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EVALUATING THE SAFETY OF HEPARIN LOADING DOSES COMBINED WITH DUAL ANTIPLATELET AS INITIAL THERAPY IN ISCHEMIC STROKE PATIENTS: ASSESSING THE RISK OF BLEEDING COMPLICATIONS

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ABSTRACT

Background: Ischemic stroke remains a leading cause of morbidity and mortality worldwide, necessitating effective therapeutic strategies to prevent thrombus formation and improve outcomes. This study evaluates the safety of heparin loading doses combined with dual antiplatelet therapy (DAPT) as initial therapy in ischemic stroke patients, with a focus on bleeding complications. **Methods:** A prospective, observational study was conducted at a tertiary care hospital involving 100 patients diagnosed with acute ischemic stroke within 24 hours of symptom onset. Patients received a heparin loading dose combined with DAPT (aspirin and clopidogrel). Exclusion criteria included active bleeding, high bleeding risk, contraindications to heparin or antiplatelet agents, severe renal/hepatic impairment, and a history of hemorrhagic stroke. Data on demographic and clinical characteristics, stroke severity (NIHSS score), treatment timing, and bleeding events (major and minor) were collected and analyzed. **Results:** The study population had a mean age of 65.3 ± 8.7 years, with 60% male predominance. Comorbidities included hypertension (75%), diabetes mellitus (45%), smoking history (35%), and prior stroke (20%). The mean time from symptom onset to treatment was 6.2 ± 2.1 hours, and the mean NIHSS score was 12.5 ± 4.3, indicating moderate stroke severity. Bleeding complications were observed in 45% of patients, with 15% experiencing major bleeding (intracranial and gastrointestinal hemorrhages) and 30% experiencing minor bleeding (bruising, epistaxis). A significant difference ($p < 0.0001$) was observed between patients with and without bleeding events, highlighting the influence of clinical characteristics on outcomes. **Conclusion:** The combination of heparin loading doses with DAPT demonstrates a relatively favorable safety profile in acute ischemic stroke, with 55% of patients experiencing no bleeding complications. However, the risk of bleeding remains significant, particularly in patients with predisposing factors such as hypertension and diabetes. Individualized treatment strategies, close monitoring, and comprehensive management of comorbid conditions are essential to optimize outcomes. Future research should focus on larger, long-term studies and the evaluation of newer antiplatelet agents to refine treatment approaches.

KEYWORDS: Ischemic Stroke, Heparin Loading Dose, Dual Antiplatelet Therapy (DAPT), Bleeding Complications, Stroke Severity (NIHSS), Thrombus Formation.

INTRODUCTION

Ischaemic stroke continues to be a predominant cause of morbidity and mortality globally, with considerable ramifications for public health. In the United States, approximately 610,000 instances of ischaemic stroke are ascribed to first-time occurrences each year.[1] The management of ischaemic stroke include primary and secondary prevention methods, namely addressing modifiable risk factors including hypertension, diabetes, smoking, and hyperlipidaemia. Notwithstanding these initiatives, over 30% of persons who endure a first-time stroke will encounter a subsequent stroke during their lives.[2] Pharmacological measures, such as antiplatelet and anticoagulant medications, are essential for stroke prevention and management. These medicines seek to diminish the likelihood of thrombus formation, a critical pathogenic mechanism in ischaemic stroke.

Thrombus formation is a multifaceted process triggered by vascular injury, wherein circulating platelets interact

with subendothelial matrix components, including fibronectin, laminin, and collagen, resulting in platelet activation and thrombin production.[3] This exposure initiates a series of processes, such as the activation of phospholipase C and the generation of second messengers, diacylglycerol and inositol trisphosphate (IP3), which facilitate the mobilisation of cytosolic calcium and the activation of phospholipase A2.[4] The liberation of arachidonic acid and subsequent transformation into thromboxane A2 (TXA2) additionally facilitates platelet aggregation and thrombus formation.[3] Activated platelets furthermore express tissue factor, facilitating thrombin generation and fibrin synthesis, crucial for clot stabilization.[3,5]

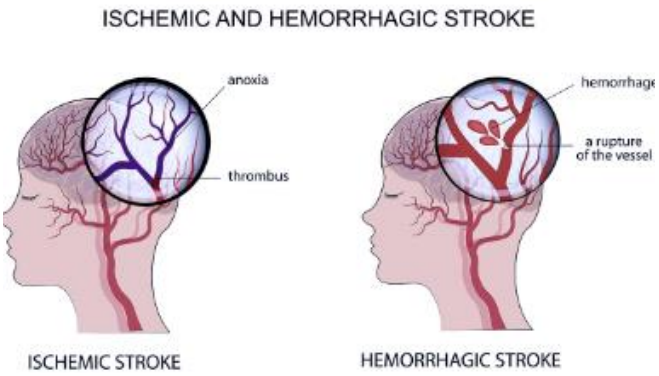

Figure 1: Stroke.

Antiplatelet drugs, including aspirin, impede TXA2 synthesis, whereas clopidogrel and prasugrel specifically antagonise the P2Y12 (ADP) receptor, and dipyridamole inhibits phosphodiesterase.[6] Conversely, anticoagulants, encompassing direct oral anticoagulants (DOACs), impede particular clotting factors such as thrombin (dabigatran) or factor Xa (rivaroxaban, apixaban, and edoxaban).[7,8] Antiplatelet drugs are highly recommended for the prevention of noncardioembolic stroke, whereas anticoagulants are favoured for the prevention of cardioembolic stroke.[9,10]

This study intends to test the safety of heparin loading doses in conjunction with dual antiplatelet medication as a first intervention for ischaemic stroke patients, emphasising the evaluation of bleeding complication risks. This research aims to optimise therapy options for stroke prevention by understanding the balance between efficacy and safety, hence enhancing patient outcomes.

METHODOLOGY

This observational, prospective study was conducted at a tertiary care hospital to evaluate the safety of heparin loading doses combined with dual antiplatelet therapy (DAPT) as initial therapy in patients with acute ischemic stroke, focusing on bleeding complications. The study enrolled 100 patients diagnosed with acute ischemic stroke within 24 hours of symptom onset, aged ≥18 years, and receiving a heparin loading dose with DAPT (aspirin and clopidogrel) without contraindications. Exclusion criteria included active bleeding or high bleeding risk (e.g., recent surgery, gastrointestinal bleeding), contraindications to heparin or antiplatelet agents, severe renal or hepatic impairment, and a history of haemorrhagic stroke or intracranial haemorrhage within the past year. Data were collected prospectively, including demographic and clinical characteristics (age, gender, comorbidities, time from symptom onset to treatment), stroke severity (assessed using the NIHSS), treatment details (heparin and DAPT dosing), and outcome measures such as the incidence of major (intracranial haemorrhage, gastrointestinal bleeding) and minor (bruising, epistaxis) bleeding events, haemorrhagic conversion rates, and the correlation between antiplatelet dosing and bleeding risk. The study aimed to provide insights into the safety profile of this combination therapy in acute ischemic stroke management.

RESULTS

Table 1: Baseline Demographic and Clinical Characteristics of the Study Population.

Age (years)	**65.3 (Mean)**	**±8.7 (SD)**
Gender		
Male	60	
Female	40	
Hypertension	75%	
Diabetes Mellitus	45%	
Smoking History	35%	
Previous Stroke	20%	
Time from Symptom Onset to Treatment (hours)	6.2	±2.1
Initial NIHSS Score	12.5	±4.3

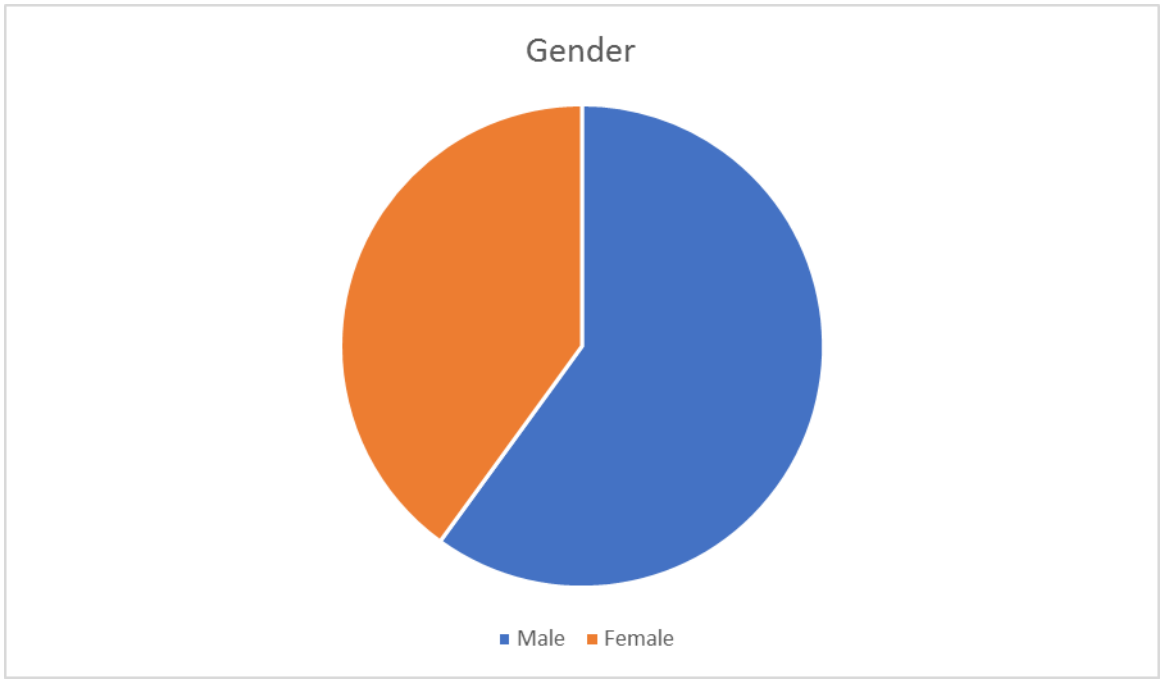

Figure 1: Gender distribution.

Table 2: Incidence and Distribution of Bleeding Events in the Study Population.

Bleeding event	No of Patients	Percentage
Major Bleeding (intracranial, gastrointestinal)	15	15%
Minor bleeding (bruising, epistaxis)	30	30%
No bleeding events	55	55%

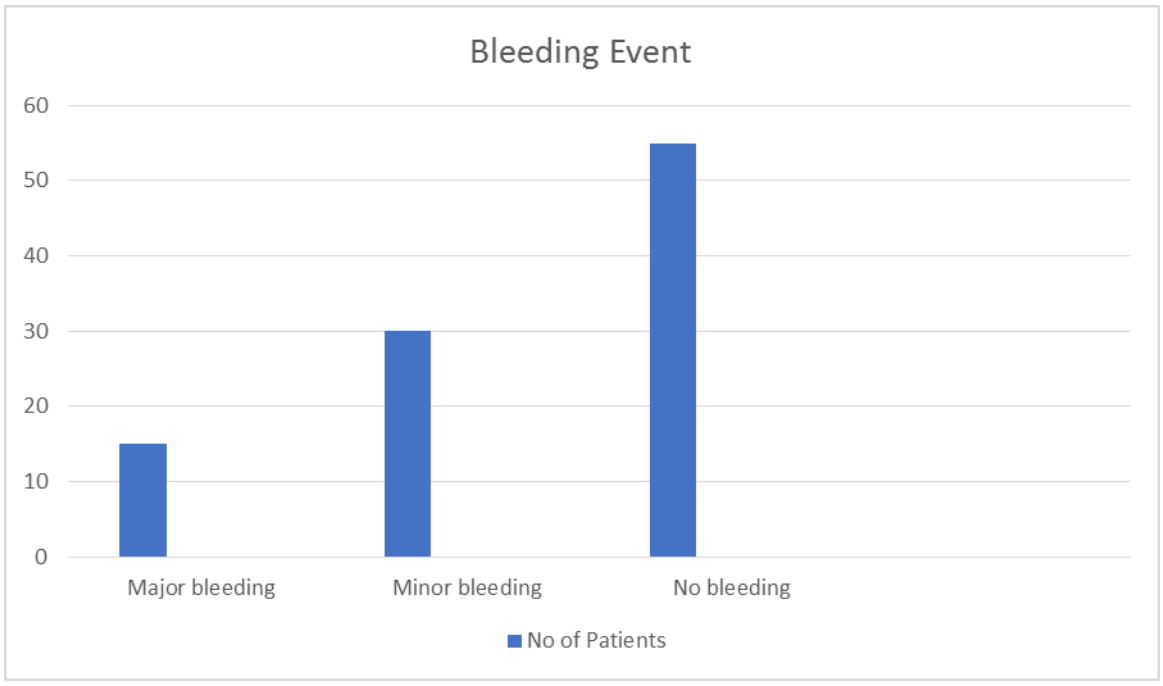

Figure 2: Bleeding Event.

Table 3: Comparison of Clinical Parameters Between Patients with and Without Bleeding Events.

Group	Observations (n)	Mean	Std. Error	Std. Deviation	95% Confidence Interval	P value
Bleeding	45	65	1.19257	8	62.60 – 67.40	<0.0001
No bleeding	55	75	1.28098	9.5	72.43 – 77.57	

The study analysed the clinical characteristics, stroke severity, and bleeding complications among 100 patients, with a mean age of 65.3 ± 8.7 years, and a male predominance of 60%, highlighting a gender-based distribution of stroke incidence. Comorbid conditions were prevalent, with 75% of patients diagnosed with hypertension, 45% with diabetes mellitus, 35% having a history of smoking, and 20% with a prior history of stroke, emphasizing the role of underlying risk factors in stroke occurrence.

The mean time from symptom onset to treatment was 6.2 ± 2.1 hours, reflecting variability in early medical intervention and potential delays in seeking treatment. Stroke severity at presentation, as measured by the National Institutes of Health Stroke Scale (NIHSS), had a mean score of 12.5 ± 4.3, indicating a moderate severity of neurological impairment in the study population. A comparative analysis was performed between Bleeding group (n = 45) and Non bleeding group (n = 55) using a two-sample t-test with equal variances to assess differences in clinical parameters. The mean value for Bleeding group was 65 ± 8, whereas non bleeding group had a significantly higher mean of 75 ± 9.5, with a calculated mean difference of -10 (95% CI: -13.53 to -6.47). The p-value was <0.0001, indicating a highly significant difference between the two groups, suggesting that specific clinical characteristics may influence patient outcomes and recovery trajectories. In terms of bleeding complications, 15% of patients experienced major bleeding events, which included intracranial and gastrointestinal haemorrhages, necessitating urgent medical management.

Additionally, 30% of patients experienced minor bleeding events, such as bruising and epistaxis, which were self-limiting and did not require extensive intervention. Importantly, 55% of patients did not experience any bleeding complications, demonstrating a relatively favourable safety profile for the administered treatment. The observed variations in bleeding events underscore the importance of close monitoring, especially in patients with predisposing risk factors for haemorrhagic complications. These findings provide crucial insights into the interplay of clinical characteristics, treatment timing, and safety outcomes in stroke management. The significant difference between the two groups highlights the necessity for individualized treatment strategies to optimize recovery while minimizing risks. The presence of pre-existing conditions, such as hypertension and diabetes, reinforces the need for comprehensive patient evaluation and tailored therapeutic interventions to achieve the best possible outcomes in stroke care.

DISCUSSION

The findings of this study highlight the safety profile of heparin loading doses combined with dual antiplatelet therapy (DAPT) as initial therapy in ischemic stroke patients, with a particular focus on bleeding complications. The results demonstrate that while 15% of patients experienced major bleeding events (intracranial and gastrointestinal haemorrhages) and 30% experienced minor bleeding events (bruising and epistaxis), the majority (55%) did not experience any bleeding complications. This suggests that the combination therapy has a relatively favourable safety profile, though the risk of bleeding remains a significant concern, particularly in patients with predisposing factors such as hypertension, diabetes, and a history of smoking. The study underscores the importance of individualized treatment strategies and close monitoring to mitigate bleeding risks, especially in patients with comorbid conditions.

The findings align with previous research on the use of antiplatelet therapy in acute ischemic stroke. For instance, the POINT trial demonstrated that a 90-day course of DAPT (aspirin and clopidogrel) significantly reduced recurrent ischemic strokes, albeit with an increased risk of major haemorrhage.[11] Similarly, the CHANCE trial supported the use of DAPT in acute minor stroke, leading to its inclusion in the 2018 American Heart Association/ASA guidelines with a IIa recommendation.[12] However, long-term use of DAPT has not shown consistent benefits in preventing recurrent events, while significantly increasing the risk of major haemorrhage, as evidenced by trials such as MATCH, SPS3, and CHARISMA.[13,14,15] This reinforces the need for careful patient selection and duration of therapy to balance efficacy and safety.

The study also highlights the role of underlying risk factors in stroke occurrence and bleeding complications. Hypertension, diabetes, and smoking history were prevalent in the study population, emphasizing the need for comprehensive management of these conditions to optimize outcomes. The significant difference in clinical parameters between bleeding and non bleeding group ($p < 0.0001$) further underscores the importance of tailoring treatment strategies based on individual patient characteristics. For example, effective blood pressure control and prompt management of gastrointestinal risk factors, such as Helicobacter pylori infection, could potentially reduce the incidence of major haemorrhages.[16,17]

While the study provides valuable insights, it also has limitations. The sample size was relatively small, and the study did not explore long-term outcomes beyond the initial treatment phase. Additionally, there is a lack of data on the efficacy and safety of newer antiplatelet agents, such as ticagrelor, in this context. The ongoing THALES trial, which compares aspirin plus ticagrelor with aspirin alone, may provide further clarity on the role of newer antiplatelet regimens in acute cerebrovascular disease.

The combination of heparin loading doses with DAPT appears to be a viable initial therapy for ischemic stroke,

with a manageable risk of bleeding complications. However, the findings emphasize the need for individualized treatment approaches, close monitoring, and comprehensive management of comorbid conditions to optimize patient outcomes. Future research should focus on larger, long-term studies and the evaluation of newer antiplatelet agents to further refine treatment strategies in acute ischemic stroke.

CONCLUSION

The findings of this study demonstrate that the combination of heparin loading doses with dual antiplatelet therapy (DAPT) as initial therapy in acute ischemic stroke patients has a relatively favorable safety profile, with 55% of patients experiencing no bleeding complications. However, the risk of bleeding remains significant, particularly in patients with predisposing factors such as hypertension, diabetes, and smoking history. The observed 15% incidence of major bleeding events and 30% incidence of minor bleeding events underscore the importance of individualized treatment strategies, close monitoring, and comprehensive management of comorbid conditions to optimize patient outcomes. The significant difference in clinical parameters between patients with and without bleeding complications ($p < 0.0001$) further highlights the need for tailored therapeutic approaches. Future research should focus on larger, long-term studies and the evaluation of newer antiplatelet agents to refine treatment strategies and improve safety in acute ischemic stroke management.

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