Original Article

Effect of Blood Pressure Augmentation on CVA Patients who are out of Injection TPA (Tissue Plasminogen Activator) and Mechanical Thrombectomy Window

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ABSTRACT

Background: Ischemic stroke is a leading cause of morbidity and mortality worldwide, prompting an urgent need for effective treatments outside the standard therapeutic window. With an estimated 6.5 million stroke-related deaths annually and a particular prevalence in the 18-49 age demographic, there is a substantial burden on healthcare systems. Intravenous thrombolysis and mechanical thrombectomy are time-sensitive treatments that are not universally accessible, highlighting the need for alternative strategies.

Objective: The study aimed to evaluate the efficacy of induced hypertension as a therapeutic intervention for ischemic stroke patients who are beyond the window for conventional reperfusion therapies.

Methods: This cross-sectional observational study was conducted at the Hyper Acute Stroke Unit (HASU) of PEMH, Rawalpindi. Over four months, 50 male patients who had suffered an ischemic stroke and were outside the therapeutic window for TPA and mechanical thrombectomy were recruited. Induced hypertension was achieved through intravenous administration of norepinephrine, titrated to maintain systolic blood pressure between 180-200 mmHg. Blood pressure was recorded at baseline, immediately before norepinephrine administration, and every 12 hours thereafter. Muscle power was assessed using the Medical Research Council (MRC) scale at 24-hour intervals over a 3-day observational period.

Results: The mean systolic blood pressure was 140±5.07 mmHg, and the mean diastolic blood pressure was 94.16±4.71 mmHg, with a mean patient age of 55±4.4 years. Following induced hypertension, 30 out of the 50 patients (60%) showed improvement in muscle power. Specifically, in Group 1 (6 patients with leg muscle weakness), 3 patients improved from an MRC scale of 2 to 3, and 1 patient improved from an MRC scale of 3 to 4. In Group 2 (15 patients with upper and lower limb weakness), 7 patients improved from an MRC scale of 2 to 3, and 4 patients improved from an MRC scale of 3 to 4. Similar improvements were observed in other groups, with overall improvements ranging from 37.5% to 80% within individual subgroups.

Conclusion: Induced hypertension via norepinephrine infusion appears to be a promising therapeutic strategy to improve muscle power in ischemic stroke patients who cannot receive standard reperfusion treatments. This intervention could potentially bridge the treatment gap for patients who present outside of the traditional therapeutic time frame.

Keywords: Ischemic Stroke, Induced Hypertension, Norepinephrine, Therapeutic Window, Muscle Power, Stroke Management.

INTRODUCTION

Cerebrovascular accident (CVA), commonly known as a stroke, is a medical condition characterized by an acute interruption of blood supply or the rupture of intracranial blood vessels within the brain tissue, leading to temporary or permanent brain damage. This condition can manifest in two primary forms: ischemic stroke and intracranial hemorrhage (1,2). Ischemic stroke, the more prevalent type, occurs due to the acute occlusion of an intracranial vessel, which drastically reduces blood flow to the brain region it supplies. The extent of flow reduction is largely dependent on individual vasculature, the occlusion site, and systemic blood pressure.

Under normal circumstances, cerebral blood flow ranges between 50 to 60 ml/min per 100 grams of brain tissue, maintaining a relative constancy over a perfusion pressure range of 50 to 150 mmHg (1). A cessation of blood flow for as little as 6 to 8 seconds can impair consciousness (2). A complete halt in cerebral blood flow inevitably leads to brain death within 4 to 10 minutes. Flow values below 16-18 ml/100 grams of brain tissue per minute can result in infarction within an hour, and values less than 20 ml/100 grams can cause ischemia without infarction, unless prolonged for several hours or days (3).

The brain's auto-regulatory mechanisms strive to maintain perfusion. If blood flow is restored before significant infarction, the clinical syndrome is known as a transient ischemic attack (TIA). However, failure to maintain or restore blood flow leads to the death of brain tissue, resulting in infarction. Another critical concept in understanding stroke is the ischemic penumbra, defined as the ischemic but reversibly dysfunctional tissue surrounding a core area of infarction (4). This area will progress to infarction if blood flow is not restored, making the preservation of the penumbra a crucial goal in vascularization therapies.

The clinical presentation of ischemic stroke varies, including symptoms such as loss of power in a limb or one side of the body, slurred speech, aphasia, or loss of consciousness, with hemiparesis being a common presentation. Clinically, a deficit that is maximal at onset or remits quickly often indicates ischemia, while a depressed level of consciousness, higher initial blood pressure, or worsening symptoms may suggest intracranial hemorrhage (5).

Various etiological factors, both genetic and environmental, contribute to ischemic stroke. These include a sedentary lifestyle, smoking, exposure to lead or hydrocarbons, diabetes mellitus, hypertension, and ischemic cardiac disease. Notably, systolic hypertension is the leading cause of stroke worldwide, accounting for 60% of cases (6).

Globally, ischemic strokes constitute over 62% of all stroke incidents (8). Annually, about 11% of ischemic strokes occur in individuals aged 15-49 years (9), while over 58% occur in those aged 65-85 years (10). There is a gender disparity in stroke incidence, with 45% occurring in men and 55% in women (11).

Focal cerebral infarction follows two primary pathways: a necrotic pathway characterized by rapid cellular cytoskeletal breakdown and symptomatic onset, usually resulting in permanent brain damage, and an apoptotic pathway. In the latter, ischemia leads to neuron starvation, decreased oxygen and glucose, mitochondrial failure, and consequent ATP depletion. This process results in an accumulation of intracellular calcium and the generation of free radicals, culminating in the catalytic destruction of neurons (12).

This study aims to observe the effects of induced hypertension on the recovery power of ischemic stroke patients who are beyond the treatment window for tissue plasminogen activator (TPA) and Mechanical Thrombectomy.

MATERIAL AND METHODS

This cross-sectional observational study was meticulously conducted at the Hyper Acute Stroke Unit (HASU) of the Department of Neurology at PEMH, Rawalpindi, over a period of four months from November 2022 to February 2023. The research was designed to observe the effects of induced hypertension on ischemic stroke patients who were not eligible for tissue plasminogen activator (TPA) and Mechanical Thrombectomy. A total of 50 patients were enrolled in the study, adhering to a set of specific inclusion and exclusion criteria.

The inclusion criteria for the study encompassed patients who were admitted within 24 hours of stroke onset, aged over 18 years, and had evidence of arterial occlusion as confirmed by CTA or MRA. These patients were also characterized as being outside the treatment window for TPA injection and Mechanical Thrombectomy. On the other hand, the exclusion criteria ruled out patients with a systolic blood pressure (SBP) greater than 200 mm Hg, those who had inter or intracranial hemorrhage, a history of myocardial infarction in the preceding seven days, or elevated levels of troponin serum concentration.

For the intervention, Injection norepinephrine (50 mg), diluted in 250 mL of normal saline, was intravenously administered to the patients at a rate of 0.3 µg/kg/min. This dosage was titrated every 30 to 60 minutes to achieve a target systolic BP of greater than 180 mmHg but less than 200 mmHg, and a mean arterial pressure (MAP) of 100. Blood pressure was monitored and recorded at three specific time points: upon initial presentation in the hospital (initial BP), immediately before the start of epinephrine administration and patient transfer to HASU (baseline BP), and subsequently every 12 hours.

Patients' progress was monitored throughout their three-day stay in HASU. The primary observation parameter was the improvement in muscle power, assessed using the Medical Research Council (MRC) Muscle Power Scale. The sample size for this study was calculated using magnitudes from previous studies and the WHO sample size calculator. A sample size of 50 was determined, considering a 10% level of significance and an 80% power of the study, with the expected percentage of improvement in clinical parameters being the determining factor.

For the analysis of the collected data, SPSS version 25 was employed. This statistical software facilitated a comprehensive analysis, enabling the interpretation of the study's findings through various statistical methods. The data analysis process encompassed

descriptive statistics to summarize the patient demographics and clinical characteristics, as well as inferential statistics to assess the effectiveness of the hypertension induction treatment on the patients' muscle power improvement.

Ethical clearance for this study was obtained from the Ethical Review Board Committee, with the reference number A/28/169. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

RESULTS

This study observed a total of 50 male patients. The mean systolic blood pressure (SBP) among these patients was 140±5.07 mmHg, while the mean diastolic blood pressure (DBP) was 94.16±4.71 mmHg. The average age of the patients was 55±4.4 years. Blood pressure was recorded at 12-hour intervals throughout the duration of the study, which spanned three days. Assessments of muscle power were conducted at 24-hour intervals. Initially, within the first 24 hours, no significant effect on muscle power was observed. However, after 24 hours, improvements in muscle power were noted across all patient groups.

Table 1 Demographics

No. of Patients	50
Gender	Male
Mean Systolic Blood Pressure (SBP)	140±5.07 mmHg
Mean Diastolic Blood Pressure (DBP)	94.16±4.71 mmHg
Mean age of patients	55±4.4 years
Blood pressure recording	12-hour intervals
Duration of patient observation	3 days
Power assessment interval	24-hour intervals
Initial effect on power	No observed effect within 24 hours
Power improvement	Observed in all groups after 24 hours

Group 1 consisted of 6 patients, with a baseline NIH Stroke Scale (NIHSS) score of 2. This group was further divided into Group 1a (4 patients, representing 66.6%) and Group 1b (2 patients, representing 33.3%). The initial Medical Research Council (MRC) power scale scores were 2 for Group 1a and 3 for Group 1b. After 72 hours, there was an improvement in muscle power, with Group 1a showing a 75% improvement (MRC scale score of 3) and Group 1b showing a 50% improvement (MRC scale score of 1). Patients in Group 1 primarily presented with weakness in their leg muscles.

Table 2 Demographic and clinical analysis of group 1 CVA patients

Group 1	
No. of patients	06
Baseline NIHSS score	2
Group 1a	4 (66.6%)
Group 1b	2(33.3%)
MRC power scale Group 1a	2
MRC power scale Group 1b	3
Power improved to MRC power scale Group 1a (After 72 hours)	3(75%)
Power improved to MRC power scale Group 1b (After 72 hours)	1(50%)
Group1; (n=6) patients presented with weakness of only leg muscles	

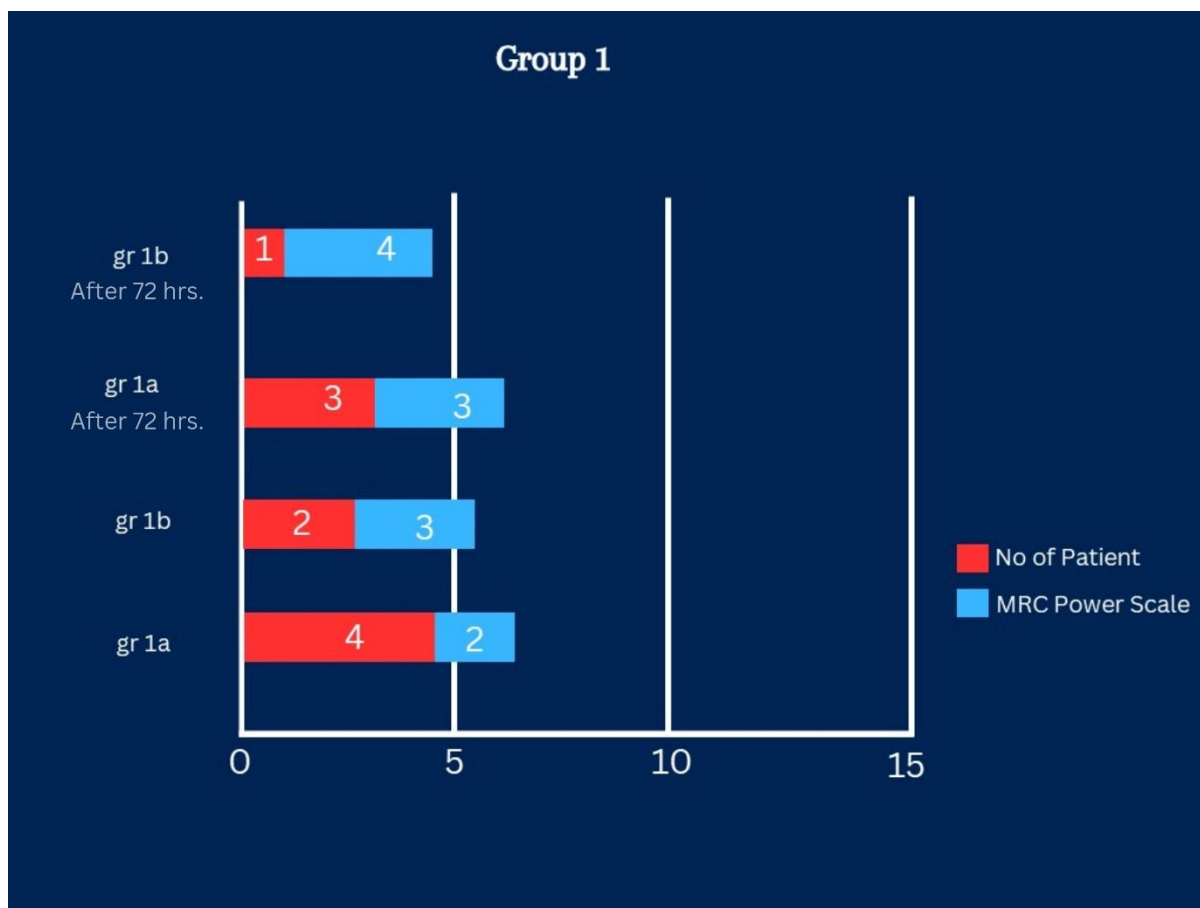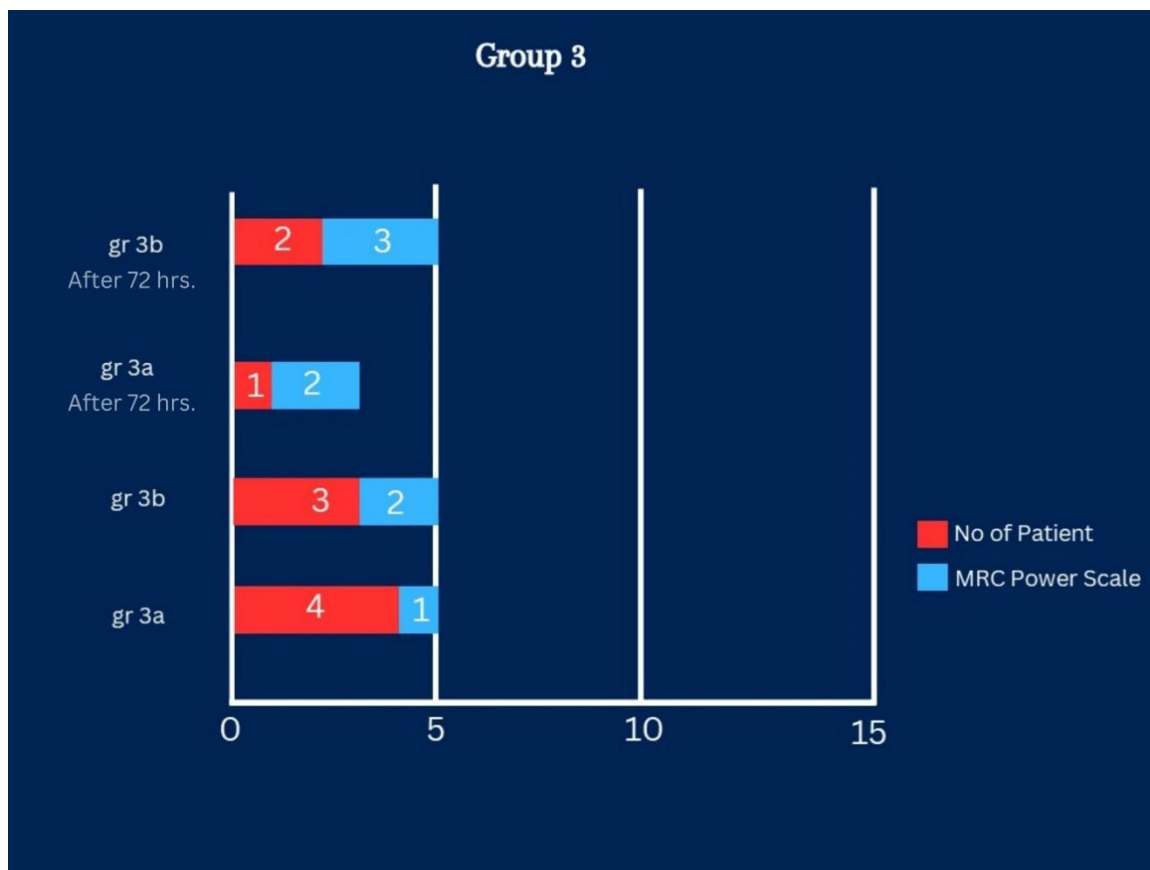*Figure 1 Demographic and clinical analysis of group 1 CVA patients*

Table 3 Demographic and clinical analysis of group 2 CVA patients

Group 2	
No. of patients	15
NIHS Stroke Scale	2
Group 2a	10(66.6%)
Group 2b	5(33.3%)
MRC power scale Group 2a	2
MRC power scale Group 2b	3
Power improved to MRC power scale. Group 2a (After 72 hours)	7(70%)
Power improved to MRC power scale. Group 2a (After 72 hours)	4(80%)

In Group 2, there were 15 patients, all with an NIHSS score of 2. This group was subdivided into Group 2a (10 patients, 66.6%) and Group 2b (5 patients, 33.3%). The initial MRC power scale scores were 2 for Group 2a and 3 for Group 2b. After 72 hours, Group 2a showed a 70% improvement in muscle power (7 patients improved), and Group 2b showed an 80% improvement (4 patients improved).

Figure 2 Demographic and clinical analysis of group 2 CVA patients

Group 4 included 14 patients, with the NIH Stroke Scale scores of 3 for upper limb and 2 for lower limb. This group was divided into Group 4a (9 patients, 64.2%) and Group 4b (5 patients, 35.7%). The initial MRC power scale scores were 1 for Group 4a and 2 for Group 4b. After 72 hours, Group 4a showed a 66.6% improvement (6 patients improved), and Group 4b showed a 60% improvement (3 patients improved). Notably, 7 patients in this group presented with more pronounced weakness in the upper limbs compared to the lower limbs.

Table 4 Demographic and clinical analysis of group 4 CVA patients

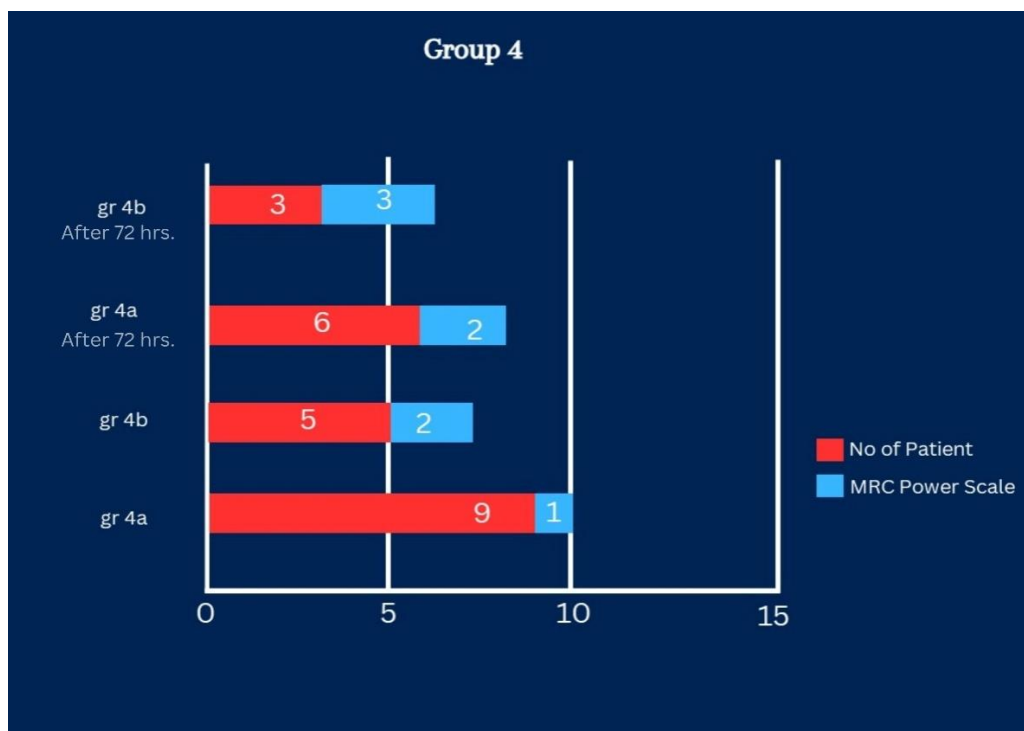| Group 4	
No. of patients	14
NIH Stroke Scale I). Upper limb II). Lower Limb	3 2
Group 4a	9(64.2%)
Group 4b	5 (35.7%)
MRC power scale Group 4a	1
MRC power scale Group 4b	2
Power improved to MRC power scale. Group 4a (After 72 hours)	6(66.6%)
Power improved to MRC power scale. Group 4a (After 72 hours)	3(60%)
Group 4; (n= 7) patients presented with weakness of upper limbs more than lower limbs	

Figure 3 Demographic and clinical analysis of group 4 CVA patients

Table 5 Demographic and clinical analysis of group 5 CVA patients

Group 5	
No. of patients	8
NIH Stroke Scale Upper limb	4
Lower limb	4
NIHSS score 02 upper limbs	0 (0%)
NIHSS 04 for upper and lower limbs	0 (0%)
Power Improvement to MRC power scale Group 5	3(37.5%)
Group 5; (n=08) patients presented with no movements in both the upper and lower limbs	

Group 5 consisted of 8 patients, all with NIH Stroke Scale scores of 4 for both upper and lower limbs. None of the patients showed improvement in the NIHSS score for the upper limbs or for both upper and lower limbs combined. However, there was a 37.5% improvement in muscle power according to the MRC power scale in this group. Notably, all 8 patients in Group 5 presented with no movements in both the upper and lower limbs.
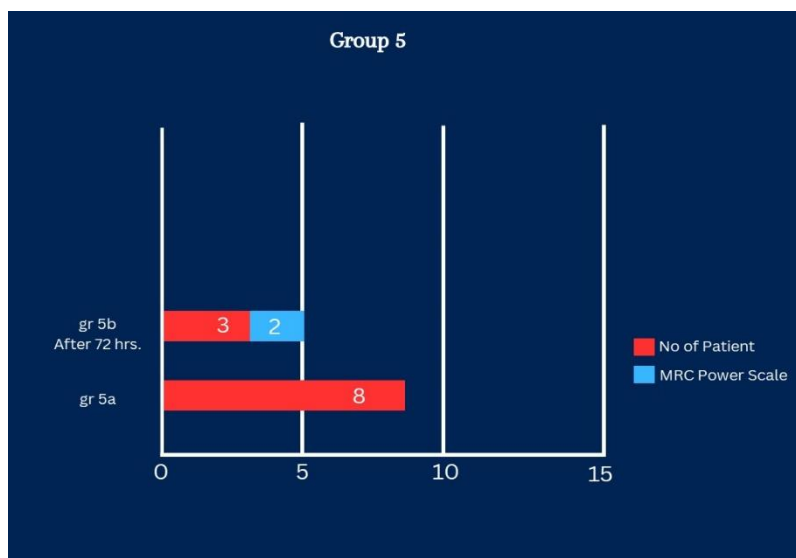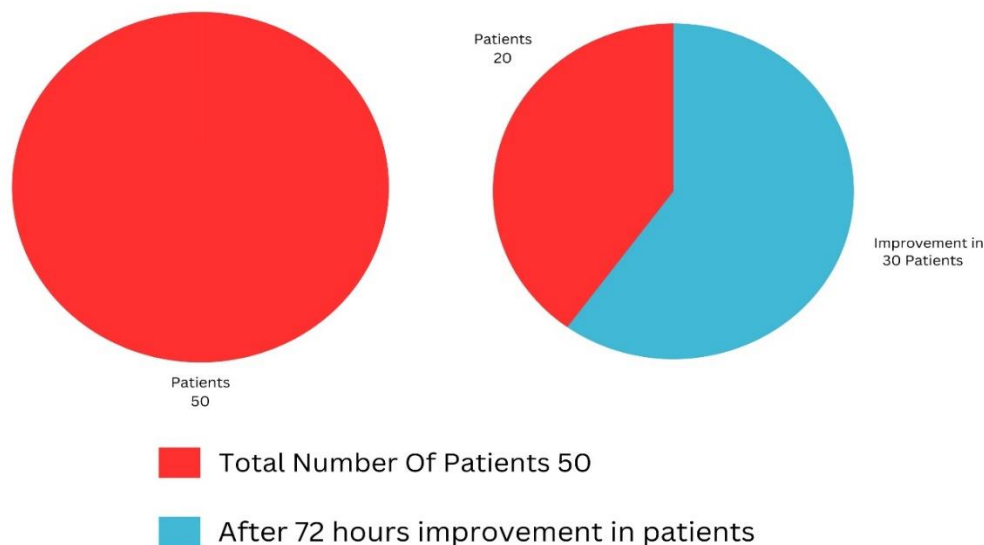

Figure 4 Demographic and clinical analysis of group 5 CVA patients

The figure presents two pie charts summarizing patient outcomes in a study. The chart on the left, entirely in red, indicates the total number of patients, which is 50. The chart on the right shows a split between red and blue segments, with the blue segment accounting for the majority, indicating that 30 out of the 50 patients showed improvement after 72 hours. The red segment represents the 20 patients who did not show improvement. Below the charts, a statement confirms that out of the 50 patients observed, a total of 30 patients exhibited improvement.

Figure 5 Total improvement

DISCUSSION

Ischemic stroke stands as a leading cause of mortality worldwide, second only to myocardial infarction in the frequency of emergency department presentations, claiming approximately 6.5 million lives annually (13). Despite the fact that prompt identification and management of risk factors have been shown to reduce incidence rates, the disease burden remains significant, particularly among individuals aged 18 to 49 years. Established treatments such as intravenous thrombolysis and endovascular revascularization have proven effective when patients are presented within the critical windows of 4.5 hours for thrombolysis and 6-8 hours for mechanical thrombectomy (14,15).

Therapeutic induced hypertension is a strategy utilized in various centers globally, which involves increasing blood pressure by 15 to 20 percent above baseline using vasoactive agents such as phenylephrine, norepinephrine, and occasionally hypertonic or normal saline, though the latter are less commonly used (16). The rationale for this approach is to enhance blood flow in ischemic tissues, particularly within the ischemic penumbra, by improving collateral circulation. Collaterals, being the small vessels branching from larger vessels and penetrating deep into cerebral tissue, play a pivotal role in cerebral perfusion at the molecular level (17). Therefore, augmenting blood pressure is posited to enhance cerebral perfusion by opening these collaterals and thereby increasing blood flow within them. This concept was supported by experimental studies in Japan and Korea, which demonstrated increased cerebral blood flow and reduced cerebral edema in infarction territories after administering phenylephrine following focal infarction in animal models (18,19). Further studies, such as those by Hillis et al., investigated the effects of induced hypertension on stroke patients who were beyond the therapeutic window for conventional interventions (20). Their trial showed that phenylephrine-induced augmentation of blood pressure by 10-20% relative to baseline, initiated within 8 hours of symptom onset, resulted in significant improvements in NIHSS scores by day 3 and even more pronounced improvements by day 7, compared to a conventional treatment group.

Conversely, Koenig et al. highlighted potential risks associated with induced hypertension, revealing a case of cerebral hemorrhage in a patient with a systolic blood pressure exceeding 200 mmHg, underscoring the need for caution and suggesting that lower blood pressure targets may be safer (22). This finding is particularly salient, indicating that the cerebral vasculature may be susceptible to damage under conditions of excessively elevated blood pressure. The ongoing Phase-III trial (SETIN-HYPERTENSION) aims to shed light on the safety and efficacy of induced hypertension using phenylephrine in patients with non-cardioembolic ischemic stroke (23).

In the current study, we observed 50 patients who were ineligible for TPA and mechanical thrombectomy. These patients were stratified into five groups to better understand the effects of induced hypertension on their condition. Notably, in groups 1 and 2, patients exhibited improvements in muscle power as measured by the MRC scale following 72 hours of induced hypertension. Group

3 demonstrated a less pronounced improvement, while group 4 showed a significant increase in muscle power in a majority of the patients. Group 5, which consisted of patients with no initial movement in the limbs, presented a challenge; however, a subset of these patients also showed improvement after the intervention. Overall, our observations indicate that 30 out of the 50 patients experienced a notable enhancement in muscle power post-treatment.

The findings suggest that blood pressure augmentation can be beneficial for improving muscle power in ischemic stroke patients who have surpassed the window for conventional therapeutic interventions. This study reinforces the concept that induced hypertension may serve as a viable 'bridging' therapy in acute ischemic stroke management until recanalization can be achieved, pending further validation from ongoing clinical trials and additional research.

CONCLUSION

The findings of this study hold significant clinical implications, suggesting that blood pressure augmentation could potentially serve as an effective therapeutic strategy for ischemic stroke patients who have missed the window for standard interventions such as tissue plasminogen activator administration or mechanical thrombectomy. By demonstrating that a substantial proportion of patients experienced improved muscle power following induced hypertension, this research contributes to a growing body of evidence that supports the utility of this approach. If these results are corroborated by larger, phase-III trials, induced hypertension could be integrated into clinical practice as a bridge therapy, potentially improving outcomes for a demographic of stroke patients currently limited by the constraints of treatment timelines.

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