# Efficacy of combined intravenous plus intrathecal nimodipine administration in patients with severe cerebral vasospasm post-aneurysmal subarachnoid hemorrhage: A retrospective cohort study

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**Abstract.** Aneurysmal subarachnoid hemorrhage (aSAH) and the ensuing cerebral vasospasm (CV) and delayed cerebral ischemia (DCI) comprise the main reasons for morbidity and mortality in affected patients. The present study aimed to evaluate the efficacy of the use of combined intravenous (IV) and intrathecal (IT) nimodipine therapy for preventing permanent neurological deterioration and DCI in patients suffering from CV post-hemorrhage. The evaluation was performed using computed tomography perfusion and transcranial doppler ultrasound. The present retrospective cohort study analyzed 14 out of 146 patients diagnosed with vasospasm due to spontaneous or aSAH. These patients were divided into two groups as follows: i) The IV group, which included patients treated with only IV nimodipine; and ii) the IV + IT group, which included patients who received IV nimodipine in combination with IT nimodipine. Of the 14 patients, 7 patients were males (50%), and the mean age was 50.9 years (SD ±19 years). In total, 6 patients [42.8%; 5 (35.7%) from group A and 1 (7.1%) from group B], who experienced clinical symptoms with severe CV, were administered intra-arterial calcium channel therapy or/and IT nimodipine following the early identification of symptomatic vasospasm. The rate of adverse ischemic events was lower with IT nimodipine management during the 1 month of follow-up (6 vs. 2 events; odds ratio, 15.00; 95% confidence interval, 1.03-218.31; P=0.031). On the whole, the findings of the present study suggest that the combined use of IT nimodipine with IV admission for patients post-aSAH who developed severe CV is a safe procedure that may prevent permanent neurological deterioration and delay unfavorable ischemic incidents.

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## Introduction

Cerebral vasospasm (CV) represents the most crucial complication encountered following an aneurysmal subarachnoid hemorrhage (aSAH). However, despite the use of different therapeutic procedures, 16-65% of these patients consequently develop delayed cerebral ischemia (DCI). The early detection of CV in aSAH may be difficult both clinically and radiographically (1).

Despite all existing treatment approaches, aSAH, and the ensuing CV and DCI are the leading causes of morbidity and mortality in affected patients (1,2). Although 40-70% of patients exhibit substantial arterial narrowing (on a doppler ultrasound or in angiography), only 20 to 30% of these patients present with DCI (3,4). Intra-arterial digital subtraction angiography

(DSA) is commonly used as a screening device for the identification of CV and focal cerebral ischemia (CI) (5). Furthermore, DSA allows for therapeutic endovascular interventions, such as balloon angioplasty and stenting in each intracranial artery if required (5). Still, the detailed delineation of the vessels may not be obtained when multiple stenoses are present, and DSA also constitutes an invasive method. By contrast, computed tomography (CT) perfusion (CTP) can identify damage which is not recognized by other methods and may be beneficial for assessing CI related to aSAH (6). CTP allows for the early detection of CI and provides essential information on the ischemic penumbra, which is of utmost importance for the early identification and management of CI (7). In addition, CTP can be used in daily practice, or it can be used as a separate diagnostic tool without the need for magnetic resonance imaging (MRI) data to predict the outcomes of patients with aSAH (7,8). With conventional MRI, performed pre- and post-contrast administration, irreversibly damaged brain tissue cannot be discriminated from infarcted brain tissue (penumbra), which is under the risk of ischemia (7). Even though a conventional MRI provides anatomical details, it does not provide functional details on the dynamic process of ischemia and its elongation. Thus, CTP has currently become an important technique (7). However, there are insufficient data on its association with other non-invasive techniques, such as transcranial Doppler (TCD) ultrasound (3,9,10).

Although several studies have only confirmed the efficacy of nimodipine in patients with CV and subsequent CI, multiple centers have included papaverine, hemodynamic (triplex) therapy and balloon angioplasty in their treatment algorithms for severe CV, despite the fact that these have yet to be established as life-saving therapies (2,11,12). In addition, since 1982, the effect of locally applied nimodipine on vasospasm has been widely used and is well-known (13). However, to the best of our knowledge, no study to date has demonstrated the efficacy of combined intrathecal (IT) and intravenous (IV) nimodipine therapy for cerebral vasospasm. In this respect, the present retrospective study aimed to evaluate the efficacy of combined IV and IT nimodipine therapy for preventing permanent neurological deterioration in patients with severe post-hemorrhagic CV. The present study also aimed to assess the effectiveness of this technique in the clinical outcomes of patients with aSAH.

## Patients and methods

*Patient information*. The present retrospective cohort study analyzed 14 out of 146 patients diagnosed with vasospasm due to spontaneous or aneurysmal SAH from August, 2019 through June, 2021 at Nicosia General Hospital, Cyprus. The inclusion criteria included the following: An age ≥21 years, surgical or endovascular repair of the ruptured aneurysm, severe vasospasm and CI on a CTP and TCD evaluation. The Institutional Review Board (IRB) of Nicosia General Hospital, Cyprus approved the study (IRB no. ΕΕΒΚ ΕΠ 2019.02.110). The study was in line with the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000). Written informed was obtained from the patients.

The patients were divided into two groups as follows: i) The IV group, which included patients treated with only IV nimodipine; and ii) the IV + IT group, which included those patients who received IV nimodipine together with IT nimodipine [20 ml (0.4 mg) bolus via the external ventricular drain (EVD) system].

Table I. Exclusion criteria used in the present study.

| |
|---|
| Factors predisposing to cerebral ischemia apart from vasospasm |
| Atrial fibrillation or other arrhythmias |
| Diabetes mellitus |
| Hyperlipidemia |
| Hypotension |
| Factors predisposing to bleeding |
| Anticoagulant agents |
| Severe liver impairment |

Subarachnoid hemorrhage secondary to traumatic or mycotic aneurysm.

Following clinical deterioration due to severe CV, all patients were placed in the intensive care unit (ICU) with intracranial pressure (ICP) monitoring. Overall, the target parameters for the prophylactic pathway were a central venous pressure >4 mm Hg and a cerebral perfusion pressure >60 mm Hg. All patients were administered prophylactic IV nimodipine at 2 mg/h for at least 21 days. The exclusion criteria are presented in Table I. The methods used for the final inclusion of patients in the study are illustrated in Fig. 1.

*Follow-up*. All participants had a follow-up for 30 days or until the day of discharge from the hospital. At 30 days, outcomes were evaluated using a CT scan and a complete neurological examination; a Glasgow Coma Scale (GCS) assessment was also performed. The clinical outcome was categorized according to neurological or radiological evidence as improved or adverse (unaltered, worse, or mortality).

*Procedure for IT nimodipine administration*. An initial IT bolus of nimodipine (Nimotop, Bayer AG) was administered in Ringer's solution (Demo S.A.) at 2 mg/100 ml (14-16). 20 ml (0.4 mg) were used for an IT bolus via the EVD after releasing 20 ml cerebrospinal fluid (CSF). The IT bolus was repeated every 24 h during the first 7 days of the event. The EVD overflow level was placed 10 cm above ear level to provide CSF outflow. The intracranial pressure values were recorded using an online ICU data management system and ICP monitoring.

*Radiological CV or CI evaluation*. During the 3rd to the 6th day following aSAH, CTP and TCD were performed on all the participants to identify a quantifiable index of CI after CV, given that angiographically detectable cerebral artery constriction is most commonly present 3-10 days after the onset. Cerebral blood volume (CBV) and cerebral blood flow (CBF) values were documented and assessed after receiving two contiguous 10-mm-thick slices placed at the anatomical point of the basal ganglia with similar angulation as for native CT. A bolus of 50 ml non-ionic contrast medium (Imeron 400, Bracco Imaging Deutschland GmbH) accompanied by 30 ml saline was then infused using a power injector (Medcomp

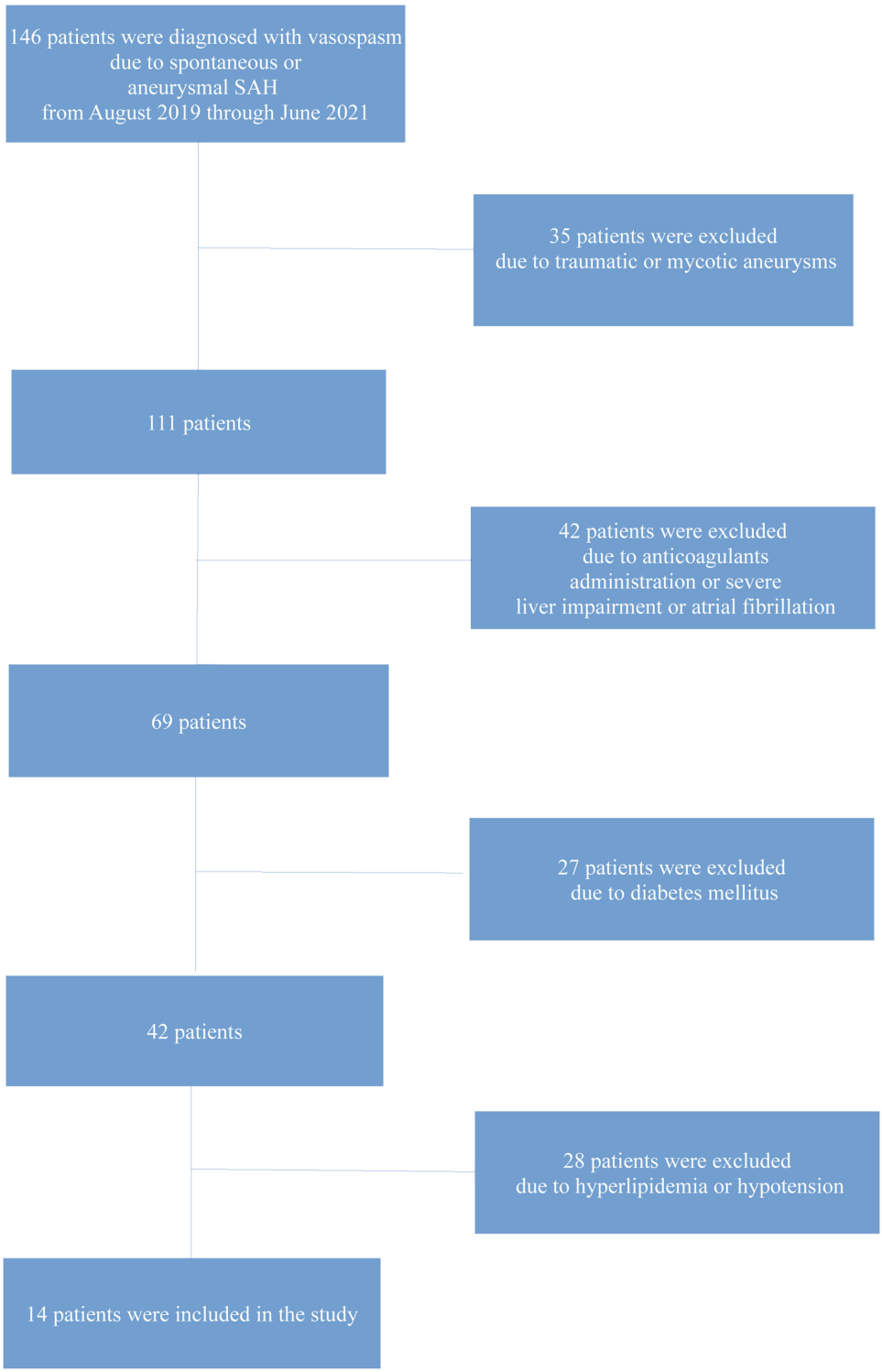


Figure 1. Diagram illustrating how patients in the study were selected for final inclusion.

USA) at a flow rate of 4 ml/sec. Subsequently, 40 images were captured at each slice level at a rate of two images per second (120 kV, 110 mAs, 512x512 matrices). CTP color maps were qualitatively assessed using a visual grading scale, and CTP parameters were established utilizing software platforms (Perfusion CT, Siemens). A positive visual measurement was recorded for side-to-side discrepancies or apparent bilateral anomalies, suggesting a decline in CBF, CBV and the mean transit time (MTT), which were related to the central volume principle: CBF=CBV/MTT (3,17). CBV was determined in milliliters of blood per 100 g of the brain and was established as the volume of blood flow for a certain amount of brain tissue (3,18). MTT was determined as the average time needed for blood to move through a particular brain volume and was calculated in seconds (3).

Moreover, 15-20 min prior to CTP, TCD via a trans-temporal window was performed to illustrate and assess flow velocities in the anterior cerebral artery (ACA), middle cerebral artery

Table II. Baseline characteristics of the patients in the present study.

| Parameters | All patients, n=14 (100%) | IV group, n=7 (50%) | IV + IT group, n=7 (50%) | P-value |
|---|---|---|---|---|
| Age, years | 50.9±19 | 52.7±16 | 49.1±23 | 0.848 |
| Sex (male), n (%) | 7 (50) | 2 (14.2) | 5 (35.7) | 0.109 |
| GCS of admission | 11.6±3 | 11.2±3 | 12.0±3 | 0.896 |
| Procedure | | | | |
| Surgical, n (%) | 8 (57.1) | 3 (21.4) | 5 (35.7) | 0.280 |
| Endovascular, n (%) | 6 (42.8) | 4 (28.5) | 2 (14.2) | |
| ICU stay, days | 38.7±17 | 40.0±11 | 37.5±23 | 0.522 |
| Duration of intrathecal nimodipine treatment, days | 6.3±1 | 6.7±0 | 6.0±1 | 0.410 |
| Hunt and Hess grade | | | | |
| I, n (%) | 4 (28.5) | 2 (14.2) | 2 (14.2) | NS |
| II, n (%) | 4 (28.5) | 1 (7.1) | 3 (21.4) | 0.237 |
| III, n (%) | 4 (28.5) | 3 (21.4) | 1 (7.1) | 0.237 |
| IV, n (%) | 1 (7.1) | 1 (7.1) | 0 (0) | 0.299 |
| V, n (%) | 1 (7.1) | 0 (0) | 1 (7.1) | 0.299 |
| Modified Fisher scale | | | | |
| I, n (%) | 4 (28.5) | 2 (14.2) | 2 (14.2) | NS |
| II, n (%) | 7 (50) | 2 (14.2) | 5 (35.7) | 0.109 |
| III, n (%) | 2 (14.2) | 2 (14.2) | 0 (0) | 0.127 |
| IV, n (%) | 1 (7.1) | 1 (7.1) | 0 (0) | 0.299 |
| Aneurysm location | | | | |
| ACoA | 2 (14.2) | 1 (7.1) | 1 (7.1) | NS |
| MCA | 6 (42.8) | 2 (14.2) | 4 (28.5) | 0.280 |
| PICA | 2 (14.2) | 1 (7.1) | 1 (7.1) | 1.000 |
| Pcom | 2 (14.2) | 2 (14.2) | 0 (0) | 0.127 |
| ICA | 2 (14.2) | 1 (7.1) | 1 (7.1) | NS |
| CT perfusion (white matter) parameters | | | | |
| CBF mean ± SD ($ml_{blood}/100g_{tissue}$) | 15.8±10 | 12.7±10 | 18.8±10 | 0.084 |
| CBVmean ± SD ($ml_{blood}/100g_{tissue}$) | 1.5±1 | 1.3±0. | 1.7±1 | 0.949 |
| MMTmean ± $SD_{(sec)}$ | 4.4±1 | 4.6±2 | 4.3±1 | 0.848 |
| TCD parameters | | | | |
| Total PSV mean ± SD (cm/sec) | 94.3±30 | 108.8±36 | 79.9±12 | 0.110 |
| Total PI mean ± SD (cm/sec) | 0.9±0 | 0.9±0 | 0.9±0 | 0.794 |

CT, computed tomography; MAP, mean arterial pressure; MCA, middle cerebral artery; ACoA, anterior communicate artery; PICA, posterior inferior cerebral artery; ICA, internal carotid artery; Pcom, posterior communicating artery; MMTmean, mean value of mean transit time; CBVmean, mean value of cerebral blood volume; ICU, intensive care unit; CBFmean, mean value of cerebral blood flow; GCS, Glasgow coma scale; PI, pulsatility index; PSV, peak systolic velocity, TCD, transcranial doppler; NS, not significant.

(MCA), posterior cerebellar artery (PCA) and posterior communicating artery. Peak systolic velocity (PSV, in cm/sec), which is the maximum flow systolic velocity value, was calculated at the peak of the waveform. End-diastolic velocity (EDV, in cm/sec) was measured at the end of diastole, traditionally at the lowest point before the start of a new waveform, and was found to be between 20 and 50% of the PSV value (3,19). The Lindegaard ratio, defined as the MCA mean CBF velocity divided by the extracranial internal carotid artery mean CBF velocity, was used to indicate systemic hemodynamic alterations. The mean flow velocity (in cm/sec) was calculated as the average of the edge frequency across a cardiac cycle, which was calculated as the EDV plus one-third of the variance between PSV and EDV [MFV (cm/sec)=(PSV + 2EDV/3)] (3,19). Sonographic CV was defined as an MFV >140 cm/sec in the MCA, ACA, and/or a PCA or >90 cm/sec in the basilar artery. As an index for intracranial pressure elevation, the pulsatility index (PI)=PSV-EDV/MFV was used (3,19).

*Statistical analysis*. The normality of the distribution of variables was determined using the Shapiro-Wilk test. Categorical variables were compared between groups using the Fisher's exact test or the Chi-squared test, and continuous data were compared using the Mann-Whitney U test. A P-value <0.05

Table III. Univariate analysis (outcome: Ischemic event at 1 month).

| Parameters | Patients with ischemic event, n=6 (42.8%) | Patients without ischemic event, n=8 (57.2%) | P-value |
|---|---|---|---|
| Groups | | | |
| IV group | 5 (35.7) | 2 (14.2) | 0.031 |
| IV + IT group | 1 (7.1) | 6 (42.8) | |
| Age, years | 53.1±18 | 49.2±21 | 0.796 |
| Sex (male), n (%) | 2 (14.2) | 5 (35.7) | 0.280 |
| GCS of admission | 11.8±3 | 11.5±3 | 0.740 |
| Procedure | | | |
| Surgical, n (%) | 2 (14.2) | 6 (42.8) | 0.119 |
| Endovascular, n (%) | 4 (28.5) | 2 (14.2) | 0.119 |
| ICU stay, days | 45.8±15 | 33.5±18 | 0.155 |
| Duration of intrathecal nimodipine treatment, days | 6.6±0 | 6.1±1 | 0.650 |
| Hunt and Hess grade | | | |
| I, n (%) | 2 (14.2) | 2 (14.2) | 0.733 |
| II, n (%) | 1 (7.1) | 3 (21.4) | 0.393 |
| III, n (%) | 3 (21.4) | 1 (7.1) | 0.124 |
| IV, n (%) | 0 (0) | 1 (7.1) | 0.369 |
| V, n (%) | 0 (0) | 1 (7.1) | 0.369 |
| Modified Fisher scale | | | |
| I, n (%) | 1 (7.1) | 3 (21.4) | 0.393 |
| II, n (%) | 3 (21.4) | 4 (28.5) | NS |
| III, n (%) | 2 (14.2) | 0 (0) | 0.078 |
| IV, n (%) | 0 (0) | 1 (7.1) | 0.369 |
| Aneurysm location | | | |
| ACoA | 1 (7.1) | 1 (7.1) | 0.825 |
| MCA | 2 (14.2) | 4 (28.5) | 0.533 |
| PICA | 1 (7.1) | 1 (7.1) | 0.825 |
| Pcom | 1 (7.1) | 1 (7.1) | 0.825 |
| ICA | 1 (7.1) | 1 (7.1) | 0.825 |
| CT perfusion (white matter) parameters | | | |
| CBFmean ± SD ($ml_{blood}/100g_{tissue}$) | 10.3±8 | 19.9±10 | 0.039 |
| CBVmean ± SD ($ml_{blood}/100g_{tissue}$) | 1.3±1 | 1.6±1 | 0.846 |
| MMTmean ± $SD_{(sec)}$ | 4.7±2 | 4.2±1 | 0.897 |
| TCD parameters | | | |
| Total PSV mean ± SD (cm/sec) | 114.4±35 | 79.3±13 | 0.039 |
| Total PI mean ± SD (cm/sec) | 1.0±0. | 0.9±0. | 0.692 |

CT, computed tomography; MAP, mean arterial pressure; MCA, middle cerebral artery; ACoA, anterior communicate artery; PICA, posterior inferior cerebral artery; ICA, internal carotid artery; Pcom, posterior communicating artery; MMTmean, mean value of mean transit time; CBVmean, mean value of cerebral blood volume; ICU, intensive care unit; CBFmean, mean value of cerebral blood flow; GCS, Glasgow coma scale; PI, pulsatility index; PSV, peak systolic velocity, TCD, transcranial doppler; NS, not significant.

was considered to indicate a statistically significant difference. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS 11; SPSS, Inc.).

## Results

A total of 14 patients were enrolled in the study (Table II). Of these, 7 patients were males (50%), and the mean age of the patients was 50.9 years (SD ±19 years). Of these, 8 patients (57.1%) underwent surgical and 6 patients (42.8%) underwent endovascular procedures. The outcomes and baseline characteristics of the participants are presented in Table II. Overall, 6 patients [42.8%; 5 (35.7%) from the IV group and 1 (7.1%) from the IV + IT group], who experienced clinical symptoms with severe CV, such as a decline in the level of consciousness, were administered hypervolemic hypertensive and intra-arterial calcium channel therapy or IT nimodipine following the early identification of symptomatic vasospasm with CTP or TCD

Table IV. Multivariate analysis (outcome: Ischemic event at 1 month).

| | | | 95% CI for Exp(B) | |
|---|---|---|---|---|
| Parameter | P-value | Exp(B)/OR | Lower | Upper |
| Groups | 0.047 | 15.00 | 1.030 | 218.310 |
| CBFmean ± SD ($ml_{blood}/100g_{tissue}$) | 0.047 | -0.456 | -0.044 | -0.001 |
| Total PSV mean ± SD (cm/sec) | 0.023 | 0.579 | 0.002 | 0.017 |
| Group | 0.042 | 0.345 | 0.004 | 0.012 |

PSV, peak systolic velocity; CBFmean, mean value of cerebral blood flow; SD, standard deviation; CI, confidence interval.

findings. These patients presented with permanent neurological deficits, as detected using a CT scan following 1 month of follow-up. The TCD and CTP data of the patients are presented in Tables II and III. In the 6 patients (42.8%) who presented with permanent neurological deficits due to vasospasm, CTP revealed reduced a CBF and prolonged MTT. However, TCD also revealed elevated PSV and PI values in the same patients (Table III).

*Diagnostics*. Univariate analysis revealed that there was a statistically significant difference in the mean values of CBF and PSV between participants who developed adverse ischemic events and those who did not develop adverse ischemic events (P<0.05, Table III). The rate of adverse ischemic events was lower with IT nimodipine management during 1 month of follow-up (6 vs. 2 events; odds ratio, 15.00; 95% confidence interval, 1.03-218.31; P=0.047) (Tables III and IV). All the variables with a statistically significant association with the adverse ischemic events of 1 month (the therapy group, CBF and PSV were included in the multivariate analysis. Multivariate analysis (Table IV) revealed that CBF, PSV and the therapy group were independent factors in detecting an ischemic event in 1 month (P<0.05).

## Discussion

The of the findings present study suggested that the combined use of IT nimodipine with IV therapy in post-aSAH patients who develop severe CV is a safe procedure that may prevent permanent neurological deterioration and delay unfavorable ischemic incidents. Until 2008, the only clinical trial evaluating the effectiveness of the local IT administration of nimodipine was reported by Auer *et al* (13). In the present study, a $2.4x10^{-5}$ M solution of nimodipine was applied either during the surgery directly to the cerebral vessels or through a catheter post-operatively, with favorable results for vasospasm (13). To date, the effectiveness of IT applied nimodipine has been tested in other clinical trials, demonstrating a notable improvement in cerebral perfusion as detected using CTP and follow-up DSA in the majority of patients (12,20-22). However, no significant adverse effects have been observed following the IT administration of calcium blocking agents (nimodipine/nicardipine) or magnesium sulfate (13). Although the present study included a small sample size, the results obtained with the IT nimodipine administration using an EVD demonstrated a favorable outcome in patients who developed severe CV following aSAH. Moreover, avoiding the risks of the invasive DSA procedure, the utility of CTP and TCD are the most common and studied imaging techniques (3,23).

According to previous studies, the use of IT vasodilating agents is time-dependent, with better effects associated with early drug placement (24). In the present study, the IT bolus was repeated every 24 h during the first 7 days of the event with positive results. Pharmacodynamics diverge between the CSF and the systemic installation, and thus, drug efficacy may vary considerably (25). Although an IT drug placement has numerous benefits, such as direct access to affected vessels, a thick clot may block the stream of drugs from the ventricle to basal blood vessels in vasospasm (26). Moreover, no existing technique can evaluate the effectiveness of nimodipine administered IT vs. systemically. To the best of our knowledge, no study to date, has demonstrated the efficacy of combined IT and IV nimodipine therapy for CV. The present study evaluated two groups of patients depending on IT nimodipine therapy uptake. The clinical outcomes without ischemic damage in CTP at 1 month of follow-up were related to those of the group treated with a combination of IV and IT nimodipine therapy administered in Ringer's solution at a concentration of 2 mg/100 ml. By contrast, the group treated with only IV nimodipine administration exhibited unfavorable clinical outcomes with ischemic damage shown in the CTP and TCD.

The present study has certain limitations. First, the present study was a small, single-center study. Another limitation is its retrospective design. Therefore, firm conclusions regarding the role of IT nimodipine in managing severe vasospasm following aSAH cannot be reached. However, the findings presented herein may serve as a basis for more extensive clinical studies in the future.

In conclusion, although in recent years, notable efforts have been made to gain a better understanding of the mechanisms of CV and the further development of therapeutic agents, IT nimodipine administration is not yet considered a mainstream standard of care. The findings of the present study suggest that the combination of IT and IV nimodipine therapy may be a viable option for treating CV following aSAH. However, the findings of the present small study should be interpreted cautiously and serve as a basis for a future, more extensive clinical investigations.

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**Availability of data and materials**

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

**Authors' contributions**

GF, AAF and VEG conceptualized the study. KF, VEG, AAF, PP, IT, DAS, NT, VT, NM and KT made a substantial contribution to the analysis and interpretation of the data, and wrote and prepared the draft of the manuscript. VEG and GF analyzed the data and provided critical revisions. VT and GF confirm the authenticity of all the data. All authors contributed to manuscript revision, and have read and approved the final version of the manuscript.

**Ethics approval and consent to participate**

The Institutional Review Board (IRB) of Nicosia General Hospital, Cyprus approved the study (IRB no. ΕΕΒΚ ΕΠ 2019.02.110). The study was in line with the Declaration of Helsinki in 1995 (as revised in Edinburgh 2000). Written informed was obtained from all the patients.

**Patient consent for publication**

Not applicable.

**Competing interests**

The authors declare that they have no competing interests.

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