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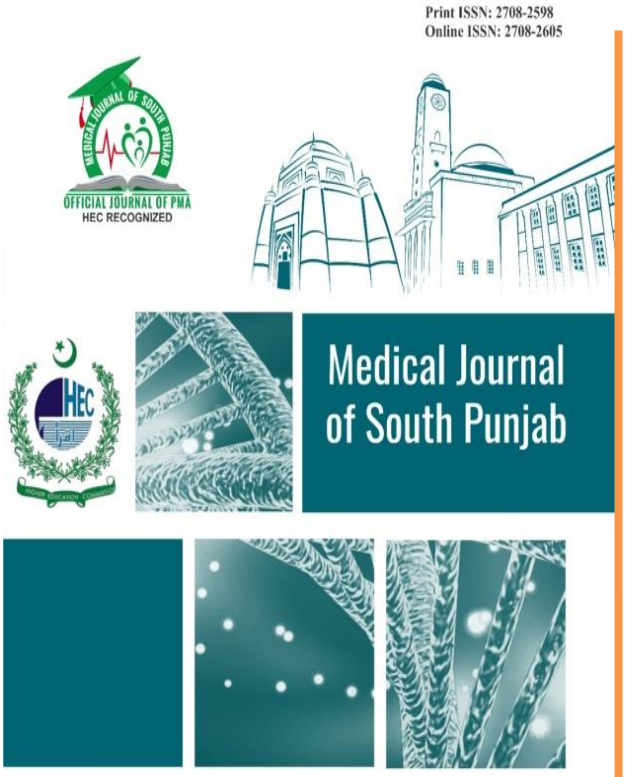

Effect of Paracetamol (Acetaminophen) on functional outcome in acute stroke patients in neurology department of a Tertiary

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Original Article

Effect of Paracetamol (Acetaminophen) on functional outcome in acute stroke patients in neurology department of a Tertiary Hospital of Sialkot

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ABSTRACT

Objective: To compare meanfunctional outcome (mRS score), and incidence of complications and mortality rate in acute stroke patients with and without acetaminophen.

Methods: This randomized controlled trial conducted at department of Neurology, Khawaja Muhammad Safdar Medical College, Sialkotfrom 11-04-2025 to 10-07-2025. A total of 200 patients were randomly divided into two equal groups. Group A was given paracetamol 1g every 6 hours, while Group B was not given paracetamol. Patients were called for follow-up, and mRS was calculated at 4 weeks and 8 weeks. During the 8-week period, the development of fever, pneumonia, UTI, sepsis, or death was recorded. mRS was compared using t-test, and mortality and complications were compared using chi-square test, taking p-value of ≤0.05 as statistically significant.

Results: At both 4 and 8 weeks, Group A demonstrated significantly better functional outcomes, with lower mean mRS scores (2.87 vs. 3.81, p=0.001; 2.15 vs. 3.44, p<0.001). Complications were less frequent in Group A, as pneumonia occurred in 20% compared to 33% in Group B (p=0.037), and sepsis in 13% vs. 24% (p=0.045). UTI was slightly higher in Group A (36% vs. 30%), though not statistically significant (p=0.367). Mortality was also significantly reduced in Group A (20%) compared to Group B (34%, p=0.026).

Conclusion: Acetaminophen use in acute stroke improved functional outcomes, reduced mortality, and lowered complication rates, supporting its potential as a simple and cost-effective adjunct therapy.

Keywords: Acetaminophen, Acute stroke, Functional outcome, Neurology

1. INTRODUCTION

Globally, stroke ranks as the second most common cause of death and the third major contributor to disability, impacting nearly one in every four individuals over their lifetime.[1]After stroke, majority of the patients develop high body temperatures which is associated with poor functional outcomes and higher mortality.[2-4]Studies have shown that within the first 12 hours of an acute stroke, each 1°C rise in body temperature is associated with a twofold increase in the risk of unfavorable outcomes.[5]Elevated body temperature worsens ischemic injury by raising cerebral metabolic demand, disrupting the blood–brain barrier, promoting acidosis, and triggering the release of excitatory amino acids.[6,7] Therefore, preventing the fever and lowering the body temperatures can help improve the functional outcomes in acute stroke patients.

Previous studies revealed that improvement in spontaneous hyperthermia was beneficial to reduce infarct volume and improve functional outcome.[3]Paracetamol (acetaminophen) has been widely used as an antipyretic agent, exerting its effect by inhibiting cerebral cyclooxygenase-2 activity and reducing the production of prostaglandin E2 in the brain. Administration of high-dose paracetamol within the first 12 hours of stroke onset may contribute to improved functional recovery.[8]In above mentioned study, beyond expectation improvement was observed in 40% of the acetaminophen and 31% of the placebo group. They observed a 14 days mortality rate to be 7% vs. 4% in the placebo vs. acetaminophen group.[8]A study observed the incidence of serious adverse events to be 26% vs 24% in the acetaminophen vs. placebo group.[9]One study found that fever exceeding 37.5°C was observed in 36.4% of patients receiving placebo, whereas only 5% of those treated with acetaminophen developed fever ($p = 0.014$).[10]This may further help in improving the functional outcome among such patients. de Jonge JC et al.[11] conducted a phase-III clinical trial and observed mRS score of 3.7±1.8 and 3.6±1.9 with and without paracetamol, respectively, without any statistically significant difference ($p=0.15$). The mRS score in placebo group was 2±0.75.[10] In another study, mRS of paracetamol group was 3.5±1.[11]

So far, in the published data, no study was found to specifically describe the effects of paracetamol use on the functional outcomes in the patients of acute stroke. Current study was planned to observe the role of paracetamol on improvement of modified Rankin scale score, adverse events and 8 weeks mortality among the patients presenting with acute ischemic or hemorrhagic stroke.

2. METHODOLOGY

This was randomized controlled trial, performed in the Department of Neurology, Khawaja Muhammad Safdar Medical College, Sialkot from 11-04-2025 to 10-07-2025, after approval from the IRB.A sample size of 200 patients (100 in each group) was calculated by using 95% significance level, 80% power of test, and mRS without paracetamol as 2±0.75[10] and with paracetamol as 3.5±1.[11]Nonprobability consecutive sampling technique was applied for selection of patients.

All the patients of both male and female gender, 18-70 years of age, diagnosed with acute stroke were included in the study. Acute stroke was defined as moderately severe to severe acute ischemic stroke or intracerebral hemorrhage, with a score of 6 or higher on the National Institutes of Health Stroke Scale (NIHSS). Patients with recurrent stroke, history of ischemic heart disease and uncontrolled diabetes mellitus were excluded.

A total of 200 patients were included in the study according to the inclusion and exclusion criteria. Informed written consent was obtained from the first-degree attendants of all the patients. Age, gender, type of stroke, body temperature, GCS, and mRS score were documented for all the patients at presentation. Patients were randomly divided into two equal groups. Group A was given paracetamol 1 g every 6 hours, while Group B was not given paracetamol. Broad-spectrum antibiotics were administered if needed. Patients were called for weekly follow-up. Functional outcome was calculated according to modified Rankin Scale after 4 and 8 weeks after start of treatment. During the 8-week period, the development of fever, pneumonia, UTI, sepsis, or death was recorded.Primary outcomes included functional status and mortality within 8 weeks of follow up. Secondary outcomes included development of complications such as fever, pneumonia, urinary tract infection and sepsis. All the data were entered in a standardized proforma by the researcher.

All the data were entered in SPSS version 27 and analyzed. Continuous variables i.e., age, temperature, GCS, and mRS score were presented as mean and standard deviation. Categorical variables i.e., gender, type of stroke, fever, and incidence of pneumonia, UTI, sepsis, and mortality were documented as numbers and percentages. mRS was compared using t-test, and mortality and complications were compared using chi-square test. Data were stratified for age, gender, and type of stroke. Post-stratification t-test and chi-square test were applied, taking p-value of ≤0.05 as statistically significant.

3. RESULTS

Table-I presents a comparison of baseline demographic and clinical characteristics between Group A (n=100) and Group B (n=100). The mean age was comparable between the two groups (51.51 ± 12.05 vs. 54.20 ± 11.14 years, p = 0.103). Gender distribution showed a predominance of females in both groups, with no significant difference (p = 0.239). The majority of patients in both groups had ischemic stroke (76% in Group A and 84% in Group B), whereas hemorrhagic stroke was less frequent; the difference was not statistically significant (p = 0.157). Mean body temperature, GCS at presentation, and mRS score at presentation were also similar across groups, with no statistically significant differences (p> 0.05 for all variables).

The mean mRS score was significantly lower in Group A both at 4 weeks (2.87 ± 2.09 vs. 3.81 ± 1.89, p = 0.001) and at 8 weeks (2.15 ± 2.31 vs. 3.44 ± 1.97, p< 0.001), indicating better functional outcomes. Among complications, pneumonia was observed more frequently in Group B compared to Group A (33.0% vs. 20.0%, p = 0.037). Similarly, sepsis occurred significantly more in Group B (24.0% vs. 13.0%, p = 0.045). UTI was slightly higher in Group A (36.0% vs. 30.0%), but the difference was not statistically significant (p = 0.367). Mortality was also significantly higher in Group B (34.0%) compared to Group A (20.0%, p = 0.026). Table-II

At 8 weeks, mortality was significantly higher in younger patients (18–50 years, p = 0.016) and in ischemic stroke patients (p = 0.032) of Group B. No significant mortality differences were noted in older age, gender, or hemorrhagic stroke subgroups. Functional outcomes (mRS) were consistently better in Group A across all strata of age, gender, and stroke type, with statistically significant differences in each category (p< 0.05).Table-III.

Table-I

Demographic and admission data

Variable	Group A (N=100)	Group B (N=100)	P value
Age, years	51.51±12.05	54.20±11.14	0.103
Gender, N (%)			

Male	40 (40.0)	32 (32.0)	0.239
Female	60 (60.0)	68 (68.0)	
Type of stroke, N (%)			
Hemorrhagic	24 (24.0)	16 (16.0)	0.157
Ischemic	76 (76.0)	84 (84.0)	
Temperature ^{o}F	10.33±2.15	100.58±2.19	0.416
GCS at presentation	10.45 ± 2.22	10.12 ± 3.07	0.386
mRS at presentation	3.79 ± 1.54	4.04 ± 1.37	0.227

Data is entered as mean ± S.D unless mentioned otherwise

Table-II: Outcome data

Variable	Group A (N=100)	Group B (N=100)	P value
mRS at 4 weeks	2.87 ± 2.09	3.81 ± 1.89	0.001
mRS at 8 weeks	2.15 ± 2.31	3.44 ± 1.97	<0.001
Pneumonia, N (%)	20 (20.0 %)	33 (33.0 %)	0.037
UTI, N (%)	36 (36.0 %)	30 (30.0 %)	0.367
Sepsis, N (%)	13 (13.0%)	24 (24.0 %)	0.045
Mortality N, (%)	20 (20.0 %)	34 (34.0 %)	0.026

Data is entered as mean ± S. D unless mentioned otherwise

Table-III
Assessment of mortality and mRS score at 8 weeks after stratification of data

	Group A (n=100)	Group B (n=100)	P value
Mortality among age, gender and stroke type			
18-50 years	12 (20.7)	20 (42.6)	0.016
51-70 years	8 (19.0)	14 (26.4)	0.398
Male (N=72)	7 (17.5)	10 (31.3)	0.172
Female	13 (21.7)	24 (35.3)	0.090
Hemorrhagic	6 (25.0)	6 (37.5)	0.398
Ischemic	14 (18.4)	28 (33.3)	0.032
mRS score at 8 week among age, gender and stroke type			
18-50 years	2.24 ± 2.41	3.72 ± 2.05	0.001
51-70 years	2.02 ± 2.19	3.19 ± 1.88	0.006
Male	1.95 ± 2.18	3.25 ± 1.79	0.008
Female	2.28 ± 2.40	3.52 ± 2.05	0.002
Hemorrhagic	2.46 ± 2.59	4.37 ± 1.54	0.006
Ischemic	2.05 ± 2.23	3.26 ± 2.01	<0.001

Data is entered as mean ± S.D unless mentioned otherwise

4. DISCUSSION

Current study demonstrated comparable baseline characteristics between groups, including age, gender, stroke type, body temperature, GCS, and initial mRS scores (p>0.05). Group A achieved significantly better functional outcomes, with lower mean mRS scores at both 4 and 8 weeks. Complications were more common in Group B, particularly pneumonia and sepsis, while UTI incidence was not significantly different. Mortality was significantly greater in Group B overall, especially among younger patients (18–50 years) and those with ischemic stroke. Across all age, gender, and stroke-type subgroups, functional outcomes (mRS) consistently favored Group A.

In the current study, Group A showed superior outcomes, including lower mRS scores at 4 weeks (2.87 vs. 3.81, p = 0.001) and 8 weeks (2.15 vs. 3.44, p < 0.001), fewer complications such as pneumonia (20% vs. 33%, p = 0.037) and sepsis (13% vs. 24%, p = 0.045), and reduced mortality (20% vs. 34%, p = 0.026). Piao ZS et al.[12] reported similar findings, showing that acetaminophen lowered 30-day (HR 0.54, p = 0.030) and 90-day mortality (HR 0.53, p = 0.013), though no difference in in-hospital mortality was observed (OR 0.95, p = 0.182). Both studies highlight acetaminophen's potential to improve survival, with our results further emphasizing enhanced functional recovery and lower complication rates.

Evidence from critically ill populations supports these observations. D'Eramo RE et al.[13] demonstrated that intravenous (IV) acetaminophenprovides faster and more pronounced antipyretic efficacy than oral administration, with greater median RIT reductions at all time points (0.25 °C vs. 0.2 °C at 0.5 h to 1.0 °C vs. 0.8 °C at 6 h; p < 0.05). Both ischemic and hemorrhagic stroke patients experienced greater temperature reductions with IV therapy. Importantly, 70% of all doses, regardless of route, reduced temperature to <38 °C within 6 hours, though IV doses achieved quicker responses. Better temperature control is clinically relevant, as it may contribute to fewer complications and improved long-term survival. Similarly, a large cohort of 15,843 critically ill sepsis

patients demonstrated significantly lower in-hospital (HR 0.44, p<0.001) and 30-day mortality (HR 0.50, p<0.001) with acetaminophen use, as well as shorter hospital (8.4 vs. 9.0 days, p < 0.001) and ICU stays (2.8 vs. 3.1 days, p < 0.05).[14] These findings align with our results, suggesting a survival and recovery benefit in both stroke and broader critical care settings.

However, previous large trials in stroke have shown more mixed results. The PAIS trial,[8] which randomized 1,400 patients, found no overall benefit of high-dose acetaminophen on 3-month functional outcomes. Yet, patients with baseline temperatures of 37–39 °C demonstrated a modest but significant benefit (OR 1.43, 95% CI 1.02–1.97), highlighting the potential importance of patient selection. Similarly, the PAIS-2 trial,[10] though underpowered with 256 patients, did not show significant differences in mRS outcomes at 3 months (adjusted OR, 1.15, 95% CI 0.74–1.79). A large VISTA database analysis[15] of 6,015 ischemic stroke patients also failed to show overall benefit on 90-day outcomes (OR 1.03, 95% CI 0.86–1.20). Notably, patients receiving acetaminophen prophylactically without fever had worse outcomes, further emphasizing that treatment effects may depend on clinical context.

Systematic reviews have reinforced these findings. Zhang et al.[16] concluded that paracetamol significantly lowers body temperature within 24 hours of stroke but does not improve functional outcomes or mortality. Similarly, Fang et al.[17] reported consistent temperature reductions, most notably at 24 hours (weighted mean difference –0.21 °C; 95% CI –0.28 to –0.14; p < 0.001), without significant impact on functional outcomes or survival. Meanwhile, Picetti et al.[18] demonstrated that intravenous paracetamol is both effective and safe for fever control in acute brain injury, lowering temperature without adverse cerebral or systemic hemodynamic effects.

Compared with these earlier studies, the current findings provide stronger evidence that acetaminophen may improve both functional recovery and survival, while also reducing complications. Several factors may explain this difference, including early treatment initiation, inclusion of both ischemic and hemorrhagic stroke patients, and systematic evaluation of complications. Biologically, better temperature control reduces secondary brain injury, lowers infection risk, and may ultimately enhance recovery.

Taken together, while previous evidence on acetaminophen in acute stroke has been mixed or neutral, our study suggests a clinically meaningful benefit when appropriately applied. Acetaminophen appears to improve functional outcomes, reduce complication rates, and lower mortality. Future large, multicenter randomized controlled trials are needed to validate these findings and identify the patient subgroups most likely to benefit.

5. CONCLUSION

Acetaminophen use in acute ischemic and hemorrhagic stroke was associated with better functional outcomes, lower mortality, and fewer complications compared to controls. These findings support its role as a safe and inexpensive adjunct in stroke care, though larger multicenter trials are needed to confirm the benefits and define optimal patient subgroups.

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