Perioperative Control Of Acute High Blood Pressure In Neurosurgical Patients Admitted To Intensive Care Unit Using Clevidipine (Neuro-Clev)

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Research Article

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Abstract

Background: Effective treatment of acute high blood pressure in neurocritical diseases is a current recommendation of guidelines to reduce mortality and severe disability. Clevidipine is a calcium channel blocker that showed effectiveness and safety for acute high blood pressure control in neurocritical patients.

Materials and methods: Retrospective, observational and cross-sectional study in adult patients admitted to Intensive Care Unit for neurocritical disease requiring surgical or interventional treatment and presenting acute high blood pressure requiring urgent treatment with clevidipine as first line or rescue therapy after failure of different intravenous antihypertensive drugs. Primary endpoint was effectiveness of clevidipine treatment. Secondary endpoint was safety of clevidipine treatment. Analysis of subgroups described patient and treatment variables on effectiveness and safety of clevidipine, mortality, functional situation and major neurologic complications. Hematoma expansion, rebleeding and vasospasm were specific neurological complications described. Comparisons was made using Fisher, chi-square, t or Mann Whitney U test. Significance was set at the 5% level. Analysis was made using IBM SPSS Statistics 23.0

Results: thirty-three patients admitted to Intensive Care Unit fulfilled inclusion criteria and were included. Clevidipine showed a higher effectiveness and safety for acute high blood pressure control in our patients. Effectiveness was higher in patients with larger brain hematomas and severe aneurysmal subarachnoid hemorrhages treated with first line and early began of clevidipine within 24 hours of admission. Adverse events were mild, transient and more frequent in patients with first line treatment. Early and effective treatment were safe with lower major neurological complications. Mortality was lower in patients with first line and effective treatment. Hematoma expansion was seen in a higher number of patients. Rebleeding and vasospasm were less frequent.

Conclusion: Clevidipine was effective and safe treatment of acute high blood pressure in neurocritical patients. Severity of neurocritical disease is a key factor but early and effective treatment could contribute to reduce mortality and major neurological complications. Nevertheless, our results need to take with caution because little size and design of our study.

Trial registration: NCT05168059

Introduction

Acute high blood pressure (HBP) is a frequent problem of patients admitted to Intensive Care Unit (ICU) after acute ischemic stroke (aIS), spontaneous intracerebral hemorrhage (ICH) and aneurysmal subarachnoid hemorrhage (aSAH) requiring surgical or interventional treatment and those under scheduled neurosurgical and neuroradiology procedures. Its effective management is challenging and must avoid significant decreases of blood pressure leading to lower cerebral perfusion pressure (CPP)

worsening ischemia and elevations probably associated with bleeding, rebleeding or hematoma expansion associated with poor prognosis [1, 2].

HBP could be a risk factor and a clinical finding of many neurocritical diseases. Chronic HBP has a higher global prevalence in adults reaching 60% of people older than 60 years [2]. Chronic untreated HBP or requiring treatment with 3 or more antihypertensive drugs before ICH could increases in-hospital mortality [3]. HBP is a major risk factor of hemorrhagic, ischemic and recurrent stroke, increases risk of hematoma expansion, death and poor neurological prognosis after ICH [2] and it is associated with higher rebleeding rates after aSAH [4].

Target blood pressure in neurocritical patients in mainly unknown and controversial [2]. Early control avoiding excessive reduction of HBP leading to CPP decrease [5] and higher Systolic Blood Pressure (SBP) variability probably related with poor outcome according to evidence [6] should be the goal of treatment. Perioperative control of HBP is especially important in patients presenting aIS, ICH and aSAH according to guidelines [7, 8, 9, 10, 11] but the optimal levels are still controversial.

The ideal antihypertensive drug in this setting should be an arterial vasodilator of rapid onset and offset of action, low blood pressure variability and a few adverse effects [6, 12]. Labetalol, nicardipine and clevidipine are most often used intravenous drugs for HBP control in neurocritical setting [7, 13, 14, 15, 16]. Clevidipine is a short-acting, dihydropyridine L-type calcium channel antagonist approved in Europe for HBP management in perioperative setting. It showed effectiveness and safety for acute HBP control in patients with ICH [10, 13, 17, 18], aIS [7, 13, 14, 15, 18], aSAH [13, 18] and after neurosurgical procedures [15, 16, 19], but little evidence exists regarding its effectiveness and safety in perioperative management of HBP after mechanical thrombectomy, embolization of aneurysm causing aSAH, ICH requiring surgical treatment and interventional neuroradiology procedures. Clevidipine has been shown not increase brain blood flow velocity or decrease brain reactivity to $C0_2$ in healthy human volunteers according to evidence [20], but the real significance of this finding is unknown in damaged brain of neurocritical patients.

This study aims to observe the effectiveness and safety of clevidipine for perioperative control of HBP in neurocritical patients admitted to ICU.

Methods

Study design and population

This is a retrospective, single-group and cross-sectional study conducted in neurocritical adult patients admitted to Cruces University Hospital Anesthesia and ICU Department between January 1, 2017 and December 31, 2018 after ICH requiring surgical treatment, mechanical thrombectomy for aIS, embolization of aneurysm causing aSAH and scheduled neurosurgical and neuroradiology procedures. Adult patients older than 18 years with acute HBP defined as SBP up to 160 mmHg or increase of up to 20% of known preoperative values for 15 or more minutes requiring urgent treatment using clevidipine as

first line or after failure of different intravenous antihypertensive drugs were included (Table 1). Patients admitted to ICU for a neurocritical condition not requiring surgical or interventional treatment or those not treated with clevidipine were excluded (Table 1).

Retrospective and observational design were decided for investigators to describe urgent acute HBP management using clevidipine as first line or rescue treatment in neurocritical population in a real theater basis and avoid serious life-threatening complications, death and poor functional outcomes associated to inaccurate or delay control of HBP making difficult to perform more powerful design studies. Ethical committee approved this study on May 28, 2019 (CEIC E19/17) and was registered on ClinicalTrials.gov NCT05168059 as NEURO-CLEV study. STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines were used for reporting results.

Definition of acute HBP as SBP up to 160 mmHg or increase of up to 20% of known preoperative values for 15 or more minutes and goal SBP were individualized to neurocritical disease in accordance with our hospital protocol based on current guidelines [1, 2, 7, 8, 9, 11]. Begin, choice or change of antihypertensive drug and transition to oral treatment were based on ICU doctors decision in accordance to our protocols. Clevidipine (Cleviprex® 0,5 mg/ml) was begin intravenously at a dose of 1 to 2 mg per hour and then increased to achieve goal SBP based on manufacturer recommendations, previous evidence [10, 16] and clinical practice of our hospital.

Table 1
Inclusion and Exclusion Criteria

Inclusion Criteria
• Adults older than 18 years
• Neurocritical condition requiring surgical or interventional treatment
• HBP: SBP ≥ 160 mmHg or ≥ 20% of preoperative values for 15 or more minutes
• Clevidipine as first line or after failure of different intravenous antihypertensive drugs
Exclusion Criteria
• Neurocritical condition not requiring surgical or interventional treatment
• Patients not treated with clevidipine

Data collection and variables:

Patient data were obtained of hospital medical records platform (Osabide global, Osakidetza, Basque Service of Health) and critical care database ICCA (IntelliSpace Critical Care and Anesthesia Information system, Phillips®).

Baseline variables were age, sex, chronic HBP history, previous antihypertensive treatment, history of ischemic heart disease, stroke and cardiovascular risk factors, neurocritical disease, Blood Pressure, Glasgow Coma Scale (GCS), ICH volume, National Institute of Health Stroke Scale (NIHSS), Fisher scale,

neurosurgical and neuroradiology procedure. ICU variables were first line or rescue treatment with clevidipine, Blood Pressure and time of begin, doses, length, volume, infusion time frame with goal SBP, adverse effects, transition to oral antihypertensive treatment, invasive mechanical ventilation (IMV) requirement, timing to coagulopathy correction, deep venous thrombosis prevention, ICU and hospital stay. Evolution variables were major neurological and other complications during ICU stay, functional situation according to modified Rankin scale (mRS) and mortality at 90 days. Rebleeding, hematoma expansion, brain swelling, intracranial hypertension (IH), vasospasm and neurological deterioration were considered major neurological complications (see Table 1 of supplemental material for definitions)

Endpoints:

Primary endpoint was effectiveness of clevidipine for HBP control defined as percentage of patients achieving goal SBP within 1 to 6 hours of infusion beginning and maintaining target SBP for more than 75% of infusion time length without need of rescue treatment with different intravenous antihypertensive drugs (see Table 2 of supplemental material).

Table 2
Baseline, ICU and evolution variables.

Variable	Result
Age (years)	62 (20)
Median (IQR)	65 (13)
Mean (SD)	
Gender (%)	55 males
	45 females
Medical history	68
Chronic Hypertension (%)	6
Ischemic Heart Disease (%)	24
Stroke (%)	21
Diabetes Mellitus (%)	42
Hypercholesterolemia (%)	12
Smoking (%)	49
Another Cardiovascular Risk Factors (%)	21
Cardiovascular Disease (%)	24
Neurological Disease (%)	15
Kidney Disease (%)	6
Peripheral Arteriopathy (%)	3
Thrombosis Sisease (%)	

IQR: Interquartile Range SD: Standard Deviation

ACE: angiotensin-converting enzyme. ARBs: Angiotensin II receptor blockers.

Variable	Result
Treated Chronic Hypertension (%)	60
1 drug (%)	50
2 drugs (%)	25
3 or more drugs (%)	25
Type of drugs	5
Alpha-blockers (%)	15
ACE inhibitors (%)	15
ARBs (%)	10
Calcium channel blockers (%)	5
Diuretics (%)	50
Combinations (%)	

IQR: Interquartile Range SD: Standard Deviation

ACE: angiotensin-converting enzyme. ARBs: Angiotensin II receptor blockers.

Variable	Result
Diagnosis	**15**
Aneurysmal Subarachnoid Hemorrhage (%):	60
Embolization (%)	20
Embolization and Intra Cranial Pressure monitoring sensor insertion (%)	20
Embolization, Intra Cranial Pressure monitoring sensor insertion and intraventricular fibrinolysis (%)	**24**
Intra Cerebral Hemorrhage (%)	50
Urgent Craniotomy and Intra Cranial Pressure monitoring sensor insertion (%)	37.5
Intracranial Pressure monitoring sensor insertion (%)	12.5
Intraventricular fibrinolysis (%)	**27**
Acute Ischemic Stroke (%)	100
Mechanical Thrombectomy (%)	**30**
Scheduled Neurosurgical procedures (%):	60
Craniotomy (%)	20
Brain Aneurysm scheduled embolization (%)	20
Deep Brain Stimulation for Parkinson´s Disease (%)	**3.2**
Brain Arteriovenous malformation (%)	100
Urgent craniotomy and Intra Cranial Pressure monitoring sensor (%)	
Glasgow Coma Scale at ICU admission	11 (4)
Mean (SD)	11 (7)
Median (IQR)	30
3–8 (%)	21
9–12 (%)	49
13–15 (%)	
Fisher score (%) at ICU admission	33
3	67
4	

IQR: Interquartile Range SD: Standard Deviation

ACE: angiotensin-converting enzyme. ARBs: Angiotensin II receptor blockers.

Variable	Result
NIHSS score at ICU admission	12 (8)
Mean (SD)	9 (13)
Median (IQR)	
SBP, DBP and MBP at ICU admission	164 (29)
SBP (mmHg)	168 (40)
Mean (SD)	83 (19)
Median (IQR)	80 (23)
DBP (mmHg)	110 (19)
Mean (SD)	111 (26)
Median (IQR)	
MBP (mmHg)	
Mean (SD)	
Median (IQR)	
Hematoma volume (ml) at ICU admission	25 (16)
All	20 (18)
Mean (SD)	24 (18)
Median (IQR)	17 (25)
IntraCerebral Hemorrhage	
Mean (SD)	
Median (IQR)	
Radiology findings at ICU admission	27
Vascular malformation (%)	3
Spot sign (%)	
Intubation and Mechanical Ventilation between 24 to 7 days of ICU admission (%)	55
Mechanical thromboprophylaxis (%)	97
Pharmacology thromboprophylaxis (%)	76

IQR: Interquartile Range SD: Standard Deviation

ACE: angiotensin-converting enzyme. ARBs: Angiotensin II receptor blockers.

Variable	Result
Normalization of coagulopathy at first 24 hours of ICU admission (%)	96
Major neurological complications (%)	51
Rebleeding, hydrocephalus and Intracranial Hypertension (%)	24
Brain swelling and Intracranial Hypertension (%)	17
Hematoma expansion and Intracranial Hypertension (%)	17
Vasospasm (%)	12
Post scheduled craniotomy brain hematoma (%)	6
Hydrocephalus and Intracranial Hypertension (%)	6
Hemorrhagic transformation and Intracranial Hypertension (%)	6
Neurological deterioration (%)	6
Brain hematoma, hydrocephalus and Intracranial Hypertension (%)	6
Time of complications onset (%)	12
‹ 12 hours	53
12–24 hours	18
24–48 hours	12
48–72 hours	6
› 72 hours	
Other complications (%)	70
Neurological (%)	78
Thrombotic (%)	13
Hemorrhagic (%)	13
Cardiology (%)	4
Respiratory (%)	17
Kidney (%)	4
Infectious (%)	61
Psychiatry (%)	13
Other (%)	9
IQR: Interquartile Range SD: Standard Deviation	
ACE: angiotensin-converting enzyme. ARBs: Angiotensin II receptor blockers.	

Variable	Result
Mortality at 90 days (%)	30
Functional situation (mRS) at 90 days	21
0–2 (%)	30
3–4 (%)	49
5–6 (%)	
ICU stay (days)	12 (10)
Mean (SD)	9 (16)
Median (IQR)	12 (17)
Hospital stay (days)	9 (12)
Mean (SD)	
Median (IQR)	
IQR: Interquartile Range SD: Standard Deviation	
ACE: angiotensin-converting enzyme. ARBs: Angiotensin II receptor blockers.	

Secondary endpoint was safety of clevidipine defined as significant adverse events related to infusion such tachycardia, atrial fibrillation, hypotension, fever and acute kidney failure, mainly (see Table 2 of supplemental material)

Effectiveness and safety of clevidipine, major neurological complications, mortality and functional situation were analyzed in subgroups of patients to describe variables potentially influencing main outcomes. Effectiveness of clevidipine in subgroups of demographic, medical history, neurocritical disease, neurosurgical procedure, poor prognosis factors and treatment characteristics were analyzed. Safety of clevidipine, major neurological complications, mortality and functional situation were analyzed according to treatment characteristics. Specific complications like hematoma expansion, rebleeding and vasospasm were described also (see Table 3 of supplemental material).

Statistical analysis:

Data of baseline, ICU and evolution variables were included for 2 independent investigators (B.E and E.A) and inconsistencies solved after discussion and agreement. A frequency tables and percentages were used for qualitative variables. Means and standard deviation or median and interquartile range were used for quantitative variables. Comparisons was made using Fisher exact test or χ^2 for categorical variables and t or Mann Whitney U test for quantitative variables. Global time with goal SBP was calculated as percentage of time after infusion stop added to infusion length with target SBP, considering total infusion length as 100%. Effectiveness was considered higher when clevidipine achieved primary endpoint in 70 to

100%, moderate in 51 to 69% and lower in 10 to 50% of patients. Adverse events were considered lower if presented in less than 20% of patients and its severity were described. Subgroup analysis considered global major neurological complications, mortality and functional situation for comparisons of patients presenting variables possibly influencing these major outcomes. Significance was set at the 5% level. Analysis was performed by a biomedical statistician (E.A) using IBM SPSS Statistics 23.0

Results

103 patients were admitted to ICU for neurocritical disease between 2017 and 2018. Only 33 patients fulfilled inclusion criteria and were included in this study.

Baseline, ICU and evolution variables:

Table 2 showed baseline, ICU and evolution variables of patients included in this study (see at end of manuscript). Mean age was 65 years old, 55% males and 45% females. Previously treated Chronic hypertension, hypercholesterolemia and another cardiovascular risk factors were seen in a higher number of patients. Scheduled neurosurgical procedures, aIS, ICH and aSAH were most frequent diagnosis at ICU admission. Mean GCS was 11 points, but half of patients presented moderate to deep coma situation at admission and required IMV. Baseline SBP was 164 mmHg. Mean hematoma volumes of 25 ml and NIHSS of 12 points were seen at ICU admission. Fisher of 4 points were present in 67% of patients with aSAH. Coagulopathy correction at admission and thromboprophylaxis was made in a higher number of patients. Major neurological complications were present in 51% of patients mainly between 12 to 24 hours after ICU admission because of IH secondary to rebleeding, hematoma expansion and brain swelling. Mortality at 90 days was 30% and functional situation according to mRS at 90 days was moderate to severe disability in a higher number of patients.

Primary endpoint: Clevidipine treatment effectiveness

Table 3 showed clevidipine treatment effectiveness. Clevidipine achieved goal SBP in 100% of patients, in first hour in 97% of cases, and target SBP was maintained for 71 hours corresponding to more than 75% of infusion time without requiring additional treatment with different intravenous antihypertensive drugs. Goal SBP was maintained 45 hours after infusion stops corresponding to a global time of 177%. We observed a higher global effectiveness of clevidipine of 73% increasing to 83% if clevidipine was first line choice treatment. Clevidipine was mainly a rescue treatment after failure of different intravenous antihypertensive drugs in 82% of patients.

Table 3
Clevidipine treatment effectiveness.

Effectiveness variable	Result
SBP lowering to goal (%)	100
Time to SBP goal	97
1 hour (%)	3
2 hours (%)	71 (48)
Time with SBP goal (hours)	64 (89)
Mean (SD)	45 (22)
Median (IQR)	42 (18)
Time with SBP goal after infusion stops (hours)	177
Mean (SD)	0
Median (IQR)	
Global time within SBP goal (%)	
Use of additional antihypertension drugs 24 to 72 hours of clevidipine treatment starts (%)	
Choice of treatment	18
First line (%)	82
Rescue (%)	
Effective treatment	73
Global (%)	83
First line (%)	

SBP baseline at begin of clevidipine treatment was higher than 160 mmHg without significant differences between patients with effective and no effective treatment (Table 4, see at end of manuscript). SBP at 1 hour was significantly lower than baseline in both effective and no effective treatment and without significant differences between groups (Fig. 1 and Table 4). Time of clevidipine infusion begin, duration, volume and minimum doses were not significantly different between effective and no effective treatment groups, but maximum doses were significantly higher in no effective treatment patients (Table 4). A significantly higher time with goal SBP during clevidipine infusion without additional intravenous antihypertensive drugs requirement were seen in effective treatment group (Table 4). Transition to oral antihypertensive treatment was not significantly different between effective and no effective treatment patients (Table 4).

Table 4
Clevidipine treatment data

Variable	Effective treatment	No effective treatment	Comparisons
SBP (mmHg)	178 (19)	183 (10)	No significant differences between effective and no effective treatment
Mean (SD)	178 (25)	184 (10)	p 0.401
Median (IQR)			
SBP at 1 hour of treatment (mmHg)	151 (13)	153 (12)	No significant differences between effective and no effective treatment
Mean (SD)	148 (18)	157 (15)	p 0.709
Median (IQR)			
Time of treatment starts (hours)	44 (56)	60 (85)	No significant differences between effective and no effective treatment
Mean (SD)	28 (46)	37 (81)	p 0.839
Median (IQR)			
Treatment duration (hours)	56 (51)	56 (39)	No significant differences between effective and no effective treatment
Mean (SD)	36 (70)	50 (81)	p 0.599
Median (IQR)			
Time with goal SBP (hours)	71 (48)	55 (43)	Significant differences between effective and no effective treatment
Mean (SD)	64 (89)	31 (62)	p 0.01
Median (IQR)	177	105	
(%)			
Doses (mg/h)	1 (1)	2 (2)	No significant differences between minimum doses of effective and no effective treatment
Minimum doses (mg/h)	1 (1)	1 (2)	
Mean (SD)	5 (4)	13 (11)	p 0.340
Median (IQR)	4 (5)	8 (17)	Significant differences between maximum doses of effective and no effective treatment
Maximum doses (mg/h)			
Mean (SD)			p 0.035
Median (IQR)			

Variable	Effective treatment	No effective treatment	Comparisons
Infusion volumes (ml) **Mean (SD)**	376 (472)	474 (486)	No significant differences between effective and no effective treatment
Median (IQR)	162 (491)	282 (792)	p 0.466
Use of additional intravenous antihypertension drugs (%)	0	78	Significant differences between effective and no effective treatment p < 0.001
Transition to oral antihypertension drugs (%)	71	89	No significant differences between effective and no effective treatment p 0.692

A significant reduction of SBP at 1 hour was seen in both effective and no effective treatment groups (p < 0.001).

Secondary endpoint: Clevidipine treatment Safety

Clevidipine treatment had a lower number of adverse events (3%). Only 1 patient presented transient atrial fibrillation solved with dose reduction.

Subgroup analysis:

1.-Treatment Effectiveness in subgroups.

Clevidipine treatment was highly effective in both males and females with medical history of ischemic heart disease, cardiovascular risk factors, stroke and treated chronic hypertension. Acute HBP during postoperative time of urgent neurosurgical procedures like ruptured aneurysms embolization and mechanical thrombectomy or scheduled procedures like brain aneurysms embolization, deep brain stimulation and craniotomy was very effectively controlled for clevidipine treatment. Patients admitted to ICU for aSAH and aIS presenting acute HBP were effectively treated with clevidipine. A highly effective treatment with clevidipine was seen also in patients with poor prognosis factors like ICH with volumes higher than 30 ml and Fisher up to 3 points. Clevidipine was highly effective as first line treatment, beginning early within 24 hours of ICU admission with length of infusion higher than 3 days and volumes higher than 500 ml (Table 5).

Moderate effectiveness of clevidipine treatment was seen in patients younger than 65 years old, admitted for IH, with deep coma situation as indicated for GCS lower than 8 points and requiring intracranial pressure monitoring sensor insertion. Clevidipine treatment had a lower effectiveness in patients older than 65 years, admitted for ICH requiring urgent craniotomy and poor prognosis factors like aIS with NIHSS higher than 10 points (Table 5).

Table 5
Clevidipine effectiveness in subgroups.

Treatment effectiveness

Treatment effectiveness
Highly (70–100%)
Sex Male 70% Female 78%
Medical History
Ischemic Heart Disease 100%
Smoking 100%
Stroke 88%
Diabetes Mellitus 86%
Hypercholesterolemia 86%
Another cardiovascular risk factors 81%
Chronic hypertension 77%
Chronic hypertension treated 75%
Neurosurgical procedure
Urgent embolization for aSAH 80%
Mechanical thrombectomy 70%
Scheduled brain aneurysmal embolization 100%
Deep Brain Stimulation for Parkinson´s Disease 100%
Scheduled craniotomy 88%
Diagnosis
aSAH 70%
aIS 70%
Poor prognosis factors
Hematoma volumes > 30 ml 70%
Fisher ≥ 3 points 70%
Treatment
First line 83%
Early begin within 24 hours of admission 73%
Infusion length > 3 days 73%
Infusion volume > 500 ml 70%

Treatment effectiveness
Moderate (50–69%)
Age < 65 years 58%
Neurosurgical procedure Intracranial Pressure Monitoring Sensor 50%
Diagnosis IH 54%
Poor prognosis factors GCS < 8 points 60%
Lower (10–49%)
Age > 65 years 42%
Neurosurgical procedure Urgent craniotomy 33%
Diagnosis ICH 43%
Poor prognosis factors NIHSS > 10 points 33%

2.-Treatment Safety in subgroups

A lower number of adverse events were observed in patients with early begin within 24 hours of ICU admission (0%). A slightly higher incidence of adverse events was observed with effective treatment (4.2%) maintaining goal SBP higher than 48 hours (5%). Adverse events were more frequent in patients with first line treatment (17%) (Table 6). All subgroups presented a number of adverse events lower than 20%.

Table 6
Clevidipine Safety in subgroups.

Variable	Adverse events
Early begin within 24 hours of ICU admission (%)	0
Effective treatment (%)	4.2
Maintenance of goal SBP > 48 hours (%)	5
First line (%)	17

3.-Major neurological complications in subgroups

Major neurological complications were seen in patients with goal SBP maintained higher than 48 hours and treated with clevidipine as a first line. A slight lower number of major neurological complications were seen in patients with effective and early treatment. Mortality of patients presenting major neurological complications was 53.3% (Table 7)

4.-Mortality in subgroups

A very low mortality was observed in patients with first line and effective treatment with clevidipine. A similar mortality than global was seen in patients with early begin of treatment

within 24 hours of ICU admission and maintaining goal SBP higher than 48 hours (Table 7)

Table 7
Major neurological complications, mortality and functional situation in subgroups.

Variables	Major neurological complications	Mortality	Functional situation
Early begin within 24 hours of admission (%)	27	33.3	mRS 0–2 points: 33 mRS 3–6 points: 67
Effective treatment (%)	38	16.7	mRS 0–2 points: 25 mRS 3–6 points: 75
Goal SBP maintained > 48 hours (%)	55	35	mRS 0–2 points: 15 mRS 3–6 points: 85
First line (%)	50	0	mRS 0–2 points: 33 mRS 3–6 points: 67

5.- Functional situation in subgroups

A similar functional situation according mRS of moderate to severe disability than global group were seen in subgroups of patients with effective treatment, first line, early begin within 24 hours of admission and maintaining goal SBP higher than 48 hours (Table 7).

6.-Specific complications:

Hematoma expansion

Hematoma expansion was seen in 42.85% of patients with ICH. SBP higher than 180 mmHg, Chronic Hypertension history and association with IH was seen in all patients. Hematoma volumes lower than 30 ml, age under 65 years old, GCS up to 8 points and association with aSAH were observed also in a higher number of patients (70%). Effective treatment beginning within 5 hours of ICU admission were seen in a lower number of patients with this complication (33%). Spot sign was not presented in brain CT in neither patient. Mortality of this complication was 66% with functional situation of mRS of 6 points in 66% and 0 points in 33% of cases.

Aneurysm rebleeding

Aneurysm rebleeding was present in 16.67% of patients with aSAH. SBP higher than 160 mmHg, aneurysms of posterior brain circulation and effective treatment with clevidipine were present in a higher number of patients (70%). IH and first line treatment with clevidipine were seen in a lower number of patients (33.3%). Mortality of this complication was 33.3% with functional situation of mRS of 4 points in 50%, 6 points in 33% and 0 points in 17% of patients.

Vasospasm

Vasospasm was seen in 33.3% of patients with aSAH. SBP higher than 160 mmHg, Fisher 4 and effective treatment was present in a higher number of patients (100%). Mortality of this complication was 0% with functional situation of mRS of 0 points in 50% and 4 points in 50% of patients.

Discussion

Acute HBP is very frequent in patients admitted to ICU after aIS, ICH, aSAH and scheduled neurosurgical procedures [10, 12, 15, 17] causing complications like hemorrhagic transformation, hematoma expansion, brain swelling, rebleeding, prolonged hospital stays, worse functional outcomes and death [4, 10, 12]. Its exact pathophysiological mechanism is mostly unknown but increase of systemic vascular resistances because of damage of brain areas regulating arterial baroreceptor reflex and activation of renin-angiotensin-aldosterone, sympathetic autonomic and hypothalamic-pituitary-adrenal systems [12] probably plays a role. Cerebral autoregulation could be impaired in these patients causing vasoconstriction and ischemia or vasodilation and increase of cerebral blood flow volume and intracranial pressure [12], both associated with brain secondary injury. For this reason, its highly recommended a thoughtful management of acute HBP in these patients.

In this study we aimed to observe effectiveness and safety of clevidipine for acute HBP management in neurocritical patients admitted to ICU after aIS, ICH and aSAH requiring surgical management and scheduled neurosurgical procedures, because in Europe clevidipine is only approved for HBP management in perioperative setting [18]. Study design was based in the unique profile of neurocritical patient requiring urgent and effective management of HBP to potentially prevent major neurological complications, reduce mortality and improve functional outcomes, making more powerful studies difficult to perform. This design permitted also to observe acute HBP management in a real theater, because guidelines suggest different antihypertensive drugs [12] making this decision on UCI doctors experience and preferences. Goal SBP is controversial also and current guidelines recommend different thresholds based on limited evidence and according neurocritical diagnosis [7, 8, 9, 11].

Our patients were median age, both gender with chronic HBP associated to other cardiovascular risk factors, as early published evidence regarding neurocritical population [16]. Chronic treated HBP seen in a higher number of patients, none with history of uncontrolled HBP and probably unknown HBP in a lower

number of patients, could influenced our results and be paradoxical because severe neurocritical diseases of our patients should be expected if uncontrolled or unknown HBP were higher.

Our study included neurocritical patients admitted to ICU with acute HBP requiring safe and fast control with intravenous treatment besides usual critical care management involving monitoring, airway control and thromboprophylaxis. Scheduled neurosurgical procedures, aIS, ICH and aSAH were most frequent diagnosis requiring individualized approaches for HBP management according to guidelines [7, 8, 9, 11] Neurological situation at admission with half of patients presenting moderate to deep disturbance of consciousness level probably resulting of severe neurocritical diagnosis as indicated for high-risk neurosurgical procedures, hematoma volumes, NIHHS and Fisher scales. Hematoma volumes were higher [17, 21] and similar [10] than previously published, including patients in a higher risk of severe complications. Major neurological complications seen in half of patients were IH secondary to rebleeding, hematoma expansion, brain swelling and vasospasm, probably explaining IMV requirement and a moderate to severe disability according mRS in a higher number of patients. Mortality was paradoxically lower than expected (30%) based on neurological situation at admission and major complications.

Clevidipine showed a higher global effectiveness of 73% for acute HBP treatment in this study. Several facts reflected its main advantages for HBP control in neurocritical patients: 97% of patients achieved goal SBP within 1 hour of treatment begin, maintained it for a media of 71 hours, corresponding to higher than 75% of infusion length, and 45 hours after stopping it without need of additional different intravenous antihypertensive drugs. Clevidipine treatment was highly safe in this study presenting 3% of transient adverse events. Fast and longer maintenance of goal SBP with one-drug presenting only a few transient adverse events could be good advantages of clevidipine for acute HBP management in neurocritical patients. Based on current guidelines choice of antihypertensive treatment should be decision of critical care doctors, probably resulting of preferences and usual practice among centers [7, 8, 9, 10, 11]. In Europe, Clevidipine is available in some centers only since a few years and different intravenous antihypertensive drugs like urapidil, nicardipine and labetalol are more used. This could explain that clevidipine was chosen after failure of different intravenous antihypertensive treatment in a higher number of our patients.

SBP thresholds requiring treatment are controversial also and vary according to neurocritical condition [7, 8, 9, 10, 11], making up to 160 mmHg or higher than 20% of preoperative basal values for 15 or more minutes a rational approach for acute HBP management. In this study, clevidipine treatment began with SBP higher than 160 mmHg and significantly decrease to goal at first hour without differences between effective and no effective groups. Minimum doses slightly lower than recommended for manufacturer (1 mg/h) and volumes than previously published [15] with infusion length not significantly different between effective and no effective groups achieved goal SBP. Clevidipine infusion began not significantly different between effective and no effective treatment groups could be paradoxical, because in a higher number of patients with rescue treatment would be expected a later began of infusion than first line group, but probably the variable onset of acute HBP requiring urgent treatment in each neurocritical disease explained this result. Transition to oral antihypertensive treatment required very frequently but not

significantly different between effective and no effective treatment groups probably resulting of chronic HBP in a higher number of patients. A significantly longer time within goal SBP, requiring lower maximum doses (4 mg/h) without need of additional intravenous antihypertensive drugs seen only in effective group were also good advantages of clevidipine treatment in neurocritical patients.

Analysis of subgroups showed a higher effectiveness of clevidipine treatment in patients admitted to ICU after urgent embolization of aneurysm causing aSAH, mechanical thrombectomy for aIS, scheduled neurosurgical procedures and presenting poor prognosis factors like ICH volumes higher than 30 ml and Fisher scores up to 3 points. Clevidipine treatment as first line, beginning early within 24 hours of ICU admission, maintained for higher than 3 days with volumes up to 500 ml showed a higher effectiveness also. These results could partly be explained for higher number of patients admitted for aSAH, aIS and scheduled neurosurgical procedures in this study, but factors related to treatment like first line, early and longer treatment for patients with severe neurocritical diseases as indicated for poor prognosis factors probably played a role and was a very interesting finding of this study not previously published as far as we know. Moderate and lower effectiveness of clevidipine treatment were probably explained for higher severity of neurocritical disease as indicated for coma, aIS with NIHHS score higher than 10 points, ICH and IH. Effective treatment was safe with a lower number of adverse events like previously mentioned for a global group. Major neurological complications and mortality of patients with effective treatment were lower, but functional situation of moderate to severe disability was not different to global group.

Clevidipine was safe in subgroups of patients with early begin and effective treatment maintaining goal SBP higher than 48 hours, according to our study definitions. Adverse events were more frequent in patients with first line treatment but as mentioned above it was lower, transient, mild and dose related not requiring treatment stopped.

Major neurological complications were lower in subgroups of patients with early begin and effective treatment. Mortality was lower in subgroups of patients with first line and effective treatment. Maintenance of SBP higher than 48 hours showed a slightly higher number of adverse events, major neurological complications and mortality than global group. Functional situation of moderate to severe disability was seen in all subgroups of patients like than global group. These results seem to indicate the benefits of effective and early treatment with clevidipine more than maintenance of goal SBP after 48 hours to reduce mortality and major neurological complications, but without changes in functional situation. First line treatment showed a higher effectiveness and lower mortality with a higher number of adverse events, probably because of a lower number of patients included in this subgroup, making this result difficult to interpretate. Nevertheless, severity of neurocritical disease probably is the key factor in these outcomes, making treatment facts of limited impact but early begin of treatment and effectiveness more than a longer maintenance of goal SBP could be played a role.

Hematoma expansion was seen in a higher number of patients than previously reported [17, 21, 22] with higher mortality and severe disability. Our results could be paradoxical because we observed hematoma volumes lower than 30 ml in a higher number of patients and spot sign in angiography brain CT in neither

patient with this complication, unlike published evidence had been showed [10, 17, 21, 22, 23]. All patients presented risk factors like SBP higher than 180 mmHg, history of chronic HBP and association with IH [3, 5, 8]. Clevidipine treatment effectiveness in a lower number of patients with this complication seems plausible since a lack of acute HBP control had been showed to be related with this complication [3, 5, 8].

Rebleeding was seen in a lower number of patients after aSAH probably because early embolization of ruptured brain aneurysm in our hospital as guidelines recommended [11], but this is a paradoxical result because a higher number of patients with Fisher scores of 4 points with higher risk of this complication included in this study. Risk factors previously associated with rebleeding like SBP higher than 160 mmHg, Fisher score of 4 points and aneurysms of posterior brain circulation were seen in a higher number of our patients [4, 11, 24] with mortality and moderate to severe disability like global group. An interesting finding of this study was that clevidipine treatment was effective in a higher number of patients, probably indicating that early embolization and effective management of acute HBP with clevidipine should reduce this complication as evidence had been showed [11].

Vasospasm was seen also in a lower number of patients with aSAH probably because of early prophylaxis treatment with nimodipine in all patients in accordance with guidelines recommendations [11]. Mortality was very low and functional situation was highly variable between mild symptoms to moderate disability. SBP higher than 160 mmHg, Fisher score of 4 points and effective treatment with clevidipine was seen in all patients with this complication. These results could be partly explained because this study included a higher number of patients with Fisher of 4 points whom are less prone to vasospasm, but additional effects of effective treatment with a calcium channel blocker like clevidipine and a lack of hypotension as indicated for SBP higher than 160 mmHg in all patients could contribute to reduce this complication. Nevertheless, the exact role of clevidipine for vasospasm prevention is difficult to observe since a higher mortality and disability related to this complication making difficult to perform more powerful studies to explore its benefits.

Our study has limitations related mainly to its little size and design. This retrospective and observational study made possible to describe the real theater of acute HBP management in neurocritical patients admitted to ICU. Our study showed a typical neurocritical population requiring urgent and effective treatment of acute HBP using clevidipine mainly as a rescue therapy, but these patients probably take advantages of a higher effectiveness and safety observed with early began of treatment. Additionally, our interesting findings related to effective and early treatment with clevidipine for reduce mortality and major neurological complications should be considered with caution because concerns about study design.

In conclusion, we observed that clevidipine was effective and safe treatment in neurocritical patients with acute HBP requiring urgent treatment with potential benefits related to mortality and major neurological complications. Clevidipine has pharmacological advantages in this population based on its shorter acting and smooth control of acute HBP. Observational design of our study in a real theater of neurocritical patients admitted to ICU prevent us to make stronger recommendations. Nevertheless, this

original study including larger population than previously published as far as we know underscore advantages of clevidipine for acute HBP management in neurocritical patients.

Declarations

Ethical Approval and Consent to participate: Cruces University Hospital Ethical Committee of Clinical Investigation approved this study on May 28, 2019 (code CEIC E19/17). Neurocritical patients admitted to ICU of our hospital were affected for severe diseases with life-threatening complications. In some cases, patients did not survive and serious concern about obtaining relatives consent make us to propose an anonymized methodology of medical records revision protecting personal data of patients according Data Protection Law 3/2018.

Consent for publication: Cruces University Hospital Ethical Committee and all authors of this manuscript gave consent to publish this study.

Data availability statement: Electronic medical records and anonymized dataset of patients included in present study are deposited in Biocruces Health Research Institute and available for revision of Critical Care and readers after Ethical Committee of Clinical Investigation acceptance in accordance with data protection required by law 3/2018.

Competing interests: None of authors received economic funding of clevidipine commercialization laboratory Ferrer for this study. Dr. Blanca Escontrela (corresponding and first author) presented a conference of acute high blood pressure management in neurocritical patients sponsored for Ferrer laboratories on April 25, 2019 in Spain.

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Author`s contribution: B.E designed this study. B.E and E.A collected data. E.A made statistical analysis of data. B.E wrote methods, results, discussion and made a final review of this study. A.M, M.M and E.A contributed to introduction, discussion and final review of this article. All authors approved this manuscript.

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Figures

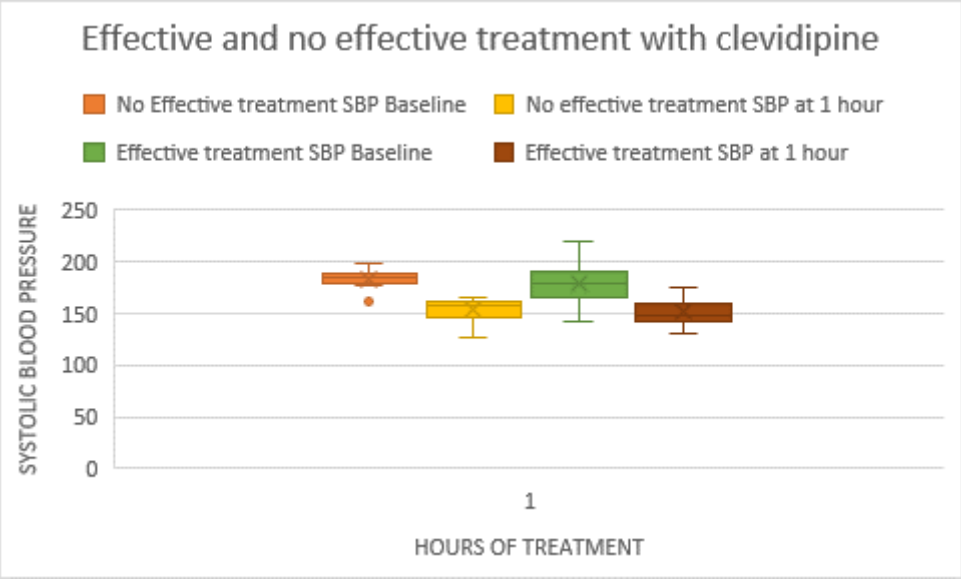

Figure 1

SBP baseline and 1 hour after clevidipine infusion begin.

A significant reduction of SBP at 1 hour was seen in both effective and no effective treatment groups ($p < 0.001$).

Supplementary Files

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