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Research article

Can a single basal cistern urokinase bolus help to prevent subarachnoid hemorrhage consequences?

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ABSTRACT

Study design: Retrospective.
Background: In the 1980s, aneurysmal subarachnoid clot lysis with urokinase or alteplase (rtPA) was proven to effectively reduce vasospasm and neurological ischemic deficits, improving survival and clinical outcomes. This therapeutic option has been less commonly used since the introduction of endovascular treatment, but renewed interest has sparked in recent years.
Aims: To investigate if single bolus cisternal urokinase subarachnoid clot lysis reduces vasospasm, neurological ischemic deficits, mortality, and permanent CSF diversion rates and improves outcomes. Additionally, we want to unveil which subgroup of patients benefit most.
Material and methods: Study period January 2007–December 2019. 415 patients with saccular aneurysms and >1-year follow-up analyzed. Six groups created according to the treatment applied: no treatment (42), only external ventricular drain (16), endovascular treatment (155), clipping (53), clipping + 100,000UI urokinase (116), and incidental brain aneurysm (33).
Results: The rates and severity of vasospasm, permanent CSF diversion, and mortality in Fisher grades ≥3 subarachnoid hemorrhages were higher with endovascular treatment than with surgical clipping with simultaneous cisternal urokinase administration. The best GOSE results on discharge and 6- and 12-month follow-ups happened in this latter group. The differences were more significant the higher the Fisher grade. We neither saw intraventricular, subarachnoid, subdural, or epidural hemorrhages nor systemic fibrinolysis or infections that could be related to the urokinase administration.
Conclusions: Single bolus cisternal 100,000UI urokinase administration during emergency aneurysm clipping reduces vasospasm, mortality, and the need for permanent CSF diversion. It is not associated with a significant increase in intracranial hemorrhages or systemic fibrinolysis.

1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) remains a severe condition with 50 % mortality and 30 % morbidity rates [1]. This

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severity can be primarily attributed to the blood extravasated into the subarachnoid space and to its degradation products [2], causing vasospasm [1], delayed cerebral ischemia (DCI) [3], delayed ischemic neurological deficits (DIND) [4], and subarachnoid space fibrosis leading to hydrocephalus [5].

The amount of extravasated subarachnoid blood correlates with the vasospasm [6], DCI [7], DIND [8], and permanent CSF diversion rates [9], as well as with the clinical outcome [10]. In fact, these complications are more frequent and severe when the subarachnoid extravasated blood volume is $>$ 20 ml [11] ($\sim$ Fisher grade 3^{11}). Correspondingly, when this subarachnoid blood is removed, there is a reduction in vasospasm [12], DCI [13], DIND [14], and permanent shunt rates [13,15,16]. The recommendation is to remove the subarachnoid clot in the first 24h post-aSAH [12,17] as a delay of more than 48h makes it less effective at improving clinical outcomes [18].

Mechanical removal of the clotted subarachnoid blood is technically demanding [19] and limited in its effectiveness [20]. It also risks damage to the perforating vessels [21]. Thus, three ways have been explored to remove the subarachnoid blood and its deleterious degradation products, namely through an External Ventricular Drain (EVD) [22], lumbar drainage [23], or cisternal administration of fibrinolytic drugs [15]. Some have combined cisternal fibrinolytic intraoperative irrigation with aggressive mechanical subarachnoid clot removal [13,20].

Insertion of an External Ventricular Drain is the way to control acute post-SAH hydrocephalus and, at the same time, remove the blood and its degradation products from the intraventricular space [24]. The recommendation is to insert it, if possible, just after aneurysm occlusion to avoid the risk of rebleeds [25]. Unfortunately, EVD insertion did not improve the SAH-related complications like vasospasm, DCI, DIND, and the need for permanent shunt insertion [9,26,27], because the CSF is drained from the ventricular compartment, leaving the subarachnoid blood [28]. This blood in the subarachnoid space will degrade with harmful effects [2]. Therefore, it is no longer recommended, except for the treatment of acute hydrocephalus, but not for the removal of the subarachnoid blood degradation products [26,29]. Some have attempted ventricular irrigation with Ringer lactate solution or with rt-PA with simultaneous continuous lumbar spinal drainage [27,30]. This therapeutic approach improves the results of the parameters mentioned above but is not as successful as direct cisternal subarachnoid blood lysis and removal [30].

Lumbar drainage removes some of the extravasated oxyhemoglobin and its degradation products, decreasing post-aSAH permanent CSF diversion [31], DIND [14], and other unfavorable outcomes at 6 months [32]. The recommendation is to start draining CSF on the third day post-SAH to allow the endogenous plasminogen to lyse the subarachnoid clot [23]. If the lumbar CSF drainage starts earlier, the endogenous fibrinolytic agents are also removed before the blood clot is lysed, making the lumbar drainage counteractive [23]. As the amount of CSF that can be removed from the lumbar thecal sac is limited without negatively affecting the intracranial pressure, some have devised a system that allows CSF drainage with clearance of hemoglobin and its degradation products before re-infusing the drained CSF again [33]. As mentioned, some have attempted to infuse Ringer lactate in the lateral ventricles through an external ventricular catheter to foster the washing of the subarachnoid space [30].

The third way is to use fibrinolytic agents. As systemically administered fibrinolytic agents did not reach the subarachnoid space [34] already in the 1980s, surgeons infused urokinase or rtPA directly into the basal cisterns to lyse the subarachnoid blood clot [35,36]. These drugs were administered in the surgical field after aneurysm clipping [37], lysing the subarachnoid hemorrhage safely with few moderate intracranial bleedings ($<$2 %) [12] or infectious complications [38]. A 2004 multicentric study compared the subarachnoid clots' mechanical removal versus rtPA [39] after clipping, finding positive results when this drug was used in Fisher grades $\geq 3^{39}$.

With the introduction of the aneurysm endovascular treatment, direct cisternal fibrinolysis during surgical clipping was not used as often. The endovascular treatment offered lesser morbidity, but vasospasm control, particularly in severe SAHs (Fisher grades $\geq$3), was poor [40]. Therefore, some attempted fibrinolytic therapy in coiled aneurysms, confirming a reduction in vasospasm and associated ischemic neurological sequelae [15,41].

In recent years, a renewed interest has sparked in cisternal clot lysis with recombinant tissue-plasminogen activator (rt-PA) and urokinase-type plasminogen activator (UK), particularly in elderly patients with massive subarachnoid hemorrhages and bad Hunt and Hess grades that would otherwise not be treated at all [13]. This treatment approach opens a window of opportunity for patients with few choices left.

The methods by which the fibrinolytic drugs are administered to the subarachnoid space also matters. Recent studies have shown that single bolus administration is as effective and safe as protracted perfusion through a cisternal catheter but has a much lesser risk of infection [42].We elected the single bolus administration. Accordingly, after emergency aneurysm clipping, we administered a cisternal single UK bolus to lyse the subarachnoid blood clots. We saw that the reduction in the subarachnoid hemorrhage volume reduced vasospasm, mortality, and the need for temporary and permanent CSF diversion rates. It also reduced the number of days in ICU and improved neurological status and general outcomes. This article presents our experience.

2. Material and methods

2.1. Study design

The study was retrospective, encompassing twelve years (2007–2019). Our hospital Research and Ethics Committees (Clinical Trial Registration number: Hospital General Universitario de Valencia, Valencia, Spain, CEIm 16/June/2019, ClinicalTrials.gov Identifier: NCT04792944) approved it, and we performed it following the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

2.2. Inclusion and exclusion criteria

Inclusion criteria: Patients age older than 18 years, with one or more saccular brain aneurysms, with or without subarachnoid hemorrhage (SAH). In the event of multiple aneurysms, treatment was primarily directed to the bleeding one and, when possible, to all of them.

Exclusion criteria: fusiform, traumatic or mycotic aneurysms, non-aneurysmal SAH (trauma, anticoagulation, antiplatelet medication, arteriovenous malformation or tumor), any medical, neurological or psychiatric condition impairing the patients' evaluation, past medical history of bleeding disorders or liver disease, anticoagulation, platelet count $<10 \times 10^9$/L or prothrombin time >15 s.

We obtained informed consent from each patient or their relatives if the clinical condition prevented it.

2.3. Assessment

We evaluated the patient's initial status with the Glasgow Coma [43] and Hunt and Hess [44] Scales. On admission, a head CT scan examination confirmed SAH diagnosis and grade according to the Fisher scale [11]. Finally, an angio-CT scan identified the aneurysm (s), helping establish the treatment plan. Vasospasm was evaluated daily with transcranial Doppler sonographic examination (CANON APLIO 400 and CANNON XARIO 200, Cannon Medical Systems, Otawara, Japan), measuring middle cerebral artery blood flow velocity on both cerebral hemispheres. AngioTC was performed in the most severe cases to help decide to apply endovascular treatment.

We describe the SAH medical treatment of our patients in Table 1S (supplementary material).

We performed endovascular treatment or craniotomy with clipping within the first 24–72 h to reduce the risk of rebleeding. We administered tranexamic acid if the aneurysm occlusion was delayed for any reason past 72 h after bleeding. We controlled and treated vasospasm with hemodilution, hypervolemia, and induced hypertension. In severe vasospasm, we used vasoactive drugs (noradrenaline). We administered nimodipine intravenously until patients could take it *per os* (60 mg/4h for 21 days post-SAH). Endovascular procedures were provided in case of severe vasospasm.

Patients with a Hunt and Hess grade 5, a bad general condition, or older than 80 years were considered for aneurysm treatment, either endovascular or surgical clipping. In the event of acute hydrocephalus, an EVD was used exclusively.

2.4. Aneurysm specific treatment

We performed endovascular treatment as soon as possible on weekdays. On Fridays, Saturdays, and Sundays, treatment was delayed until the following Monday morning. Some would argue against this treatment approach. However, when the patients were enrolled, this was a reasonable option.

In all the surgically clipped aneurysms, surgeons performed cisternostomy with subarachnoid clot removal through suction and lavage. The lamina terminalis opening was added to all anterior circulation aneurysms.

The fibrinolytic agent used in our study was UK (Vedim Pharma S.A., Plaza de Manuel Gómez Moreno, s/n, Edificio Bronce, planta 5, 28020 Madrid, Spain).

Intraoperatively, the aneurysm was clipped first, and then the UK was administered to the basal cistern. We decided to use a UK dose of 100,000 IU based on results from previously published studies [12,45]. We diluted it in 20 ml of normal saline solution and injected it slowly into the exposed cisterns. Small brain lacerations or minor brain tissue resections created during aneurysm exposure (i.e., gyrus rectus) were not contraindications to UK administration. We removed the intracerebral hematomas and injected the UK into their cavity. After 15 min, we sealed the dura, avoiding aspirating the CSF with the UK. Contrary to other studies, we did not rinse the cisterns with normal saline solution [39]. We did not insert cisternal drains, but surgeons could use external ventricular or subcutaneous drains.

EVD insertion was performed on an emergency basis when needed.

2.5. Follow-up examinations

Patients' evaluations included daily neurological examinations until discharge from the hospital.

Angio-CT scan examinations took place 24 h post-treatment unless the medical condition prevented it. They were repeated once a week, in case of clinical deterioration or if the ICU team deemed it necessary.

Vasospasm was evaluated daily using transcranial Doppler sonography (TCD) until discharge from the hospital. Vasospasm was defined as a maximum mean flow velocity (MMFV) > 120 cm/s. Following Findlay et al. [39], we classified vasospasm as mild (<25 %), moderate (25–50 %), or severe (>50 %) and focal when only one intracranial artery was involved and diffuse when more than one was involved [39]. In addition, we considered clinical vasospasm in case of neurological deterioration without hydrocephalus, postoperative intracranial bleeding, infection, or metabolic disturbance.

We requested postoperative cerebral angiograms if there was any new bleeding or if complete aneurysm occlusion was dubious after clipping. Otherwise, evaluation of the clipped aneurysms took place with angio-CT [46].

Follow-up variables included neurological status (level of consciousness, orientation in time and place, memory, speech, movement, cranial nerve deficits), DIND, and GOSE [46]. DIND was assessed with daily clinical examinations and with MR studies when there was a clinical suspicion. These variables were evaluated at discharge and six and twelve-month follow-ups. MR studies were also requested at discharge from the hospital, as well as at one-, three-, six-, and twelve-month follow-up appointments. In addition, we

asked for brain angiograms at 1-year follow-up, repeating it each year in partial aneurysm obliteration and at five-year intervals for those with complete occlusion.

We scrutinized any postoperative bleeding that might be related to UK administration.

2.6. Outcomes

Our primary outcome was to find out the feasibility and safety of this therapeutic approach.

The secondary outcomes were to assess the vasospasm, DCI, DIND, permanent shunt, and mortality rates, as well as GOSE at discharge, 6 and 12-month follow-ups.

2.7. Statistical methods

We analyzed the data using R software (version 3.5.1), conducting a basic descriptive analysis of the mean, median, standard deviation, and range calculation. We compared quantitative variables between groups using the Kruskal-Wallis test and performed multiple comparisons using Bonferroni all-pairs. We compared rates between groups using the Chi-squared test or Fisher test. A p-value below 0.05 was considered statistically significant.

3. Results

We evaluated 415 patients admitted to our hospital between January 1st, 2007, and December 31st, 2019, due to saccular brain aneurysms with or without subarachnoid hemorrhage. We included those with at least 1-year follow-up.

We classified patients according to the Fisher grade on admission and the treatment administered thereafter, comparing the different groups. We did not withhold UK administration based on the patient's clinical condition.

We made six groups of patients: no treatment (NO TREATMENT) (42), external ventricular drain only with no endovascular treatment or clipping (EXT VENT DRAIN) (16), endovascular group (EMBOL) (coiling, stenting + coiling or flow diverter) (155), surgical clipping (CLIPPING) (53), surgical clipping with cisternal UK administration (CLIPPING + UROKINASE) (116) and those with clipping of incidental aneurysm finding with no SAH (NO SAH CLIPPING) (33).

Table 1 presents patients' demographics and clinical status. There were more female patients in the treatment categories of clipping with UK administration, no treatment, and external ventricular drain groups. The no-treatment and external ventricular drain groups had a higher average age because advanced age is often a reason to withhold aggressive treatment. All groups had a similar BMI.

The GCS on admission for the endovascular treatment group showed no statistically significant differences compared to the clipping group (p 0.438) but better than clipping with simultaneous UK administration ($p < 0.001$). So, a selection bias favored endovascular treatment for patients with a better neurological status.

Fisher scores on admission were better for the endovascular group (2.167 ± 1.236) than for the clipping with (2.560 ± 1.203) or without (2.452 ± 1.264) UK administration, confirming again the bias of endovascular treatment for less severe subarachnoid hemorrhages. These Fisher grades were the worst for those with only an EVD (3.5 ± 0.89), followed by those for whom endovascular and surgical aneurysm treatment had been discarded (3.0 ± 1.306).

The maximum aneurysm diameter was smaller for the endovascular treatment group compared to surgical clipping (p 0.055), surgical clipping with cisternal UK administration ($p < 0.001$) and incidental aneurysm clipping with no SAH ($p < 0.001$). Thus, endovascularly treated aneurysms were, on average, smaller than those clipped surgically.

The neck/fundus ratio was more prominent for the incidental aneurysm clipping with no SAH than in the endovascular group (p 0.036). Still, there were no statistically significant differences from the other groups.

The percentage of patients with multiple aneurysms was not statistically significantly different between the clipped and endovascular groups.

Other factors evaluated, such as tobacco use, alcohol intake, comorbidities (diabetes mellitus, hypertension), medications (anticoagulation, antiplatelet therapy), and family history of brain aneurysms, showed no statistically significant differences between groups (in all instances, $p < 0.05$).

3.1. Post-treatment CT scan subarachnoid clot evaluation

Post-treatment Fisher grades: endovascular treatment (2.354 ± 1.236), those undergoing only an external ventricular drain (3.875 ± 0.341), no-treatment group (3.261 ± 1.060), clipping (2.640 ± 1.21), clipping with simultaneous UK administration 1.030 ± 0.371), and incidental aneurysm finding with no subarachnoid hemorrhage (0.636 ± 0.548). Thus, compared to the situation on admission, only the aneurysm clipping with simultaneous UK administration group showed improvement in the post-treatment Fisher grade ($p < 0.001$) (Fig. 1).

The complete aneurysm occlusion rate was significantly lower for endovascular treatment than for surgical clipping (Chi-Squared test $p < 0.001$) (Table 2).

The permanent CSF diversion rate was highest for the surgically clipped aneurysms with limited cisternal clot removal (23.3 %), followed by the endovascularly treated patients (16.8 %), and the lowest for those undergoing surgical clipping with subarachnoid cistern UK administration (15.58 %).

Patients' age was negatively associated with survival (p 0.001). In addition, the endovascular treatment had a higher risk of death

Table 1
On admission, patients' demographics, clinical status, Glasgow Coma Scale (GCS), Hunt and Hess classification, and aneurysm characteristics. We supply all data except the sex distribution as mean ± standard deviation. EMBOL (Endovascular group, coiling, stenting + coiling or flow diverter), EXT VENT DRAIN (external ventricular drain only with no endovascular treatment or clipping), NO TREATMENT (no treatment), CLIPPING (surgical clipping), NO SAH CLIPPING (clipping of incidental aneurysm finding with no SAH and CLIPPING + UROKINASE (surgical clipping with cisternal UK administration).

GROUP	Nº CASES (% TOTAL)	GENDER (% Female)	AGE	BMI	GCS	HUNT & HESS	FISHER ON ADMISSION	MAXIMUM ANEURYSM DIAMETER	DIAMETER NECK ANEURYSM	RATIO NECK/ FUNDUS	>1 ANEURYSM
EMBOL	**155 (37 %)**	**65**	**55.9 ± 13.4**	**29.0 ± 4.2**	**13.5 ± 2.7**	**1.7 ± 1.1**	**2.1 ± 1.2**	**7.4 ± 4.6**	**4.3 ± 3.1**	**1.8 ± 0.7**	**32 (20 %)**
EXT VENT DRAIN	**16 (4 %)**	**81**	**63.8 ± 16.4**	**30.6 ± 5.4**	**9.4 ± 3.4**	**3.3 ± 1.3**	**3.5 ± 0.8**	**9.7 ± 7.2**	**5.7 ± 4.2**	**1.8 ± 0.5**	**4 (25 %)**
NO TREATMENT	**42 (10 %)**	**80**	**71.9 ± 13.5**	**31.4 ± 5.7**	**8.2 ± 4.8**	**3.4 ± 1.6**	**2.9 ± 1.3**	**11.4 ± 11.3**	**5.4 ± 4.8**	**2.1 ± 1.2**	**6 (14 %)**
CLIPPING	**53 (13 %)**	**69**	**54.4 ± 13.3**	**29.0 ± 4.5**	**12.8 ± 3.0**	**1.9 ± 1.2**	**2.4 ± 1.2**	**9.2 ± 5.3**	**5.0 ± 2.3**	**1.8 ± 0.6**	**12 (22 %)**
NO SAH CLIPPING	**33 (8 %)**	**78**	**52.3 ± 13.6**	**27.7 ± 4.5**	**15.0 ± 0.0**	**1.0 ± 0.0**	**0.0 ± 0.0**	**9.9 ± 6.5**	**6.2 ± 4.2**	**1.6 ± 0.7**	**1 (3 %)**
CLIPPING + UROKINASE	**116 (28 %)**	**72**	**56.3 ± 11.1**	**29.3 ± 4.2**	**12.4 ± 3.2**	**2.1 ± 1.4**	**2.5 ± 1.2**	**9.3 ± 6.5**	**5.6 ± 3.7**	**1.7 ± 0.8**	**22 (19 %)**

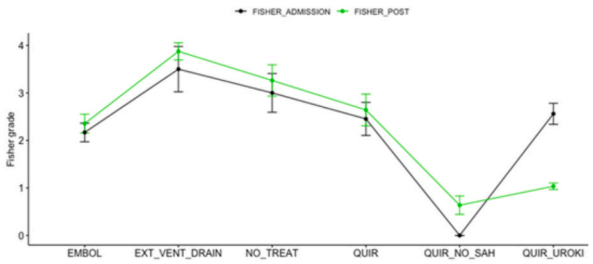

Fig. 1. Fisher grade on admission (FISHER_ADMISSION) and post-treatment (FISHER_POST) according to the group. Groups: EMBOL (endovascular treatment), EXT VENT DRAIN (external ventricular drain only with no endovascular treatment or clipping), NO TREATMENT (no treatment), CLIPPING (surgical clipping), NO SAH CLIPPING (those with incidental aneurysm finding with no SAH) and CLIPPING + UROKINASE (surgical clipping with cisternal UK administration). FISHER_ADMISSION (Fisher scale on admission to hospital). FISHER_POST (Fisher scale inmediately afte the treaament modality applied).

Table 2
Degree of aneurysm occlusion according to the group. The complete aneurysm occlusion rate was significantly lower among the endovascularly treated patients than those who underwent surgical clipping. EMBOL (Endovascular group, coiling, stenting + coiling or flow diverter), EXT VENT DRAIN (external ventricular drain only with no endovascular treatment or clipping), NO TREATMENT (no treatment), CLIPPING (surgical clipping), NO SAH CLIPPING (clipping of incidental aneurysm finding with no SAH and CLIPPING + UROKINASE (surgical clipping with cisternal UK administration).

DEGREE ANEURYSM OCCLUSION	GROUP						TOTAL NUMBER OF CASES
	EMBOL	EXT VENT DRAIN	NO TREATMENT	CLIPPING	NO SAH CLIPPING	CLIPPING + UROKINASE	
Aborted embolization	**1 (0.6 %)**	-	-	-	-	-	**1 (0.24 %)**
By-pass + trapping	-	-	-	-	-	**1 (1 %)**	**1 (0.24 %)**
Complete occlusion	**78 (50 %)**	**1 (6 %)**	-	**43 (81 %)**	**33 (100 %)**	**115 (99 %)**	**270 (65 %)**
Failed clipping	-	-	-	**1 (2 %)**	-	-	**1 (0.24 %)**
Failed clipping & embolization	-	**1 (6 %)**	-	-	-	-	**1 (0.24 %)**
Failed embolization	**7 (4 %)**	-	-	-	-	-	**7 (1.68 %)**
Neck patent	**63 (40 %)**	**2 (12 %)**	-	**2 (4 %)**	-	-	**67 (16 %)**
No treatment	-	**12 (75 %)**	**42 (100 %)**	-	-	-	**54 (13 %)**
Sac patent	**6 (4 %)**	-	-	**2 (4 %)**	-	-	**8 (2 %)**
Trapping	-	-	-	**3 (6 %)**	-	-	**3 (0.72 %)**
Wrapping	-	-	-	**2 (5 %)**	-	-	**2 (0.48 %)**
TOTAL NUMBER OF CASES PER GROUP	**155**	**16**	**42**	**53**	**33**	**116**	**415**

than surgical clipping with cisternal UK administration (p 0.012).

3.2. Vasospasm incidence

The highest incidence of vasospasm was for those undergoing only an external ventricular drain (87.5 %), followed by aneurysm clipping with limited subarachnoid clot removal (71.7 %), those treated endovascularly (68.39 %), those undergoing no treatment (54.76 %), those undergoing clipping with simultaneous UK administration (32.76 %) and finally by those with incidental aneurysms

Table 3
Incidence and severity of symptomatic vasospasm according to the group. The surgical clipping patients with simultaneous cisternal lavage with urokinase show the second-lowest incidence, just behind those with incidental aneurysm findings and no subarachnoid hemorrhage. EMBOL (Endovascular group, coiling, stenting + coiling or flow diverter), EXT VENT DRAIN (external ventricular drain only with no endovascular treatment or clipping), NO TREATMENT (no treatment), CLIPPING (surgical clipping), NO SAH CLIPPING (clipping of incidental aneurysm finding with no SAH and CLIPPING + UROKINASE (surgical clipping with cisternal UK administration).

VASOSPASM	GROUP					
	EMBOL	EXT VENT DRAIN	NO TREATMENT	CLIPPING	NO SAH CLIPPING	CLIPPING + UROKINASE
NO	49 (31 %)	2 (12 %)	19 (45 %)	15 (28 %)	31 (94 %)	78 (67 %)
YES	106 (69 %)	14 (88 %)	23 (55 %)	38 (72 %)	2 (6 %)	38 (33 %)

and no subarachnoid hemorrhage (6.06 %) (Table 3).

3.3. Length of ICU stay

This data is not applicable for external ventricular drain only and no treatment groups. There were no statistically significant differences in the length of the ICU stay between endovascular treatment and surgically clipped aneurysms with simultaneous cisternal lavage with UK (p 0.999). Meanwhile, clipping with no UK administration showed a statistically significant more extended ICU stay ($p < 0.001$). Finally, the incidental aneurysm clipping with no SAH compared to endovascular treatment had the shortest ICU stay ($p < 0.001$) (deceased patients are omitted).

3.4. GOSE

Endovascular treatment versus surgical clipping with simultaneous UK administration showed no statistically significant differences in GOSE at discharge from the hospital (p 0.378) and at six (p 0.054) and twelve months (p 0.603) follow-up. However, these differences were present between endovascular treatment and incidental aneurysm clipping with no SAH at discharge from the hospital (p 0.008) and at six (p 0.002) and 12 months (p 0.005) follow-up. Fig. 2 and Table 4 show the discharge, six and 12-month GOSE scores according to the group.

3.5. Rebleeding rate while awaiting for aneurysm treatment

The highest rates correspond to those primarily treated with only external ventricular drain (81.2 %) and the no-treatment group (61.90 %), as none had aneurysm occlusion. Among the groups that did undergo aneurysm occlusion, the rates of rebleeding were lower. Endovascular treatment had the highest rates (9 %), followed by elective clipping (5.7 %) and emergency clipping with subarachnoid UK administration (1.7 %).

Recanalization of aneurysms after treatment happened mostly with endovascular treatment (21.3 %), seldom with surgical clipping (3.8 %), and not at all for surgical clipping with simultaneous UK administration (0 %).

Patients with multiple aneurysms received endovascular treatment or clipping for the one that was the most likely cause of the bleeding. Still, if possible, we attempted to clip and embolize all aneurysms through a single surgical approach.

Patients with severe aSAH and a bad clinical status were not treated with endovascular treatments or clipping, and ICU and palliative care werepreferred.

3.6. Comparison of patients with Fisher scores 1 and 2 versus 3 and 4

Next, we did a new analysis, splitting the patients according to their Fisher scores on admission, with subgroup 1 for patients with Fisher scores 1 and 2 and subgroup 2 for those with scores 3 and 4. The idea was to see if removing the subarachnoid clot impacted vasospasm, the need for external ventricular drain, definitive CSF shunt and GOSE at discharge and six and 12-month follow-up.

3.7. Subgroup 1

We found no statistically significant differences in the vasospasm rate between the endovascular treatment and surgical clipping with simultaneous UK administration (p 0.678).

The need for an EVD or a definitive CSF shunt was more prominent for the endovascular treatment than for the clipping with simultaneous UK administration (Fisher's Exact Test p 0.004 and 0.056, respectively).

The survival rate was higher for aneurysm clipping with simultaneous UK clot lysis than for endovascular treatment (Fisher's Exact Test p 8.396e-07).

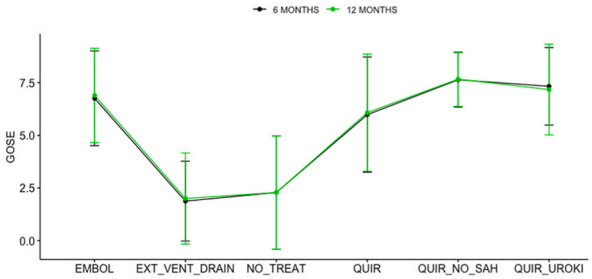

Fig. 2. GOSE (Glasgow Outcome Scale-Extended) at 6 and 12 months follow-up, according to the group. Groups: EMBOL (endovascular treatment), EXT VENT DRAIN (external ventricular drain only with no endovascular treatment or clipping), NO TREATMENT (no treatment), CLIPPING (surgical clipping), NO SAH CLIPPING (those with incidental aneurysm finding with no SAH) and CLIPPING + UROKINASE (surgical clipping with cisternal UK administration).

Table 4
According to the group, GOSE at discharge from the hospital and at six and 12-month follow-up showed statistically significant differences ($p < 0.001$, $p < 0.000$ and p 0.003, respectively). The recovery is better for the incidental aneurysm clipping and no subarachnoid hemorrhage, followed by surgical clipping with simultaneous urokinase administration. Meanwhile, the endovascular and surgical clipping fare worse, particularly the latter group. Patients undergoing external ventricular drain only or no treatment are faring worst as expected. EMBOL (Endovascular group, coiling, stenting + coiling or flow diverter), EXT VENT DRAIN (external ventricular drain only with no endovascular treatment or clipping), NO TREATMENT (no treatment), CLIPPING (surgical clipping), NO SAH CLIPPING (clipping of incidental aneurysm finding with no SAH and CLIPPING + UROKINASE (surgical clipping with cisternal UK administration).

GROUP	*EXITUS*	DAYS ICU	GOSE DISCHARGE	p-value	GOSE 6 MONTHS	p-value	GOSE 12 MONTHS	p-value
EMBOL	21 out of 155 (13 %)	11.3 ± 12.2	6.50 ± 2.20	0.378	6.7 ± 2.2	0.054	6.8 ± 2.2	0.603
EXT VENT DRAIN	14 out of 16 (87 %)	19.5 ± 22.9	1.75 ± 1.61	0.001	1.8 ± 1.8	0.000	2.0 ± 2.1	0.001
NO TREATMENT	34 out of 42 (81 %)	4.5 ± 4.4	2.42 ± 2.77	0.001	2.2 ± 2.6	0.003	2.2 ± 2.6	0.002
CLIPPING	13 out of 53 (24 %)	17.5 ± 18.7	5.83 ± 2.59	0.018	5.9 ± 2.7	0.001	6.0 ± 2.7	0.001
NO SAH CLIPPING	2 out of 33 (6 %)	4.2 ± 8.5	7.57 ± 1.29	0.008	7.6 ± 1.2	0.002	7.6 ± 1.2	0.005
CLIPPING + UROKINASE	12 out of 116 (10 %)	13.0 ± 13.0	7.04 ± 1.77	0.05	7.3 ± 1.8	0.03	7.1 ± 2.1	0.04

Contrarily, in the GOSE, there were no statistically significant differences between the endovascular treatment and surgical clipping with simultaneous UK administration (p 0.395 at discharge and 0.506 at 6 and 0.518 at 12-month follow-up).

3.8. Subgroup 2

The vasospasm rate was lower for the surgical clipping with simultaneous UK administration than for the endovascular treatment (Fisher's Exact Test p 2.924e-07). Moreover, this latter group more frequently needed an external ventricular drain (Fisher's Exact Test p 2e-09) and a permanent CSF shunt diversion ($p < 0.001$) and had a higher *exitus letalis* rate (Fisher's Exact Test p 2.434e-149).

Surgical clipping with concurrent UK administration showed statistically significantly better GOSE scores than endovascular treatment (on discharge p 0.05 and at six p 0.03, and 12-month follow-up p 0.04) (Fig. 3).

To summarize, patients with Fisher grades ≥3 on admission had better results with clipping plus simultaneous subarachnoid clot lysis with UK compared to endovascular treatment or surgical aneurysm clipping with cisternal UK administration.

3.9. Hemorrhagic complications attributable to the treatment (UK)

No patient developed intraventricular, subarachnoid, subdural, epidural hemorrhages or systemic bleedings that could be attributed to the UK cisternal administration. Systemic fibrinolysis was not detected in regular blood tests.

4. Discussion

Our study shows that single bolus 100.000UI UK cisternal irrigation has a positive effect on patients with Fisher grades ≥3. This positive effect was reflected in reduced rate of vasospasm, external ventricular drain, and definitive CSF shunt rates, as well as GOSE scores at discharge and 6 and 12-month follow-ups. In Fisher grades 1 and 2, these differences were not as evident. However, as the

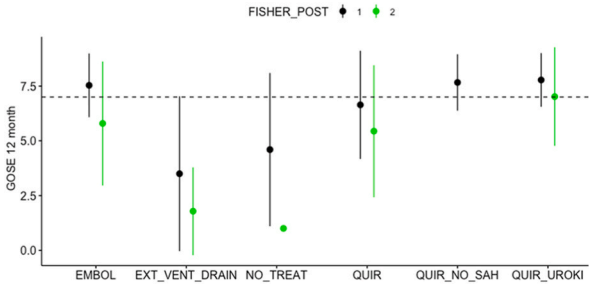

Fig. 3. GOSE (Glasgow Outcome Scale-Extended) at 12 months, according to the group, split the patients included in subgroup 1 (Fisher scores on admission 1 and 2) versus subgroup 2 (Fisher scores on admission 2 and 3). Groups: EMBOL (endovascular treatment), EXT VENT DRAIN (external ventricular drain only with no endovascular treatment or clipping), NO TREATMENT (no treatment), CLIPPING (surgical clipping), NO SAH CLIPPING (those with incidental aneurysm finding with no SAH) and CLIPPING + UROKINASE (surgical clipping with cisternal UK administration). FISHER_POST (Fisher scale inmediately afte the treatment modality applied). 1 and 2 refer to the two subgroups created. (1) corresponds to patients with Fisher scale grades 1 and 2 and (2) to those with grades 3 and 4.

amount of subarachnoid blood increases, so does the need for cisternal fibrinolysis. A fascinating study shows how older people with wider subarachnoid spaces are prone to bigger subarachnoid hemorrhages and how the cisternal fibrinolytic treatment particularly benefits them [13].

The data on ICU stays cannot be taken into consideration in this study for the external ventricular drain only and no treatment groups because these patients die sooner and in more significant numbers due to rebleeds and their poor general condition compared to patients that had the aneurysm occluded either endovascularly or surgically. The lack of statistically significant differences between endovascular treatment and surgically clipped aneurysms with simultaneous cisternal UK administration reflects that although these latter patients have, on average, higher Fisher grades, bigger aneurysms, and a worse medical condition than the other group, they have similar ICU stay lengths. Meanwhile, clipping with no UK administration showed a statistically significant more extended ICU stay ($p < 0.001$), reinforcing the idea that subarachnoid clot lysis with UK seems to reduce complications and improve the patient's clinical outcomes. Finally, clipping of the incidental aneurysms with no SAH had the shortest ICU stay, an expected result, as the amount of subarachnoid blood is the main leading cause of the patient's bad outcome [2,32].

Our results are corroborated in two recent metanalyses [15,16].

4.1. Historical steps in UK administration in the treatment of SAH

Yoshida et al. [36], in 1983, first reported cisternal irrigation with UK to lyse the aSAH blood clot. The results were unsatisfactory, perhaps because the dose was insufficient (36,000 UI). Kodama et al. [35] in 1988 increased the dose and added ascorbic acid, improving the results. Suzuki et al. [47] introduced head shaking (NEUROSHAKER, Mizuho, Tokyo, Japan) to improve UK basal cistern diffusion, a method later adopted by others [38]. In 2004, Amin-Hanjani et al. [48] published a meta-analysis including rtPA and UK, showing a DIND reduction and vasospasm control improvement.

In recent years, the cisternal UK administration has seen a renewed interest [13,15,16,20]. In 2011 Kai et al. [49] made an effort to make it available to the increasing number of patients undergoing endovascular aneurysm occlusion. As a result, we re-introduced the cisternal UK administration to speed up the subarachnoid clot lysis, reduce vasospasm and the need for CSF diversion as well as improving neurological outcomes. Our results are encouraging.

4.2. Effect of UK on the vasospasm

Many studies have repeatedly reported the positive effect of UK cisternal clot lysis in reducing vasospasm and (DIND) [13,15,16,20,41,45,49,50], particularly in Fisher grades ≥ 3[15,16,39,45,49,50]. Our study corroborates these findings.

Most studies have reported a significant reduction in the vasospasm rate and severity [38,51], varying from 35.2 to 14.2 % [51], 23 to 5 % [50], 12 to 6 % [52], and 15 to 2.8 % [45]. Ota et al. [20] reported a 3.6 % symptomatic vasospasm with intraoperative UK cisternal irrigation after aneurysm clipping. The best results are for Hamada et al. [12], who reported a zero vasospasm incidence when they infused the UK in the first 24 h post-aSAH.

The reduction in the vasospasm rate and severity correlates with a decrease in mortality and improved patient outcomes [15,16].

4.3. UK administration during aneurysm clipping versus after endovascular treatment

Administering this drug is just as effective after endovascular treatment as during craniotomy just after clipping [50], provided it reaches the basal cisterns [49]. Non-surgical administration is achieved by inserting a microcatheter in the lumbar thecal sac and navigating it through the spinal subdural space as far as the cisterna magna [49]. However, this procedure is not technically easy or readily available everywhere, and in fact, our institution did not have the facilities for it. Therefore, we administered the UK directly in the surgical field just after the aneurysm clipping.

4.4. UK effect of reducing the need for permanent CSF diversion

In surgically clipped aneurysms, the reduction in the hydrocephalus rate can be attributed, at least in part, to *lamina terminalis* fenestration [53]. Meanwhile, many research groups have reported that aSAH blood clot lysis with rtPA or UK is associated with a marked reduction in the post-hemorrhagic hydrocephalus rate [16,49], with some studies reporting zero incidence in patients with Fisher grades ≥ 3[49,54]. The average decrease in the need for permanent shunt insertion ranged from 19.2 to 5.7 % [54]. Our analysis also confirms the significant reduction in the necessity for permanent CSF diversion when administering UK in the subarachnoid space for patients with Fisher grades on admission ≥ 3.

Lumbar drainage is better than external ventricular drainage in reducing post-hemorrhagic hydrocephalus incidence [28,55], as only the former promotes CSF circulation [28,56]. Some have successfully combined intraventricular fibrinolytic drug administration with simultaneous lumbar CSF drainage [27]. We did not investigate this in our study.

4.5. Single bolus versus continuous catheter UK administration

Although some have relied on single-bolus administration just after aneurysm clipping [42] or endovascular treatment [57], others prefer infusion through implanted catheters over 2[58], 3[38,50,51], 7[57], 10[45] or even 14[59] days. Both administration methods appear equivalent, but the former reduces the risk of infection [58].

The reported infection rate for UK catheter infusion ranges from 0.92 % [45], 2.72 % [59], 3.47 % [38], 3.57 % [37], and 5.2 % [60], except Nakagomi et al. [50], who reported no cases of bacterial meningitis in 250 patients. Nor have we seen any case of bacterial meningitis in our series with intraoperative single bolus UK administration and no cisternal catheter insertion.

4.6. Site of the safe and most effective method of UK administration

UK diffuses with difficulty in a subarachnoid space blocked with blood clots. Only its intra-cisternal administration reduces the delayed ischemic events [50] while its intraventricular administration does not [7,61] unless a III^{r} ventriculostomy at its floor or the *lamina terminalis* is performed. The UK administration in the *cisterna magna* through a microcatheter inserted in the lumbar thecal sac has also proved helpful [49,54]. Meanwhile, injecting the UK in the lumbar thecal sac minimally affects aSAH clot lysis [51].

The head's passive rotation may improve the diffusion of the fibrinolytic agents and thus its positive effects [50].

4.7. Basal cistern UK dose administered

It varies between 36,000 [52], 48,000 [36], 60,000 [20,49], 120,000 [13,54], 144,000 [38], 420,000 [50,56,57], 432,360 [57], 440,000 [62], 480,000 [59], 691,000 [58], and 864,000 [45] UI. Some groups administer the UK through continuous irrigation or repeated boluses over several days (between 2 and 14 days) [38,50]. The effectiveness increases with the dose, as do the side effects. A total dose of 100,000UI has the most significant efficacy with fewer side effects, and, in fact, some researchers report hemorrhagic complications when administering doses beyond 100,000UI [45,50,62]. In our study, we administered 100,000UI of UK with zero hemorrhagic complications.

4.8. Timing of UK administration

The advice is to administer the intrathecal fibrinolytic agents as soon as possible after aneurysm occlusion, especially before the CSF levels of the plasminogen activator inhibitor increase [12]. Hamada et al. [12] reported a faster cisternal blood lysis rate if UK was administered before the first 24 h after aSAH. Direct UK cisternal irrigation just after aneurysm obliteration was used with very encouraging results and without additional hemorrhagic events by Yoshikane et al. [13] in elderly patients (120.000UI UK) and Ota et al. [20] 60.000UI UK. In our study, we administered the UK directly into the basal cisterns in a single 100.000UI bolus immediately after aneurysm occlusion with similar positive results despite not pursuing an aggressive subarachnoid clot removal. This maneuver can induce extra iatrogenic damage due to manipulation of the perforating vessels and the added risk of brain lacerations.

4.9. Why use UK or rtPA

rtPA is more potent than UK [57], which means that the hemorrhagic complications with basal cistern administration are higher with rtPA (ranging from 0 to 70 % [36,57]) than with UK (always under 2 % [38,50]). In addition, rtPA is significantly more expensive, and the hospital's finances might influence which one is available.

4.10. Nicardipine intrathecal administration

Both intraventricular and cisternal Nicardipine administration reduce the vasospasm severity and rate with fewer angioplasties needed [63–65]. Still, the cisternal administration has a more significant positive effect [63]. Unfortunately, it seems to increase the rate of permanent CSF diversion [65].

5. Limitations

Our study's limitations are that it is a single-center one, with a limited number of cases, particularly in some groups, its retrospective nature, its lack of randomization, and the interobserver variability in evaluating the amount of subarachnoid blood. Another drawback is that we treated posterior circulation aneurysms primarily by endovascular means. The most vital point of our study is that it has six groups, allowing comparisons between them. Further cooperative studies to expand the evidence obtained are currently being planned.

6. Conclusions

Basal cistern UK single bolus 100,000UI administration is safe and associated with neither intracranial hemorrhages nor systemic fibrinolysis. In addition, the lysis of the subarachnoid blood clot reduces the vasospasm rate and severity, the DINDs, the mortality, and the need for permanent CSF diversion. It also improves the neurological outcome and GOSE at discharge and six- and twelve-month follow-up.

CRediT authorship contribution statement

Vicente Vanaclocha: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Methodology,

Investigation, Formal analysis, Data curation, Conceptualization. **Juan-Manuel Herrera:** Writing – review & editing, Validation, Software, Resources, Methodology, Data curation. **Marlon Rivera-Paz:** Writing – review & editing, Software, Resources, Project administration, Methodology, Formal analysis. **Nieves Saiz-Sapena:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Investigation, Data curation. **Leyre Vanaclocha:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Formal analysis.

Data availability

The data collected for the study and analysis methods will be made available upon request from any qualified investigator.

Ethics approval

Research and Ethics Committees (Clinical Trial Registration number: Hospital General Universitario de Valencia, Valencia, Spain, CEIm 16/June/2019, ClinicalTrials.gov Identifier: NCT04792944). We performed the study following the ethical standards in the 1964 Declaration of Helsinki and its later amendments. Informed consent was obtained from each patient.

AI-assited technologies

We did not use any of these technologies.

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Declaration of competing interest

The authors declare that they have no competing financial interests of personal relationships that could have apperared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e40080.

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