PRELIMINARY DATA FROM CLEVIDIPINE ADMINISTRATION VERSUS OTHER ANTIHYPERTENSIVE TREATMENTS IN PATIENTS WITH ACUTE HYPERTENSIVE INTRACEREBRAL HEMORRHAGE

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ABSTRACT

Background and Aims: Intracerebral haemorrhage (ICH) has been associated with worse functional outcome and increased mortality, related to hematoma volume and expansion. Blood pressure (BP) reduction may attenuate hematoma expansion. We sought to investigate whether clevidipine, an intravenous administered calcium-channel blocker, achieved better ICH volume reduction and better functional outcome in patients with hypertensive ICH compared to standard-of-care antihypertensive treatment. **Methods:** This is a prospective case-control study, assessing the clinical severity, the hematoma size differentiation and the clinical outcome in patients with hypertensive ICH, who received intravenous clevidipine in the acute phase versus standard-of-care antihypertensive treatment (clonidine and/or labetalol). **Results:** This study included forty-four ICH patients (clevidipine-group: 17 – controls: 27). There was no difference in demographic characteristics and admission National Institutes of Health Stroke Scale (NIHSS) score. A statistically significant ICH volume change on 24h follow-up brain computed tomography was observed in the clevidipine group (11.8% reduction vs 0.4% increase in the control-group; p-value: 0.04). Moreover, a non-significant trend towards NIHSS-score improvement at discharge was observed in clevidipine group [ΔNIHSS score 4 (1-7) in the clevidipine group vs 2 (0-4) in the control group], whereas functional outcomes and mortality at 3 months were similar. No serious adverse events were detected among patients treated with clevidipine. **Conclusions:** The present study highlights that clevidipine represents a safe and effective alternative in terms of hypertension control among ICH patients in the acute phase. However, these findings, indicating superiority of clevidipine, require confirmation in larger studies.

Key-words: intracerebral hemorrhage, clevidipine, antihypertensive agents, hematoma.

ΠΡΟΚΑΤΑΡΚΤΙΚΑ ΔΕΔΟΜΕΝΑ ΑΠΟ ΤΗ ΧΟΡΗΓΗΣΗ ΚΛΕΒΙΔΙΠΙΝΗΣ ΕΝΑΝΤΙ ΛΟΙΠΩΝ ΑΝΤΙΥΠΕΡΤΑΣΙΚΩΝ ΣΤΗΝ ΕΚΒΑΣΗ ΑΣΘΕΝΩΝ ΜΕ ΟΞΕΙΑ ΕΝΔΟΕΓΚΕΦΑΛΙΚΗ ΑΙΜΟΡΡΑΓΙΑ ΥΠΕΡΤΑΣΙΚΗΣ ΑΙΤΙΟΛΟΓΙΑΣ

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ΠΕΡΙΛΗΨΗ

Ιστορικό: Στην ενδοεγκεφαλική αιμορραγία (ΕΑ), ο όγκος και η επέκταση του αιματώματος σχετίζονται με αυξημένη θνησιμότητα και δυσμενέστερη λειτουργική έκβαση. Η μείωση της αρτηριακής πίεσης ενδέχεται να περιορίσει την επέκταση του αιματώματος. Σκοπός της παρούσας μελέτης είναι η διερεύνηση της αποτελεσματικότητας της κλεβιδιπίνης ως προς τη μείωση του όγκου της αιμορραγίας και τη βελτίωση της λειτουργικής έκβασης σε ασθενείς με ΕΑ υπερτασικής αιτιολογίας, σε σύγκριση με τη συνήθη αντιϋπερτασική αγωγή. **Μέθοδοι**: Πρόκειται για προοπτική μελέτη ασθενών-μαρτύρων με στόχο την αξιολόγηση της κλινικής βαρύτητας, της μεταβολής του όγκου του αιματώματος και της κλινικής έκβασης σε ασθενείς με υπερτασικής

αιτιολογίας ΕΑ, οι οποίοι έλαβαν ενδοφλέβια κλεβιδιπίνη κατά την οξεία φάση, συγκριτικά με ασθενείς που έλαβαν την καθιερωμένη αντιϋπερτασική αγωγή.
Αποτελέσματα: Συνολικά εντάχθηκαν στη μελέτη 44 ασθενείς (ομάδα κλεβιδιπίνης: 17– ομάδα ελέγχου: 27). Δεν παρατηρήθηκαν διαφορές όσον αφορά τα δημογραφικά χαρακτηριστικά και τη βαρύτητα της κλίμακας National Institutes of Health Stroke Scale (NIHSS) κατά την εισαγωγή. Στην ομάδα της κλεβιδιπίνης καταγράφηκε στατιστικώς σημαντική μείωση του όγκου αιματώματος στο 24ωρο (μείωση 11,8% έναντι αύξησης 0,4% στην ομάδα ελέγχου, p=0,04). Μη στατιστικά σημαντική τάση μεγαλύτερης βελτίωσης της κλίμακας NIHSS παρατηρήθηκε στην ομάδα της κλεβιδιπίνης κατά το εξιτήριο, [διάμεση μεταβολή NIHSS: 4 (1–7) έναντι 2 (0–4), αντίστοιχα], ενώ η λειτουργική έκβαση και τα ποσοστά θνησιμότητας στο τρίμηνο ήταν παρόμοια.
Συμπεράσματα: Η παρούσα μελέτη υποδεικνύει ότι η κλεβιδιπίνη αποτελεί μια ασφαλή και ενδεχομένως αποτελεσματική επιλογή στην οξεία φάση της ΕΑ. Ωστόσο, η πιθανή υπεροχή της ως προς τις άλλες θεραπείες χρήζει επιβεβαίωσης σε μεγαλύτερες μελέτες.

Λέξεις-κλειδιά: Ενδοεγκεφαλική αιμορραγία, αντιυπερτασική αγωγή, κλεβιδιπίνη, αιμάτωμα

INTRODUCTION

Intracerebral haemorrhage (ICH) is a significant cause of morbidity and mortality and has been associated with severe long-term disability.[1] It accounts for 10% to 15% of all strokes, with an incidence of 24.6 per 100,000 person-years and increasing frequency due to the use of anticoagulants, antiplatelet agents, and aging population.[1-3] The economic impact of haemorrhagic strokes stems partly from their high mortality rate, with up to half of the patients dying within the first 30 days, often despite prolonged stays in Intensive Care Units.[4]

Management of ICH ranges from conservative to surgical treatment, depending on the location and the size of the haemorrhage, as well as the severity of neurological symptoms.[2,5] The therapeutic approach to ICH focuses on managing arterial hypertension, preventing haematoma expansion (HE) and controlling intracranial pressure (ICP).[6] Elevated blood pressure (BP) has been associated with higher risk of HE, unfavourable functional outcomes and higher mortality rates.[7-10] HE is a common cause of secondary neurological deterioration and is directly associated with survival and functional independence in up to one-third of patients after ICH onset. Expansion typically occurs within 24 hours, although delayed expansion has also been reported.[11] Its strong prognostic significance stems mainly from its potential to cause midline shift and herniation. Even relatively minor hematoma expansion can lead to neurological deterioration.[12,13]

To prevent hematoma expansion, the European Stroke Organisation (ESO) recommends initiating antihypertensive therapy as early as possible, ideally within 2 hours of symptom onset.[14] The reduction in systolic BP (SBP) should not exceed 90 mmHg from baseline. In patients with hyperacute ICH (<6 hours), a target SBP of less than 140 mmHg is suggested to reduce HE.[14,15] Intensified BP management in acute ICH appears safe. According to a meta-analysis by Tsivgoulis et al., patients without strict BP control had worse outcomes during 3-month follow-up. Furthermore, aggressive BP reduction was associated with less HE at 24 hours.[16]

Available treatment options for BP control include oral and intravenous (iv) antihypertensive medications. In the acute setting with severe hypertension, iv administration is recommended.[14] Antihypertensive drugs, administered iv and available in Greece, include labetalol (a beta-blocker) and clonidine (an α2 agonist). Recently, clevidipine, a dihydropyridine calcium channel blocker, was introduced.[17] According to the Evaluation of Patients with Acute Hypertension and Intracerebral Hemorrhage with Intravenous Clevidipine Treatment (ACCELERATE) trial, clevidipine monotherapy proved effective and safe for rapid BP reduction in a cohort of 35 ICH patients, also showing a positive impact on HE.[18]

In this observational study we sought to prospectively investigate the clinical severity, treatment, haematoma size evolution – expansion or reduction – and clinical outcome of ICH patients admitted to the Stroke Unit of the Second Department of Neurology of the National and Kapodistrian University of Athens, who received intravenous clevidipine for BP management during the acute phase of ICH. These patients were compared to a control group of age- and sex-matched ICH patients from previous five years, who received labetalol and/or clonidine during the acute ICH phase.

MATERIALS AND METHODS

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

ETHICAL APPROVAL AND PATIENT CONSENT

This study is in accordance with the Declaration of Helsinki principles, and institutional review board approval was obtained from the Ethics Committee of ''Attikon'' University Hospital (decision number: EDB 302/25-04-2024). Written informed consent was obtained from all patients or their legal representatives before enrolment.

Participants

This study was performed in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for reporting observational research.[19] Participants were recruited from a prospective cohort of patients who were diagnosed with spontaneous hypertensive ICH (SBP on admission ≥140mmHg), admitted to the Stroke Unit of the Second Department of Neurology of the National and Kapodistrian University in Athens, Greece and treated with iv clevidipine within the first 24 hours of symptom onset.[14] The recruitment of the participants took place from January 2024 until April 2025, since clevidipine administration became available in our hospital in January 2024. A retrospective chart review from January 2018 up to December 2023 was also conducted for age- and sex-matched hypertensive ICH patients previously treated with other antihypertensive medications (labetalol, clonidine). The underlying cause for the ICH in both the clevidipine and the control group was found to be uncontrolled hypertension, excluding other common causes of ICH such as anticoagulant use, trauma or aneurysm rupture.

The patients were included in the present study if they were older than 18 years old, had a diagnosis of acute ICH and signed the informed consent. The exclusion criterion was refusal to provide informed consent or death withing the first 24 hours post admission, a fact which rendered the repeat CT scan impossible. Moreover, anticoagulant-related ICH were also excluded.

For each patient, demographics and previous history of arterial hypertension were recorded. All patients underwent an initial brain CT scan at admission and a follow-up brain CT 24 hours following admission. Hematoma volume, based on the ABC/2 formula, was calculated on both scans, and the ICH score was determined.[20,21] Both measurements were performed by two independent neurologists with experience in stroke neurology and the mean values of these measurements were used. Evidence regarding the BP upon admission, the National Institutes of Health Stroke Scale (NIHSS) score at admission and discharge and modified Rankin Scale (mRS) score at 3 months were documented.[22]

Additionally, in the clevidipine group, the time from clevidipine administration initiation to BP control, the days of clevidipine therapy and the maximum required clevidipine dose were recorded. Clevidipine was initiated and titrated according to the prescribing information to achieve the target SBP range. The clevidipine infusion rate could be titrated to control the SBP within the target range.

The primary endpoint of the present study was the evolution of the hematoma volume. HE was defined as a relative increase of ≥ 33% or an absolute increase of ≥ 6 mL in hematoma volume from baseline to follow-up CT. Secondary outcomes included 3-month mRS score, 3-month good functional outcome (defined as an mRS-score 0-2), ΔNIHSS between admission and discharge and 3-month mortality. Adverse events observed in the clevidipine group were also documented.

Statistical Analysis

Continuous variables were presented as mean with standard deviation (SD), in case of normal distribution, and as median with interquartile ranges (IQR), in case of skewed deviation. Continuous variables were tested with the Student's ***t***-test (normally distributed data) or Mann–Whitney U-test (non-normally distributed data). Categorical variables were presented as the number of patients with the corresponding percentages. For dichotomised variables, the chi-square test was used. All statistical analyses were conducted using the R software version 2025.05.0+496.[23]

RESULTS

In this study fourty-four ICH patients (clevidipine-group: 17 – controls: 27) were included. The baseline characteristics are summarised in **Table 1**. There was no significant difference in demographic characteristics. More specifically, the mean age in the clevidipine group was 61.9±10.6 years and 70.6% of the participants were male, whereas in the control group the mean age was 66.3±8.5 years and the participants were male in 66.7%. Moreover, there was no difference regarding the coexistence of known arterial hypertension. There was a trend of higher SBP values upon admission in the clevidipine group, without it reaching statistical significance. The diastolic BP values difference upon admission was significantly higher in the clevidipine group (absolute value of 109.4±16.4 mmHg vs 94.0±13.6 mmHg in the control group; p-value=0.001), supporting the trend in the SBP values. Pre-stroke mRS score and admission NIHSS score did not differ between the two groups. Clevidipine group presented with a significantly higher hematoma volume (21.8 ± 20.3 ml vs. 10.2 ±13.3 ml; p-value: 0.028) and a significantly higher ICH score [1 (1-1) vs. 0 (0-1); p-value 0.017] when compared to the control group. In the clevidipine group, the target SBP was achieved in 153.5±106.0 min,

the medication was administered for approximately 4 (3-5) days and the maximum dose of clevidipine recorded was 16.4±7.1 ml.

With regards to follow up and outcomes, data on ICH volume in the follow up imaging, the percentage of ICH volume change, and 3-month mRS score, 3-month good functional outcome, the ΔNIHSS during hospitalisation and the 3-month mortality were collected and are summarised in **Table 2**. A statistically significant ICH volume change on 24h follow-up brain CT, was observed in the clevidipine group (11.8% reduction vs 9.4% increase in the control-group; p-value: 0.041). Nevertheless, similar incidence of hematoma expansion [0 (0.0%) vs. 3 (11.1%); p-value: 0.155] was detected across the two groups. Moreover, a non-significant trend towards NIHSS-score improvement at discharge was reported in the clevidipine-group [ΔNIHSS score 3 (1-7) in the clevidipine group vs. 2 (0-4) in the control group; p-value: 0.169], whereas 3-month mRS scores and 3-month mortality were similar between the two groups. No serious adverse events were detected among patients treated with clevidipine and the medication was well tolerated. Adverse events of specific interest such as acute renal failure and rebound hypertension were not recorded.

DISCUSSION

In the present study, we investigated the effect of iv administered clevidipine on the HE among patients presenting with acute ICH and associated elevated BP. We compared data from clevidipine-treated patients with retrospectively collected data from patients with ICH that were treated with other iv antihypertensive agents in the previous years. Patients receiving iv clevidipine showed significant hematoma volume reduction without however significant differences in 3-month mRS scores compared to patients treated with other antihypertensive agents.

When assessing the findings, we deducted that clevidipine was effective in managing the arterial hypertension. Clevidipine monotherapy achieved BP control in all our patients within 3 hours without the additional use of another antihypertensive agent. This observation could greatly assist in every day clinical practice reducing the polytherapy, implementing easier to adhere to medication schedule and administration, and reducing potential side effects from drug interactions. Additionally, it is also deducted that a mean dose of 16mg of clevidipine was used, a dose that can be safely titrated to higher values if required by a patient with more refractory hypertension. The results of the present study are in accordance with findings of previous studies, indicating that clevidipine is suitable for use as a novel therapeutic agent in the assessment of acute hypertension, thereby overcoming the challenges of providing rapid BP control in emergency situations.[24,25]

Additionally, the hematoma volume reduction when compared to the control group further highlights the effectiveness and the positive clinical correlation of clevidipine. Elevated BP during the first few hours from ICH onset is associated with an increased risk of rebleeding and HE, which leads to poor outcomes at 3 months in patients with ICH.[9,26,27] The Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage (INTERACT) trial has previously proposed the need for early intensive lowering of SBP on the basis of decreased HE, with a target SBP of 140 mmHg in ICH.[28] This recommendation was also implemented in the very recently published ESO guidelines for the management of spontaneous acute ICH.[15]

Given our original data and the findings highlighted above, it is safe to assume that clevidipine represents a safe and effective alternative in terms of hypertension control among ICH patients in the acute phase. The quick onset of action, easy administration and the dynamic titration which can suit the personalised needs of each patient render this medication ideal for this specific subgroup of patients. Moreover, the fact that no adverse effects were reported, especially acute kidney failure which is common in the setting of BP control in ICH patients, strongly suggest that this medication should be implemented as standard of care treatment. These conclusions are in accordance with what has been already reported in the existing literature in the ACCELERATE trial, the ongoing Clevidipine for the Antihypertensive Treatment of Acute Intracerebral Haemorrhage (CLUTCH) trial (NCT06402968) and the recent ESO guidelines.[15,18]

A key strength of our study lies in its matched-control design, combined with the absence of alternative antihypertensive agents during the acute phase of ICH. This ensures that the observed BP reduction can be attributed exclusively to clevidipine, minimising the risk of therapeutic confounding. Nevertheless, the suggestion of clevidipine's superiority is constrained by the relatively small sample size analysed to date. The pronounced reduction in ICH volume observed in the clevidipine group – in contrast to the volumetric increase documented in the control group at the 24-hour follow-up scan – may also, at least in part, reflect the limited number of participants. Furthermore, patients in the control cohort were treated in a standard ward setting rather than within a dedicated stroke unit. This represents a potential source of bias, given the well-established evidence that organised stroke unit care is associated with improved survival, greater functional independence, and an increased likelihood of home discharge within one year of the event.[15,29]

In conclusion, the present study supports the efficacy and safety of iv clevidipine for the rapid management of arterial hypertension in the acute phase of ICH. The significant reduction in hematoma volume observed in the clevidipine group suggests a potential benefit in limiting HE, although no significant differences in 3-month functional outcomes or mortality were detected. These findings highlight clevidipine as a promising therapeutic option in this clinical setting, but confirmation through larger prospective studies or randomised-controlled clinical trials is warranted.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

Table 1. Baseline characteristics.

BASELINE CHARACTERISTICS			
	Clevidipine (n=17)	**Controls (n=27)**	**p-value**
Age; mean (sd)	61.9 (10.6)	66.3 (8.5)	0.136
Sex (male); n (%)	12 (70.6%)	18 (66.7%)	0.999
Known History of Hypertension; n (%)	16 (94.1%)	15 (57.7%)	0.999
Systolic Blood pressure$_{adm}$ (mmHg); mean (sd)	197.2 (23.4)	167.2 (20.4)	0.056
Diastolic Blood pressure$_{adm}$ (mmHg); mean (sd)	109.4 (16.4)	94.0 (13.6)	**0.001**
pre-stroke mRS; median (IQR)	0 (0 – 0)	0 (0 – 0)	0.739
NIHSS$_{adm}$; median (IQR)	8 (2 – 14)	5 (3 – 9)	0.282
ICH Volume$_{adm}$ (ml); mean (sd)	21.8 (20.3)	10.2 (13.3)	**0.028**
ICH – Score; n (%) 0 1 2	3 (17.6%) 13 (76.5%) 1 (5.9%)	16 (59.3%) 9 (33.3%) 2 (7.4%)	**0.017**
ICH score; median (IQR)	1 (1 – 1)	0 (0 – 1)	**0.019**
Time from clevidipine therapy begin to blood pressure control (min); mean (sd)	153.5 (106.0)	NA	NA
Days of Clevidipine Therapy; median (IQR)	4 (3 – 5)	NA	NA
Max dose (ml) of clevidipine required; mean (sd)	16.4 (7.1)	NA	NA
adm: Admission, ICH: Intracerebral Haemorrhage, IQR: Interquartile Range, mRS: modified Rankin Scale, NA: Not available, NIHSS: National Institutes of Health Stroke Scale, sd: standard deviation			

Table 2. Follow up and outcomes.

FOLLOW-UP AND OUTCOMES			
	Clevidipine (n=17)	**Controls (n=27)**	**p-value**
ICH Volume - follow-up (ml); mean (sd)	20.3 (19.1)	14.7 (29.9)	0.493
ICH-Volume change%; mean (sd)	**–11.8 (8.1)**	**+ 9.4 (98.9)**	**0.041**
Hematoma expansion; n (%)	0 (0.0)	3 (11.1)	0.155
$NIHSS_{discharge}$; median (IQR)	4 (1 – 10)	3 (0 – 5)	0.479
ΔNIHSS; median (IQR)	3 (1 – 7)	2 (0 – 4)	0.169
Good functional outcome at 3 months (mRS: 0-2); n (%)	12 (70.6)	18 (66.7)	0.999
3month mRS; median (IQR)	2 (0 – 3)	2 (0 – 3)	0.524
3month mortality; n (%)	1 (5.9)	1 (7.4)	0.999
ICH: Intracerebral Haemorrhage, IQR: Interquartile Range, mRS: modified Rankin Scale, NIHSS: National Institutes of Health Stroke Scale, sd: standard deviation			

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