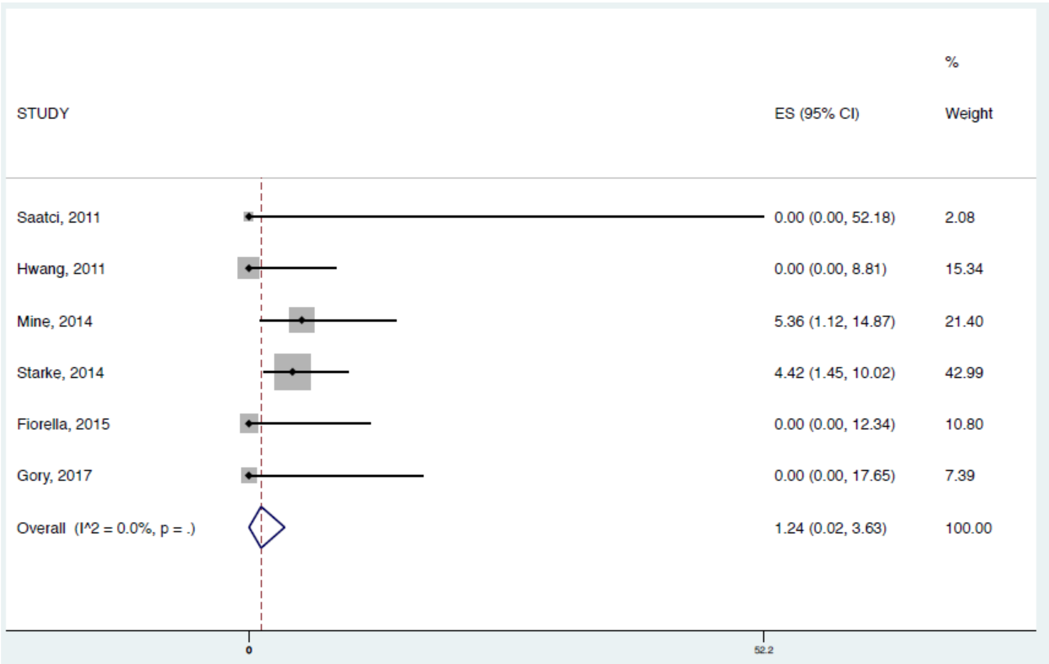

Fig.11 Forest plot presenting the meta-analysis of in-stent stenosis based on event rates for case series. Event rates in the individual studies are presented as squares with 95% confidence intervals (CLs) presented as extending lines. The pooled event rate with its 95% CI is depicted as a diamond. ES, Effect size.

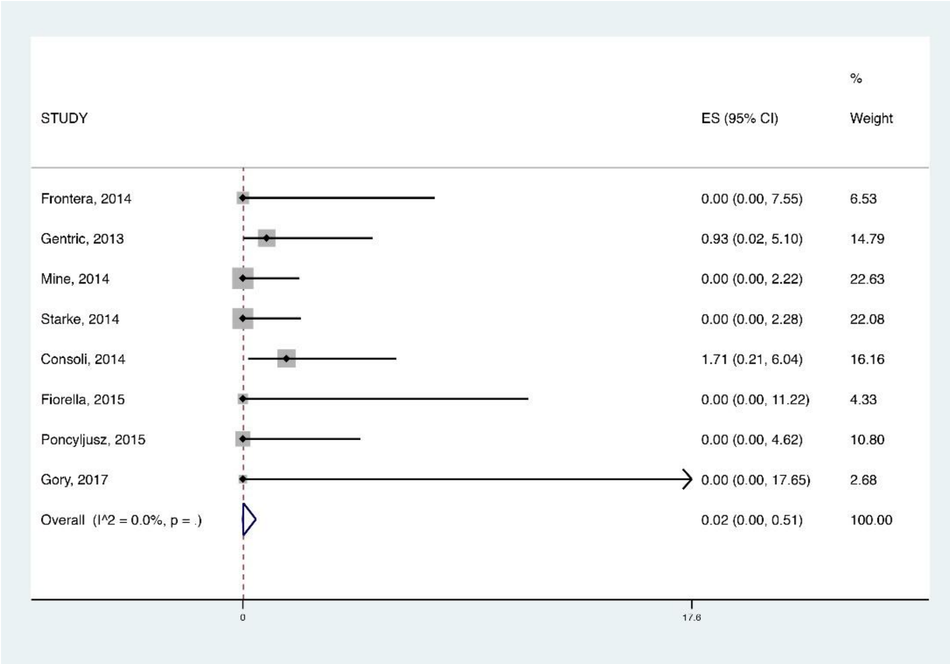

Fig.12 Forest plot presenting the meta-analysis of mortality based on event rates for case series. Event rates in the individual studies are presented as squares with 95% confidence intervals (CLs) presented as extending lines. The pooled event rate with its 95% CI is depicted as a diamond. ES, Effect size.

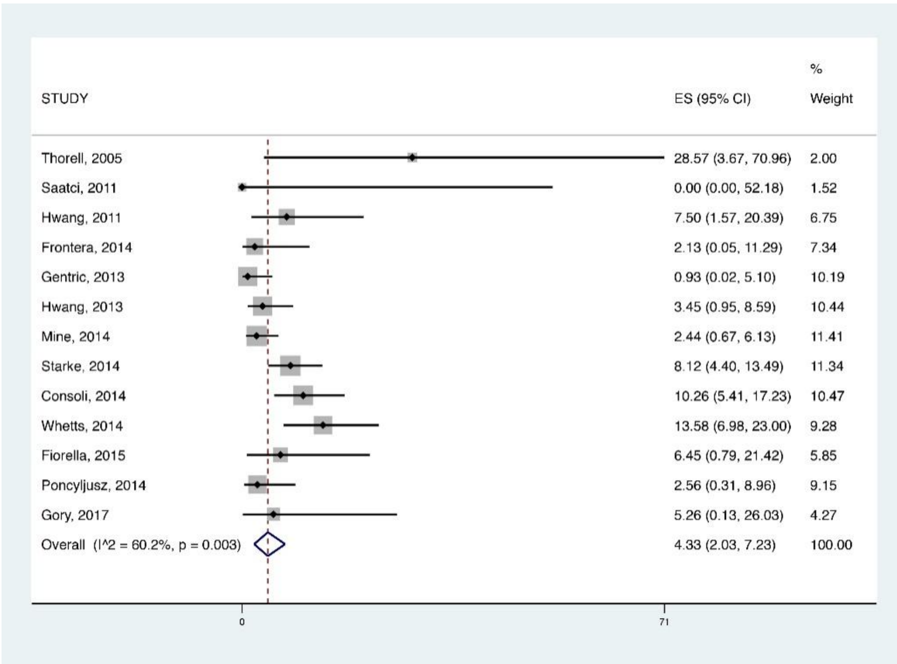

Fig.13 Forest plot presenting the meta-analysis of neurological complications based on event rates for case series. Event rates in the individual studies are presented as squares with 95% confidence intervals (CLs) presented as extending lines. The pooled event rate with its 95% CI is depicted as a diamond. ES, Effect size.

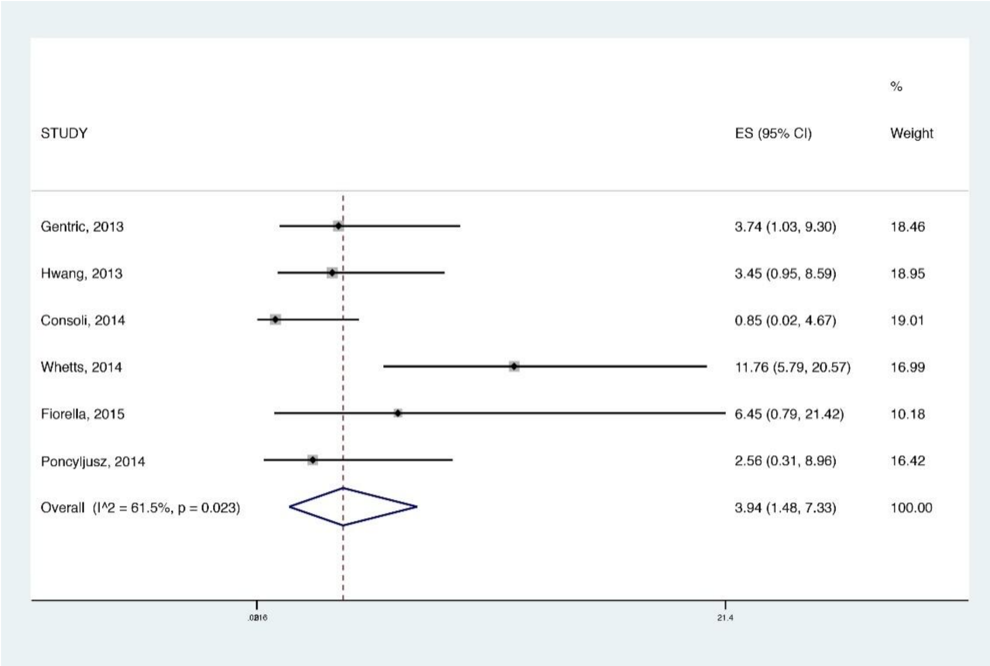

Fig.14 Forest plot presenting the meta-analysis of stroke based on event rates for case series. Event rates in the individual studies are presented as squares with 95% confidence intervals (CLs) presented as extending lines. The pooled event rate with its 95% CI is depicted as a diamond. ES, Effect size.

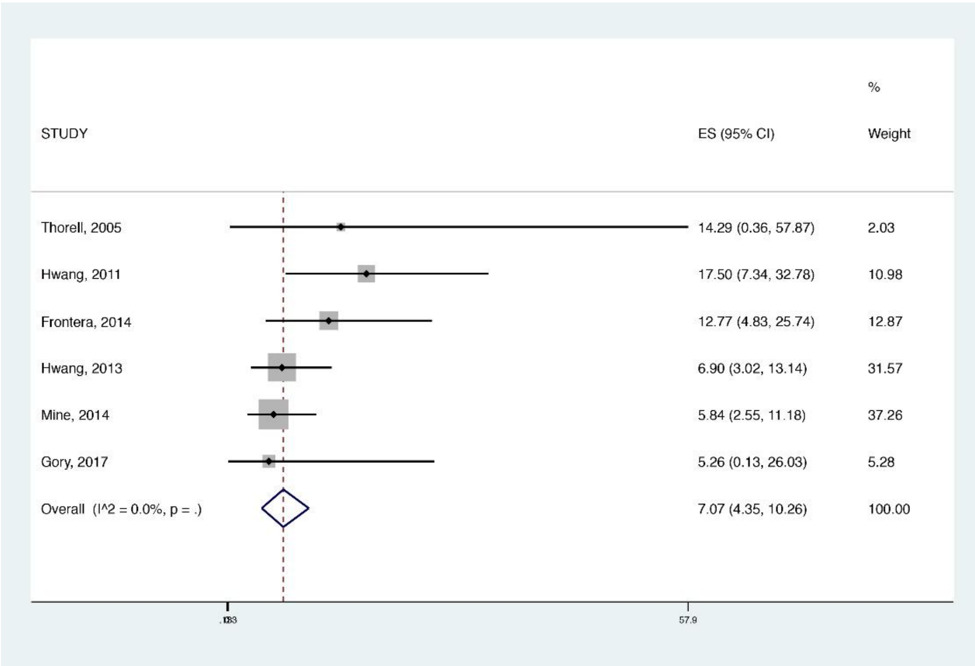

Fig.15 Forest plot presenting the meta-analysis of recanalization based on event rates for case series. Event rates in the individual studies are presented as squares with 95% confidence intervals (CLs) presented as extending lines. The pooled event rate with its 95% CI is depicted as a diamond. ES, Effect size.

5. DISCUSSION

The meta-analysis derived from a comprehensive review of 13 case series and provided pooled outcome rates for patients treated with stent assisted coiling for intracranial aneurysms with wide neck. Although high risk patients constituted our study cohort, a high technical success rate of 98.43% was recorded.

Concerning anatomical results, our rate of immediate complete occlusion is lower (50.20%) than in meta-analyses for stand-alone coiling (86,1%) [18].This can be explained by the fact that coil packing after stent placement maneuverability and the use of dual antiplatelet therapy and heparin during the procedure may limit thrombosis around coil mass. The low rates of complete occlusion show difficulties of stent assisted coiling in relation to aneurysmal morphology such as the size and localization. Despite relatively unsatisfying immediate anatomical results, a 63,83% rate of complete occlusion was achieved at follow-up. Several hypotheses may explain this progressive thrombosis. First, computational and animals have showed that conventional self-expanding stents induce a reduction of the flow velocity to the aneurysm and secondary wall shear stress [20-23]. Intracranial stents also induce an arterial angular remodeling with migration and narrowing of the flow impingement zone and a decrease in apical pressure. The straightening induced by stent placement could also modify the inflow to the sac and promote thrombosis [24]. Finally, the stent struts bridging the aneurysmal neck may serve as a bioactive scaffold for neointimal growth [25].For the same reasons that promote progressive aneurysm occlusion, the rate of recanalization of intracranial aneurysms by stent assisted coiling is low as confirmed by our studies (7,07%). This rate is significantly lower than in meta-analyses for a stand-alone coiling (24,4%) [18].

The mortality and neurological complication rates (0.02% and 4,33% respectively) that we report also compare favorably with those reported in meta-analysis for stand-alone coiling (1,2% and 4,8% respectively) and for clipping (1,7% and 6,7% respectively) [18,19].Regarding frequency of stroke, this was a mere 3,94%. Several factors may explain our low rate of stroke. Firstly, patients followed a string and strong antiplatelet protocol. Second, as we expect a progressive thrombosis of the sac thanks to the stent, we do not take higher risks to obtain an immediate occlusion or a very dense packing. Third, we did not include ruptured intracranial aneurysms that may be associated with high risk of stroke, since subsequent subarachnoid hemorrhage (SAH) causes vasospasm [4]. Furthermore, in the setting of SAH, the interventional neuro-radiologists usually try to obtain a denser packing to achieve complete occlusion and minimize the risk of re-bleeding. Therefore, the risk of coil protrusion at the neck or in the parent artery, potentially resulting in thromboembolic events (TE), might be higher than in unruptured aneurysms. Finally, the availability of the intracranial stents probably contributes to decrease the rate of symptomatic TE complications of coiling alone as a rescue therapy in case of coil protrusion or instability and clot formation at the neck [26].

In our series, we did not observe intraprocedural aneurysmal ruptures, while this rate was 2,6% according the meta-analyses for stand-alone coiling [18].This 0% rate of aneurysmal rupture may be partially related to the fact that, when possible, we do not place the guide wire in the sac but try to gently advance the microcatheter through the stent. It is worth noting that the overall late rupture was only 0,41%, which could be explained partially by the fact that additional treatment with coils was decided in some cases [13] and the discontinuance of the antiplatelet therapy after some months according the protocols.

In stent stenosis is a well-known complication of stenting for atheromatous stenosis secondary to endothelial and fibroelastic reaction. Although self-expanding stents used for stent assisted coiling (SAC) induce minor intimal damage, this phenomenon somehow occurs and probably contributes to stabilize or improve the occlusion of intracranial aneurysms with SAC. However, it may also induce some degree of intrastent stenosis, which in our series is rare (1.25%).

It seems that stent tolerance should not be a major concern anymore when physicians discuss the choice of SAC. The remaining limitation of SAC is related to the doubled antiplatelet therapy that should be maintained at least one month but further technical developments will probably assess this limitation by providing coated or even resorbable stents [5].

These results suggest that SAC represents a major technical evolution in the endovascular management of intracranial aneurysms (IA). It is associated with a low mortality and morbidity rate allowing a safe treatment of wide-necked unruptured IA. The total number of 976 patients included in our systemic review increase the power of the results.

5.1 Limitations

There are several limitations of this study. Firstly, in the meta-analysis we included mainly retrospective studies that did not directly compare different techniques. Secondly, follow-up images were homogenous as they were mainly MRA and DSA. However, MRA has been reported to be highly effective and reliable for the follow-up of SAC [27]. Thirdly, heterogeneous aneurysm morphology and location can contribute to treatment bias, since they are related with difficulties of endovascular techniques (Table I). Similarly, modality of treatment including different choice of stents by physicians in different institutions is related with treatment bias (Table I). Other limitations of the eligible studies included in the meta-analysis are that not all patients complied with treatment during follow up along with the fact that some results are attributed to small number of cases, which are referred during follow-up. These two aforementioned limitations might have been an indirect publication bias in our study.

Finally, in our series, morbidity is associated with thromboembolic events. This may reflect the importance of adequate antiplatelet agent preparation before and even after the successful procedure. Practically, checking for antiplatelet agent resistance on a regular basis would be helpful, but it was not available in the eligible studies.

6. CONCLUSIONS

Our review and meta-analysis pooled together outcome rates of relevant studies and highlighted the feasibility and safety of stent assisted coiling of unruptured intracranial aneurysms (UIA) with wide neck. SAC is a relatively new technique and we might need more experience before sound conclusions can be drawn. Although, it is early to generalize the results, the first impression is that this technique might be promising for the treatment of UIA with wide neck. Even if immediate anatomical results are relatively unsatisfying in our study, mid- and long-term follow-up show a major improvement with a high rate of adequate occlusion that is stable over time. Moreover, the long term clinical and angiographic tolerance of intracranial stents was excellent. Stent assisted coiling represents an acceptable alternative to surgical clipping.

ΠΕΡΙΛΗΨΗ

Σκοπός: Η συχνότητα των ανευρυσμάτων είναι δύσκολο να εκτιμηθεί. Η συχνότητα τους στις αυτοψίες είναι 0,2-7,9%. Πρόσφατες μελέτες υποδεικνύουν ένα ποσοστό της τάξεως του 5%. Το ποσοστό διεγχειρητικής τους ρήξης (40%) σχετίζεται με υψηλό ποσοστό νοσηρότητας και θνησιμότητας το οποίο είναι 30-35%. Στις μέρες μας, οι ενδοαγγειακές τεχνικές, κυρίως ο εμβολισμός με σπειράματα και ο υποβοηθούμενος από νάρθηκα εμβολισμός με σπειράματα χρησιμοποιούνται ευρέως. Διεξήγαμε μια συστηματική ανασκόπηση και μετα-ανάλυση προκειμένου να ερευνήσουμε το ρόλο του υποβοηθούμενου από νάρθηκα εμβολισμού με σπειράματα μη ραγέντων ενδοκράνιων ανευρυσμάτων με φαρδύ αυχένα (Stent assisted coiling of unruptured intracranial aneurysms with wide neck).

Μεθοδολογία: Η τρέχουσα μετα-ανάλυση διεξήχθη χρησιμοποιώντας τα προτιμώμενα στοιχεία αναφοράς για οδηγίες συστηματικής ανασκόπησης και μετα-ανάλυσης. Ερευνήσαμε τα βασικά χαρακτηριστικά των ασθενών μαζί με τα περιεγχειρητικά και τα μετεγχειρητικά αποτελέσματα μετά του υποβοηθούμενου από νάρθηκα εμβολισμού με σπειράματα μη ραγέντων ενδοκράνιων ανευρυσμάτων με φαρδύ αυχένα. Σε αυτή την ανασκόπηση 13 μελέτες συμπεριελήφθησαν και οι συγκεντρωμένες αναλογίες με διαστήματα αξιοπιστίας (confidence intervals, CI) 95% από τα ποσοστά αποτελεσμάτων υπολογιστήκαν.

Αποτελέσματα: Οι συμπεριλαμβανόμενες μελέτες δημοσιεύτηκαν από το 2005-2017. Μεταξύ των 976 ασθενών με μέσο όρο ηλικίας 50 ετών που συμπεριελήφθησαν στην συστηματική μας ανασκόπηση 384 ήταν γυναίκες (72,6%). Για τους άλλους 447 ασθενείς το φύλλο δεν διευκρινίστηκε. Η συσκευή προωθήθηκε κυρίως μέσω της μηριαίας αρτηρίας (το αγγείο προσέγγισης σημειώθηκε στους 466 από τους 976 ασθενείς) και η διαδικασία διεξήχθη υπό γενική αναισθησία στους μισούς σχεδόν ασθενείς. Η τεχνική επιτυχία της μεθόδου ήταν 98.43 % (95% CI: 95.62-99.95). Τα άμεσα αποτελέσματα συμπεριλάμβαναν την ολική απόφραξη περιεγχειρητικά με 50.20% (95% CI: 36.09-64.30) και την περιεγχειρητική ρήξη με 0.00% (95% CI: 0.00-0.43). Ο μέσος όρος παρακολούθησης των ασθενών κυμαινόμενος από 6 μήνες ως 2 χρόνια έδειξε ότι η ολική μετεγχειρητική απόφραξη ήταν 63.83% (95% CI:

45.80-80.18) και η συνολική καθυστερημένη ρήξη ήταν 0.41% (95% CI: 0.00-2.38).Το συγκεντρωμένο ποσοστό στένωσης του ενδονάρθηκα ήταν 1.24% (95% CI: 0.02-3.63). Εκτιμήσαμε επίσης το συγκεντρωμένο ποσοστό της τάξεως του 0.02% (95% CI: 0,00-0,51) and 4.33% (95% CI. 2.03-7.23) για την ολική θνησιμότητα και τις συνολικές νευρολογικές επιπλοκές αντίστοιχα όπως επίσης και το ποσοστό της τάξεως του 3.94% (95% CI. 1.48-7.33) για το έμφρακτο. Τελικά η επανασηραγγοποίηση του ανευρύσματος (recanalization) καταγράφηκε σε ποσοστό 7.07% (95% CI: 4.35-10.26).

Συμπεράσματα: Ο υποβοηθούμενος από νάρθηκα εμβολισμός με σπειράματα (Stent assisted coiling) μη ραγέντων ενδοκράνιων ανευρυσμάτων με φαρδύ αυχένα φαίνεται να είναι ασφαλής και αποδεκτή εναλλακτική μέθοδος της χειρουργικής θεραπείας. Ακόμη και αν τα άμεσα ανατομικά αποτελέσματα είναι σχετικά μη ικανοποιητικά στη μελέτη μας, η μεσοπρόθεσμη και μακροπρόθεσμη παρακολούθηση δείχνει μείζων βελτίωση με ένα ικανοποιητικό ποσοστό απόφραξης το οποίο είναι σταθερό με την πάροδο του χρόνου.

ABSTRACT

Objective: Incidence of cerebral aneurysms is difficult to be estimated. Range of autopsy prevalence of aneurysms is 0,2-7,9%.Recent studies indicate prevalence of 5%. Their intraoperative rupture rate (40%) is associated with high morbidity and mortality rate which is 30-35%. Nowadays, endovascular techniques, mainly coil embolization and stents in conjunction with coils are highly used. We conducted a systematic review and meta-analysis to investigate the role of stent assisted coiling for unruptured intracranial aneurysms with wide neck.

Methods: The current meta-analysis was conducted using the Preferred Reporting items for Systematic Review and meta-analyses guidelines. We investigated patients' baseline characteristics along with periprocedural and postprocedural outcomes after stent assisted coiling limited to unruptured intracranial aneurysms with wide neck. In this review 13 studies were included and pooled proportions with 95% confidence intervals (CLs) of outcome rates were calculated.

Results: The included studies were published from 2005-2017. Among 976 patients with a mean age of 50 years included in our systemic review 384 were female (72,6%).For another 447 patients' gender is not specified. The device was usually delivered though femoral artery (the access vessel was noted in 466 of 976 patients) and the procedure took place under general anesthesia in nearly half of the patients. Technical success of the method was 98.43 % (95% CI: 95.62-99.95). Immediate outcomes included total obliteration- periprocedural with 50.20% (95% CI: 36.09-64.30) and rupture- periprocedural with 0.00% (95% CI: 0.00-0.43). The median follow-up ranged from 6 months to 2 years showed that total postprocedural obliteration was 63.83% (95% CI: 45.80-80.18) and overall late rupture was 0.41% (95% CI: 0.00-2.38). The pooled in-stent stenosis rate was 1.24% (95% CI: 0.02-3.63). We also estimated a pooled rate of 0.02% (95% CI: 0,00-0,51) and 4.33% (95% CI: 2.03-7.23) for total mortality and overall neurological complications respectively as well as 3.94% (95% CI: 1.48-7.33) for stroke. Finally, recanalization was recorded in 7.07% (95% CI: 4.35-10.26).

Conclusions: Stent assisted coiling of unruptured intracranial aneurysms with wide neck seems to be safe and an acceptable alternative to surgical clipping. Even if immediate anatomical results are relatively unsatisfying in our study, mid- and long-term follow-up show a major improvement with a high rate of adequate occlusion that is stable over time.

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