



# Arachnoid Plasty to Prevent and Reduce Chronic Subdural Hematoma after Clipping Surgery for Unruptured Intracranial Aneurysm : A Meta-Analysis

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**Objective :** Recent studies have reported that arachnoid plasty (ARP) using gelatin sponges with fibrin glue reduced the occurrence of chronic subdural hematoma (CSDH) following clipping surgery for unruptured intracranial aneurysm (UIA). This meta-analysis was conducted to collate further evidence for the efficacy of ARP in preventing postoperative CSDH.

**Methods :** Data of patients who underwent clipping surgery were extracted from PubMed, EMBASE, and Cochrane Central Register of Controlled Trials by two independent reviewers. A random effects model was used to investigate the efficacy of ARP by using odd ratios (ORs) and 95% confidence intervals (CIs). A meta-regression analysis for male sex was additionally performed.

**Results :** Data from six studies with 1715 patients were consecutively included. Meta-analysis revealed that ARP was significantly associated with lower rates of CSDH development after surgical clipping for UIA (ARP group vs. control group : 3.2% vs. 7.2%; OR, 0.40; 95% CI, 0.18–0.93;  $I^2=44.3\%$ ;  $p=0.110$ ). Meta-regression analysis did not highlight any modifying effect of the male sex on postoperative CSDH development ( $p=0.951$ ).

**Conclusion :** This meta-analysis indicated that ARP reduced the incidence rates of CSDH following clipping surgery for UIA. If feasible, ARP would be implemented as an additional surgical technique to prevent postoperative CSDH development during surgical clipping of UIA.

**Key Words :** Aneurysm · Surgery · Hematoma, Subdural, Chronic · Arachnoid.

## INTRODUCTION

Surgical clipping is an effective treatment modality for unruptured intracranial aneurysm (UIA). Overall advancements in microsurgical techniques have markedly reduced postoperative complications. However, chronic subdural hematoma (CSDH) is one of the challenging postoperative complications

for UIA clipping<sup>13,15</sup>, and the incidence of CSDH development after the surgery ranges from 0.9% to 5.1%<sup>3,11,15,16</sup>. Although postoperative CSDH shows a relatively benign clinical course with spontaneous resolution, it sometimes required surgical treatment to relieve mass effect.

There are many known risk factors for CSDH after surgical clipping, such as age, brain atrophy, anticoagulant medication,

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and postoperative subdural air; however, its underlying mechanism remains poorly understood<sup>3,6,8,16</sup>. Recent studies reported that increased subdural fluid collection could also be a significant risk factor for postoperative CSDH<sup>14,16</sup>. Previous studies have reported that arachnoid plasty (ARP) with fibrin glue and gelatin sponge has been helpful in the prevention of postoperative CSDH via reducing subdural fluid collection. However, the effectiveness of ARP has not been fully validated<sup>7,8,11-14,20</sup>.

Therefore, we aimed to collate the available evidence on the efficacy of ARP in prevention of CSDH after surgical clipping of UIA with a meta-analysis of the relevant clinical studies.

## MATERIALS AND METHODS

A study of this type, such as meta-analysis, does not require informed consent or Institutional Review Board's approval. This study was conducted and documented in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines (Supplementary Table 1). The supplementary material describes the methods of this study in detail.

### Data sources and searches

PubMed, EMBASE, the Cochrane Central Register of Controlled Trials, and relevant web sites were systematically searched for relevant articles including randomized controlled trials and retrospective observational studies. The organized search strategy was established per the Population, Intervention, Comparison and Outcome (PICO) format<sup>17</sup> with systematic and concrete terms supplemented with keywords (Supplementary Table 2). Additional electronic search strategy was complemented by a manual screening of bibliographies of full-text articles such as recent reviews, editorials, and meta-analyses. There were no restrictions on the language of publication, study period, or sample size.

### Eligibility criteria and study selection

The articles identified by the search strategy were subjected to the following inclusion criteria : 1) enrolled patients who underwent surgery with clipping for UIA; 2) surgery with craniotomy such as the pterional or supraorbital approach; 3) patients with additional ARP closing the sylvian cistern after an-

eurysmal repair; 4) studies presenting CSDH development as the outcome regardless of ARP implementation; and 5) articles presenting controls as patients with unexecuted ARP. We excluded studies that : 1) were technical notes, case reports, conference abstracts, study protocols, or editorial letters; 2) enrolled patients who underwent surgery for ruptured intracranial aneurysm (RIA); 3) included participants having non-aneurysmal subarachnoid hemorrhage or intracerebral hemorrhage; and 4) presented not CSDH but subdural effusion as the comparable outcome for ARP. Two different authors (KMJ and HYM) independently screened the abstracts titles, identified duplicates, reviewed full-text articles, and determined their eligibility for inclusion in the meta-analysis. In case of a disagreement between the reviewers, consensus was sought through a discussion with the corresponding author.

### Data extraction and quality assessment

Data were obtained independently in duplicate by two authors using a standardized form for extracting study characteristics, design, sample size, age, sex, surgical method, number of patients that underwent surgery with ARP, technique for ARP, and aneurysmal characteristics (e.g., rupture and/or locations). In addition, the authors investigated the prescriptions given before the surgery including antiplatelet and anti-coagulant medication.

The authors established that the outcome was postoperative CSDH by referring to new occurrence of symptomatic CSDH after clipping surgery in patients without any history of traumatic brain injury at the latest available follow-up time point. Requiring additional surgery was not considered in establishing the outcome.

The quality of eligible studies was assessed using the Newcastle-Ottawa Scale (NOS) for non-RCTs and retrospective studies. Both authors assessed the study quality on the basis of eight items within three different categories : selection, comparability, and outcome. We did not rule out articles in accordance with the thresholds of NOS checklists.

### Data analysis

Statistical analysis was performed using Review Manager and STATA/SE 15.0 (Stata Corp LP, College Station, TX, USA). Postoperative CSDH development according to ARP implement was considered the main outcome, analyzed using the random effects model with generic inverse variance meth-

od, and presented with the odds ratio (OR) and 95% confidence interval (CI) as a summary statistic. We excluded data presented as medians with interquartile range and those that did not report the standard deviation values. To homologue the results and make them comparative, an analysis for articles with only UIA was conducted. Sensitivity analysis was carried out with all except one study that showed a high risk of bias. Meta-regression analysis for male sex, a proven risk factor for CSDH, was additionally conducted.

Statistical heterogeneity was estimated using the  $I^2$  statistic, to evaluate the degree of inconsistency across studies in the meta-analysis.  $I^2 < 25%$ ,  $< 50%$ , and  $> 75%$  were considered to indicate low, moderate, and severe heterogeneity, respectively. The authors investigated publication bias by visual asymmetry of funnel plots and Egger's and Begg's tests. Two-sided  $p$ -values  $< 0.05$  were considered to indicate statistical significance.

## RESULTS

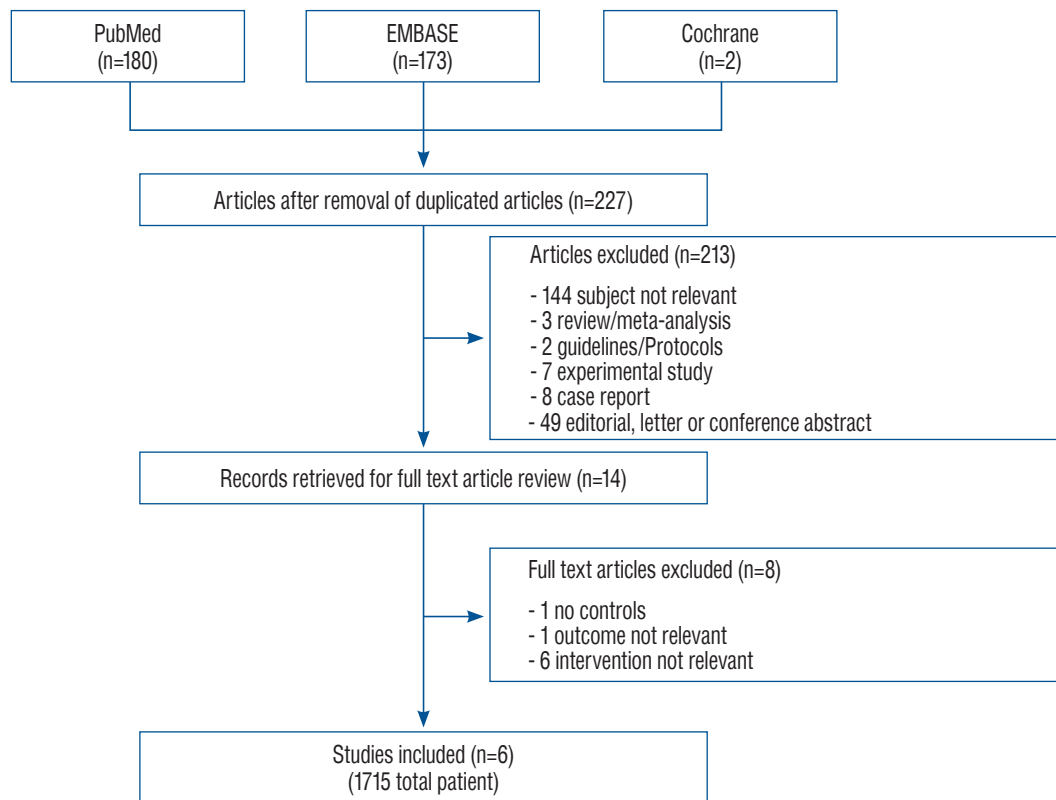
### Search results and risk of bias within studies

From the initial 355 candidate articles (180 in PubMed, 173 in Embase, and two in the Cochrane Central Register) found via the systematic literature search, 128 duplicates were removed. Of the remaining 227 articles, 14 were extracted for full article review by screening the titles and abstracts (Supplementary Table 3). Finally, six articles fulfilled the eligibility criteria for inclusion (Fig. 1).

Based on the quality of eligible studies per the NOS checklist, the majority of included studies ranged from having low to moderate risk of bias. However, we determined that the risk of bias was high only in one study and performed an additional sensitivity analysis after excluding that study. The NOS data presenting individual judgments for risk of bias are documented in Supplementary Table 4.

### Study characteristics

The six studies with a total of 1715 patients that underwent



**Fig. 1.** Flow diagram for the selection of relevant studies.

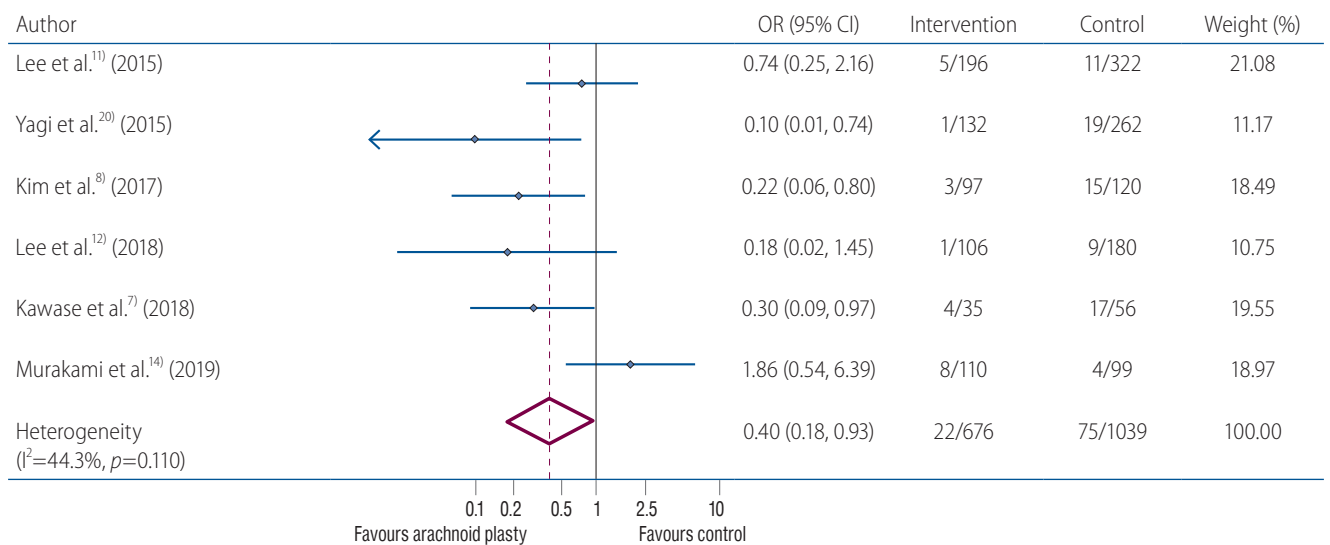
clipping surgery and reported CSDH development as the primary outcome were included in this pooled analysis. All six articles were single-center, retrospective case-control studies. Further, all six studies analyzed patients with UIA. Regarding the surgical methods, the supraorbital and pterional approach were used in one and three studies, respectively. One study used both approaches in accordance with clinical perspec-

tives. The incidence rate of overall postoperative CSDH development was 5.7% (97/1715). The implementation rates of pterional and supraorbital approach were 67.2% (1092/1624) and 32.8% (532/1624), respectively, except for the Kawase trial, which did not provide information on the approach used. Among the five studies with available data for ARP techniques, the procedure was performed using gelatin sponge

**Table 1.** Baseline characteristics of included studies

Study	Design	Setting	Aneurysm	Number of patients			Age* (years)	Male	Surgical approach	ARP technique
				Total	ARP	Control				
Lee et al. <sup>11)</sup> (2015)	RO	Single	UIA	518	196 (37.8)	322 (62.2)	56.6	173 (33.4)	Pterional : 52.5% Lateral supraorbital : 47.5%	Oxidized cellulosis (SURGICEL® FIBRILLAR™) + Fibrin glue
Yagi et al. <sup>20)</sup> (2015)	RO	Single	UIA	394	132 (33.5)	262 (66.5)	62.9	92 (23.4)	Pterional : 100.0%	Gelatin sponge + Fibrin glue (Gelfoam® + Beriplast®)
Kim et al. <sup>8)</sup> (2017)	RO	Single	UIA	217	97 (44.7)	120 (55.3)	NR	83 (38.3)	Pterional : 100.0%	Gelatin sponge + Fibrin glue (Cutanplast® + Tisseel®)
Lee et al. <sup>12)</sup> (2018)	RO	Single	UIA	286	106 (37.1)	180 (62.9)	NR	93 (32.5)	Lateral supraorbital : 100.0%	Gelatin sponge (SPONGOSTAN™) + Fibrin glue
Kawase et al. <sup>7)</sup> (2018)	RO	Single	UIA	91	35 (38.5)	56 (61.5)	67.5	21 (23.1)	Pterional : 100.0%	NR
Murakami et al. <sup>14)</sup> (2019)	RO	Single	UIA	209	110 (52.6)	99 (47.4)	NR	55 (26.3)	NR	Oxidized cellulosis (SURGICEL®) + Fibrin glue

Values are presented as number (%). \*Values are expressed as mean. ARP : arachnoid plasty, RO : retrospective observational study, UIA : unruptured intracranial aneurysm, NR : not recorded



**Fig. 2.** Efficacy of arachnoid plasty in the chronic subdural hematoma reduction after clipping surgery for unruptured intracranial aneurysm. OR : odds ratio, CI : confidence interval.

with fibrin glue in three studies, while oxidized cellulose with glue was used in the remaining two. The gelatin sponge with glue was more frequently applied in the ARP procedure than oxidized cellulose (55.2% vs. 44.8%, respectively) Regarding overall baseline demographics, female patients were included relatively more than males (69.6% vs. 30.4%, respectively). The baseline characteristics of the six individual studies are summarized in Table 1.

### CSDH development after clipping for UIA

The ARP implementation rates after clipping surgery for UIA was 39.4% (676/1715). The incidence rate of overall postoperative CSDH development was 5.7% (97/1715). Additionally, the CSDH rates from the pooled analysis were 3.2% (22/676) in the ARP group and 7.2% (75/1039) in the control group. Integrating the results of the six included studies showed that UIA clipping surgery with ARP was significantly associated with a reduced risk of postoperative CSDH development compared to the control (pooled OR, 0.40; 95% CI, 0.18–0.93;  $I^2=44.3\%$ ;  $p=0.110$ ) (Fig. 2). Despite visual asymmetry in the funnel plot, noticeable publication bias was not identified with the Egger’s and Begg’s tests ( $p=0.225$  and  $p=0.260$ , respectively) (Supplementary Fig. 1).

### Sensitivity analysis

An additional sensitivity analysis was conducted after exclusion of the Kawase 2018 trial that had a high risk of bias according to the NOS checklist. The result was in line with the integrated analysis and indicated that the ARP was signifi-

cantly associated with lowering CSDH development after surgery (pooled OR, 0.55; 95% CI, 0.30–0.98;  $I^2=54.7\%$ ;  $p=0.065$ ) (Fig. 3). In addition, meta-regression analysis did not highlight any modifying effect of male sex on postoperative CSDH development ( $p=0.951$ ) (Fig. 4).

## DISCUSSION

This meta-analysis contained integrated data from 1715 patients treated for UIA by clipping surgery, and revealed that implementation of ARP was associated with prevention of postoperative CSDH development. Furthermore, male sex was not a confounding factor between ARP application and

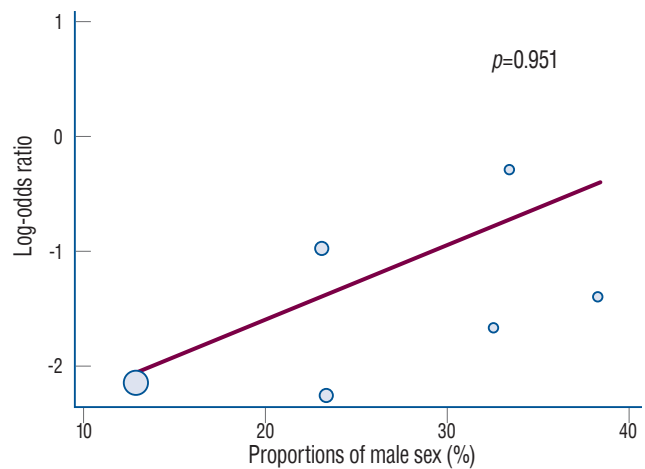


Fig. 4. Meta-regression analysis for male sex on postoperative chronic subdural hematoma development.

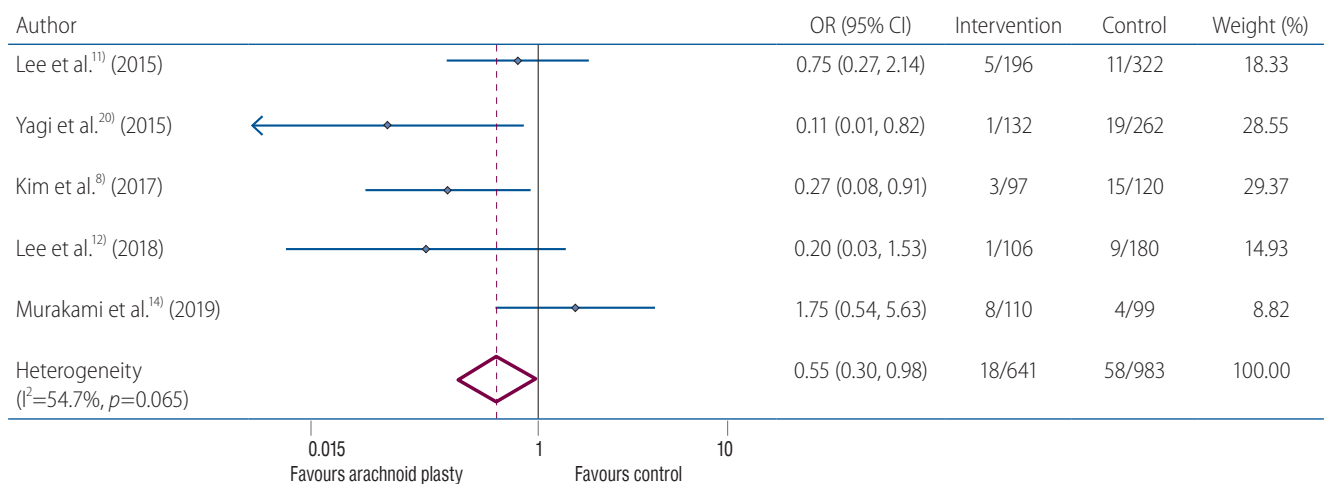


Fig. 3. Sensitivity analysis for arachnoid plasty efficacy, excluding the Kawase trial. OR : odds ratio, CI : confidence interval.

CSDH development. These results provided further evidence that ARP following the surgery would be effective in prevention and reduction for postoperative CSDH development.

CSDH after aneurysmal clipping surgery is a relatively common complication, and sometimes requires additional surgical evacuation. The reported incidence rates of CSDH are 2.8% in UIA and 0.9% in RIA<sup>15)</sup>. Kwon et al.<sup>9)</sup> also reported higher incidence rates of CSDH in UIA than RIA (10.9% vs. 3.1%, respectively). To explain this difference, the author suggested two possible mechanisms: one entails the potential subdural space obliteration by the residual hematoma with brain edema, and the other is the osmotic gradient theory of the CSDH likely contributing to lower incidence rates<sup>2)</sup>. The wall of CSDH is composed of two layers with semi-permeable membranes, and the hematoma gradually increases in size because of the difference between the internal and external osmotic pressures<sup>1,18,21)</sup>. Accordingly, increased internal pressure reduces the pressure gradients, ultimately leading to lesser rate of CSDH and effectiveness of ARP in patients with RIA. Therefore, we investigated the effectiveness of ARP in surgical treatment of UIA, but excluded RIA, to homologate the results from this meta-analysis.

Increased postoperative subdural fluid collection was a sole predictor for postoperative CSDH<sup>14)</sup>. Park et al.<sup>16)</sup> stated that advanced age, male sex, and deep location of the aneurysm were correlated with the occurrence of subdural fluid collection and CSDH after clipping surgery for UIA. The authors suggested that the possible mechanism of correlation was through a one-way valve phenomenon<sup>10,22)</sup>. Clipping surgery requires the dissection of the arachnoid membrane covering the sylvian fissures. Therefore, a persistent opening state of the subarachnoid space causes communication between the cerebrospinal fluid (CSF) cistern and subdural space. The healing process of the injured membrane induces the one-way valve from the subarachnoid to the subdural space, and results in persistent CSF leakage, eventually leading to CSDH development. Several additional studies also supported the correlation between subdural fluid collection and CSDH<sup>4,5,8,9,14)</sup>. Therefore, ARP implementation can likely be considered to inhibit persistent CSF leakage, to essentially reduce postoperative CSDH development. The current study also observed that patients with ARP showed a lower incidence of CSDH than the controls; hence, we believe our results have provided further evidence to demonstrate the effectiveness of ARP in preven-

tion of postoperative CSDH.

The ARP technique using fibrin glue was first introduced by Tsuruno<sup>19)</sup> in 1995. Since then, it has been developed into a technique that combines gelatin sponge or oxidized cellulose to enhance the sealing effect; more recently, a modified ARP technique using multiple gelatin pieces has also been introduced<sup>12)</sup>. In this meta-analysis, gelatin sponge with fibrin glue and oxidized cellulose with the glue were applied in 55.2% and 44.8% cases, respectively. Although we were unable to clarify which of the two methods was more effective, we believe that ARP implementation could be an effective prevention method for postoperative CSDH development, and thus helpful to neurosurgeons conducting clipping surgery for UIA.

Male sex has been associated with brain atrophy and recognized as presenting a higher risk of postoperative CSDH than females<sup>12,16,20)</sup>. However, Murakami et al.<sup>14)</sup> recently reported that male sex did not show a significant relationship with CSDH and that only subdural fluid collection was the sole risk factor. According to our results incorporating six studies with 1715 patients, male sex did not highlight any modifying effect between ARP and CSDH.

Several limitations should be noted in this meta-analysis. First, our results should be interpreted with caution, given that they were not based on a relatively high level of evidenced studies. In other words, all individual studies were designed retrospectively, with relatively low level evidence of single-institutional study. Although we utilized a concrete search strategy, prospective, randomized-controlled, multi-center studies on ARP could not be identified. Second, this analysis was conducted on studies that had inconsistent protocols, such as those for the ARP techniques. Although there were minor differences in the detailed techniques, there was no significant difference in the method of using space-occupying substances with sealing materials such as fibrin glue gelatin sponges. Therefore, it was not assumed to cause fundamentally confounding errors. Last, patient age that is recognized as the major predictor of CSDH development was excluded in this analysis. Because most of the included studies did not provide overall and baseline patient age<sup>6,16)</sup>, we tried to reveal the correlation between the age and postoperative CSDH, but could not extract this information. Therefore, prospective, multi-center, and centrally adjudicated studies with completely matched patient characteristics are required to further validate our findings.



## CONCLUSION

ARP implementation showed effectiveness in reduction of CSDH development following clipping surgery for UIA. If feasible, ARP implementation would be considered as an additional surgical technique to prevent postoperative CSDH development during surgical clipping of UIA.

## CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

## INFORMED CONSENT

This type of study does not require informed consent.

## AUTHOR CONTRIBUTIONS

**Conceptualization :** KMJ, HHC, YSP

**Data curation :** KMJ, TKN

**Formal analysis :** KMJ, HHC

**Funding acquisition :** HHC

**Methodology :** KMJ, HHC

**Project administration :** HHC

**Visualization :** HHC

**Writing - original draft :** KMJ

**Writing - review & editing :** HHC, TKN, JTK

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## • Supplementary materials

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