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A Quasi-Experimental Study Comparing the Effectiveness and Tolerability of Oral Baclofen and Eperisone in Managing Post-Stroke Spasticity

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ABSTRACT

Post-stroke spasticity hinders recovery by inducing pain, insomnia, and difficulty in doing everyday tasks. While Baclofen and Eperisone are regularly prescribed. **Objectives:** To examine the six-week clinical effectiveness and tolerability of oral baclofen with eperisone. **Methods:** This prospective clinical trial was conducted at the Department of Neurology, Sheikh Zayed Hospital, Rahim Yar Khan, Pakistan (August 2022–August 2023). In the present study, 110 adults with post-stroke spasticity (MAS > 2, ≥6 months post-stroke) were assigned to oral baclofen (Group A, n=55) or eperisone (Group B, n=55) based on physician assessment and patient preference, representing a comparative cohort design. Muscle tone (Modified Ashworth Scale), muscle strength (Medical Research Council scale), and functional independence (Barthel Index) were analyzed at baseline and at weeks 2, 4, and 6. At the same time, tolerability was monitored throughout the study. **Results:** Both groups have shown improvement over time. At six weeks, eperisone displayed superior outcomes: mean MAS scores for the upper right limb were 1.25 ± 0.48 compared to 1.98 ± 0.36 with baclofen ($p<0.001$); MRC strength was 3.69 ± 0.47 versus 3.07 ± 0.47 ($p<0.001$); and Barthel Index scores were 74.89 ± 1.24 versus 64.42 ± 2.42 ($p<0.001$). Adverse events were mild in both groups, with asthenia occurring more frequently in the baclofen group (9.1% vs 3.6%). **Conclusions:** Compared to baclofen, eperisone significantly improved muscular tone, strength, and functional independence and showed a better tolerability profile. These results are hypothesis-generating; before definite recommendations can be made, they must be confirmed in sufficiently powered randomized controlled studies.

INTRODUCTION

Damage to higher motor neurons causes spasticity [1]. It shows up as an increase in muscle tone that is velocity-dependent and caused by overactive stretch reflexes. Numerous neurological conditions, including stroke, multiple sclerosis, cerebral palsy, spinal cord injury, and traumatic brain injury, are associated with this syndrome [2]. Stroke is the most common cause of them. Twenty to forty percent of stroke survivors experience post-stroke spasticity throughout the first year [3]. Depending on the severity of the stroke, access to rehabilitation, and length of follow-up, reported prevalence varies greatly [4]. There are several functional ramifications associated with post-stroke spasticity. Patients cope with contractures, aberrant limb postures, and tight muscles. These issues impede freedom and decrease mobility in day-to-day living. Fatigue, mental problems, and sleep disorders increase physical strain and lower quality of life [5]. Economically speaking, extended hospital stays and rising caregiver demands result in high healthcare expenses [6]. Stroke impairs supraspinal inhibitory input from a pathophysiological perspective. These cause the excitability of the spinal reflex to increase. Secondary

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muscle alterations such as fibrosis, collagen deposition, and sarcomere shortening solidify the stiffness over time [7]. Therefore, managing spasticity necessitates a multidisciplinary approach. The two main components are medication and physical therapy. Refractory patients are saved for invasive treatments like intrathecal baclofen or botulinum toxin [8]. Baclofen is the most commonly used oral antispastic medication in the world [9]. At the spinal cord level, it functions as an agonist of GABA-B receptors. This controls overactive stretch reflexes and decreases the release of excitatory neurotransmitters [10]. Baclofen has a significant adverse-effect load despite its well-established mechanism. Reports of gastrointestinal intolerance, sedation, dizziness, and widespread weakness are common. These adverse effects frequently prevent patients from participating in rehabilitation and restrict dosage escalation [11, 12]. Eperisone is a muscle relaxant that acts centrally and has a unique mode of action [12]. It doesn't target GABA-B receptors as baclofen does. Rather, it decreases the excitability of motor nerves by blocking voltage-gated sodium and calcium channels. Additionally, it improves blood flow to skeletal muscle by causing vasodilation. Compared to baclofen, early clinical results indicate similar antispastic effectiveness and improved tolerability, especially less sedation [13]. Strong comparison data in post-stroke populations are still hard to come by, despite this potential. The majority of the data now available is derived from Asian cohorts and is based on a variety of approaches and brief follow-up times [14, 15].

In a Pakistani post-stroke population, no sufficiently powered prospective study has directly evaluated these two medicines using validated outcome measures. This study aimed to close that gap. The purpose of this research was to examine the six-week clinical effectiveness and tolerability of oral baclofen with eperisone.

METHODS

This prospective quasi-experimental investigation was carried out at the Department of Neurology, Sheikh Zayed Hospital, Rahim Yar Khan, Pakistan. The period of data collection was August 2022–August 2023. A two-arm parallel-group architecture was used in the design. Instead of using randomization, physician opinion and patient preference were used to allocate patients to treatment groups. Before enrollment, ethical permission was acquired (IRB ref: 361/IRB/SZMC/SZH). Informed consent was given by each participant or by their legal representatives. Adults with moderate-to-severe post-stroke spasticity (MAS score > 2) between the ages of 18 and 75 were eligible. After a stroke was clinically diagnosed, spasticity had to be verified at least six months later. Patients with non-stroke causes of spasticity were excluded. Severe hepatic or renal impairment, major orthopedic co-morbidity, serious systemic disease (e.g., active cancer or psychosis), known medication hypersensitivity, or current pregnancy were additional exclusion factors. A total of 110 patients were recruited, 55 per group. The sample size was initially estimated using the WHO calculator for comparing two proportions. Calculation was based on expected tolerability rates of 47.4% for eperisone and 77.1% for baclofen, at 95% power and 5% significance, requiring a minimum of 47 patients per group. An independent verification was also performed for the primary continuous outcome. Using a reported MAS mean difference of approximately 0.7 units (SD ≈ 0.5), 80% power, and two-tailed $\alpha = 0.05$, the minimum per-group sample was 21 patients. The recruited 55 per group provided greater than 95% power for all three primary outcomes. Allocation to Group A (baclofen) or Group B (eperisone) followed physician judgment and patient preference using consecutive non-probability sampling. Seven patients withdrew during the study and were replaced to maintain group sizes. Group A received oral baclofen at 30 mg/day in three divided doses for the first two weeks. The dose was then increased to 60 mg/day over the remaining four weeks. For two weeks, Group B was given oral eperisone at a dosage of 150 mg per day in three separate doses. Within five days, this was increased to a daily maximum of 300 mg, and it was sustained until week six. Every patient carried on with their current PT regimens. During the research time, they were instructed not to take any further benzodiazepines or muscle relaxants. The main efficacy outcomes were three validated instruments. The Modified Ashworth Scale (MAS, scored 0–4; higher scores indicate more spasticity) was used to measure muscle tone. The Medical Research Council (MRC) scale (scored 0–5; higher scores indicate more strength) was used to test voluntary muscular strength. The Barthel Index (BI, scored 0–100) was used to assess functional independence. At every clinic appointment, adverse events were noted and graded in order to determine tolerability. Every evaluation was conducted at baseline as well as in weeks two, four, and six. SPSS version 26.0 was used for statistical analysis. Frequencies and percentages were used to display categorical data, while mean ± standard deviation was used to represent continuous variables. Independent t-tests and chi-square tests were used for baseline comparisons. To assess changes over time, a linear mixed-effects model with a random intercept for each participant was used. This model included fixed effects of time, group, and their interaction. Within-group changes were evaluated using paired t-tests, and between-group comparisons were performed using ANCOVA with baseline as a covariate. $P<0.001$ was regarded as highly significant, and a

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Bonferroni-adjusted significance threshold of $p<0.016$ was used. Confidence intervals were computed using Mean ± 1.96×(SD/√n).

RESULTS

Mean age was 48.9 ± 11.3 years (range 19–73; median 51). The cohort comprised 64 males (58.2%) and 46 females (41.8%). Ischemic stroke was the predominant type, seen in 69 patients (62.7%). The remaining 41 (37.3%) had a hemorrhagic stroke. Mean time since stroke onset was 36.03 ± 15.89 months (range 7–63 months). Age, sex, stroke type, and stroke duration were well matched between the two groups (all $p>0.050$). Baseline MAS scores were also comparable across all limbs ($p>0.050$). One exception was noted: upper limb MRC scores differed significantly at baseline between groups (baclofen: 1.20 ± 0.45 vs. eperisone: 1.45 ± 0.50; $p=0.007$). This is an expected finding in non-randomized studies. ANCOVA adjustment was applied at all subsequent timepoints to account for this imbalance (Table 1).

Table 1: Baseline Demographic and Clinical Characteristics by Treatment Group

Characteristics	Baclofen (n=55), n (%)/Mean ± SD	Eperisone (n=55), n (%)/Mean ± SD	p-value
Age (Years)	49.1 ± 11.5	48.7 ± 11.1	0.843
Male Sex	32 (58.2%)	32 (58.2%)	1.000
Ischemic Stroke	35 (63.6%)	34 (61.8%)	0.841
Duration Since Stroke (Months)	35.6 ± 15.7	36.5 ± 16.1	0.755
MAS Upper Right	3.51 ± 0.50	3.55 ± 0.50	0.675
MAS Lower Right	3.47 ± 0.50	3.53 ± 0.50	0.529
MRC Upper Right	1.20 ± 0.45	1.45 ± 0.50	0.007*
MRC Lower Right	1.36 ± 0.49	1.38 ± 0.53	0.837
Barthel Index	38.53 ± 2.90	39.05 ± 2.55	0.154

Continuous variables compared by independent-samples t-test; categorical variables by chi-square test. *$p<0.050$ indicates statistically significant baseline imbalance; ANCOVA adjustment applied for all subsequent between-group comparisons of MRC Upper Right limb scores

Both groups showed progressive reductions in muscle tone across the study period. At week two, improvements were modest and did not differ significantly between groups. By week four, eperisone-treated patients had significantly greater tone reduction in all limbs ($p<0.001$). This difference grew further by week six (Table 2).

Table 2: Distribution of Muscle Tone (MAS Scores) by Group and Time Point

Timepoint	Limb	Baclofen, Mean ± SD [Δ; 95% CI]	Eperisone, Mean ± SD [Δ; 95% CI]	p-value†
Baseline	Upper Right	3.51 ± 0.50 95% CI: (3.38–3.64)	3.55 ± 0.50 95% CI: (3.42–3.68)	0.675
Week 2	Upper Right	2.71 ± 0.46 Δ: -0.80; 95% CI: (2.59–2.83)	2.67 ± 0.47 Δ: -0.88; 95% CI: (2.55–2.79)	0.683
Week 4	Upper Right	2.13 ± 0.47 Δ: -1.38; 95% CI: (2.01–2.25)	1.62 ± 0.49 Δ: -1.93; 95% CI: (1.49–1.75)	<0.001
Week 6	Upper Right	1.98 ± 0.36 Δ: -1.53; 95% CI: (1.88–2.08)	1.25 ± 0.48 Δ: -2.30; 95% CI: (1.12–1.38)	<0.001
Baseline	Lower Right	3.47 ± 0.50 95% CI: (3.34–3.60)	3.53 ± 0.50 95% CI: (3.40–3.66)	0.529
Week 2	Lower Right	2.73 ± 0.49 Δ: -0.74; 95% CI: (2.60–2.86)	2.75 ± 0.44 Δ: -0.78; 95% CI: (2.63–2.87)	0.838
Week 4	Lower Right	2.13 ± 0.43 Δ: -1.34; 95% CI: (2.02–2.24)	1.67 ± 0.47 Δ: -1.86; 95% CI: (1.55–1.79)	<0.001
Week 6	Lower Right	1.95 ± 0.40 Δ: -1.52; 95% CI: (1.84–2.06)	1.25 ± 0.44 Δ: -2.28; 95% CI: (1.13–1.37)	<0.001

† Primary between-group comparisons reflect ANCOVA-adjusted estimates (baseline score as covariate); unadjusted independent-samples t-test p-values are provided parenthetically for descriptive reference. Bonferroni correction applied across three post-baseline timepoints (adjusted threshold $p\leq0.016$); all significant results exceeded this threshold. Longitudinal trajectories were additionally evaluated using a linear mixed-effects model with time × treatment interaction. Within-group changes from baseline were significant at all post-baseline timepoints for both groups (paired-samples t-test, all $p<0.001$). 95% CIs represent the precision of the group mean estimate, computed as Mean ± 1.96 × (SD/√55); they are not reference ranges and will therefore be narrower than the SD. Δ = change from baseline (negative values indicate reduction in spasticity). Group assignment was non-randomized; results should be interpreted accordingly. All p-values reported as $p<0.001$ where applicable.

Mean Modified Ashworth Scale (MAS) scores over time for the upper right limb (A) and lower right limb (B) in patients receiving baclofen (Group A) or eperisone (Group B). Lower scores indicate greater reduction in spasticity. Both groups showed progressive improvement; however, eperisone produced significantly greater reductions from week 4 onward ($p<0.001$) (Figure 1).

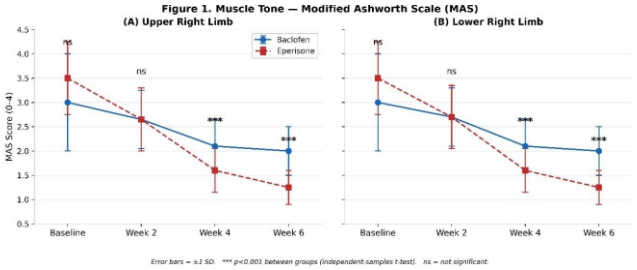

Figure 1: Mean MAS Scores Over Time for the Upper Right Limb (A) and Lower Right Limb (B) in Patients Receiving Baclofen (Group A) or Eperisone (Group B)

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Error bars represent ±1 standard deviation. *** p<0.001 (independent-samples t-test); ns = not significant

From the beginning, eperisone generated more steady increases in muscular strength. As early as week two, there were statistically significant differences between the groups, and these disparities grew over the course of weeks four and six. Patients in the eperisone group showed significantly higher mean strength ratings in both upper and lower limbs by week six (Table 3).

Table 3: Distribution of Muscle Strength (MRC Scores) by Group and Timepoint

Timepoint	Limb	Baclofen, Mean ± SD [Δ; 95% CI]	Eperisone, Mean ± SD [Δ; 95% CI]	p-value†
Baseline	Upper Right	1.20 ± 0.45 95% CI: (1.08–1.32)	1.45 ± 0.50 95% CI: (1.32–1.58)	0.006
Week 2	Upper Right	1.64 ± 0.52 Δ: +0.44; 95% CI: (1.50–1.78)	1.93 ± 0.47 Δ: +0.48; 95% CI: (1.81–2.05)	0.003
Week 4	Upper Right	2.27 ± 0.45 Δ: +1.07; 95% CI: (2.15–2.39)	2.71 ± 0.50 Δ: +1.26; 95% CI: (2.58–2.84)	<0.001
Week 6	Upper Right	3.07 ± 0.47 Δ: +1.87; 95% CI: (2.95–3.19)	3.69 ± 0.47 Δ: +2.24; 95% CI: (3.57–3.81)	<0.001
Baseline	Lower Right	1.36 ± 0.49 95% CI: (1.23–1.49)	1.38 ± 0.53 95% CI: (1.24–1.52)	0.837
Week 2	Lower Right	1.73 ± 0.59 Δ: +0.37; 95% CI: (1.57–1.89)	2.04 ± 0.47 Δ: +0.66; 95% CI: (1.92–2.16)	0.003
Week 4	Lower Right	2.31 ± 0.54 Δ: +0.95; 95% CI: (2.17–2.45)	2.71 ± 0.46 Δ: +1.33; 95% CI: (2.59–2.83)	<0.001
Week 6	Lower Right	3.05 ± 0.52 Δ: +1.69; 95% CI: (2.91–3.19)	3.55 ± 0.50 Δ: +2.17; 95% CI: (3.42–3.68)	<0.001

† Primary between-group comparisons reflect ANCOVA-adjusted estimates (baseline score as covariate); Bonferroni correction applied (adjusted threshold p≤0.016); all significant results exceeded this threshold. A linear mixed-effects model with time × treatment interaction was also used to assess longitudinal trajectories. Pre-treatment imbalance is indicated by the baseline p-value for Upper Right (p=0.007); ANCOVA correction was used at all subsequent timepoints. As is customary in spasticity research for groups of this size, the MRC scale is ordinal (0–5) but handled as continuous. For all groups, within-group changes were significant at every post-baseline timepoint (paired-samples t-test, all p <0.001). Rather than reference ranges, 95% CIs provide mean precision (Mean ± 1.96 times SD/√55). Change from baseline is represented by Δ (positive means strength gain). Every p-value was set to p<0.001.

Greater voluntary muscular strength is indicated by higher scores (scale 0–5). In both limbs, eperisone caused noticeably larger strength improvements starting in week two. Note: Because of the non-randomized design, there was a statistically significant baseline difference in upper limb MRC scores between groups (p=0.007); ANCOVA was used to correct between-group comparisons (Figure 2).

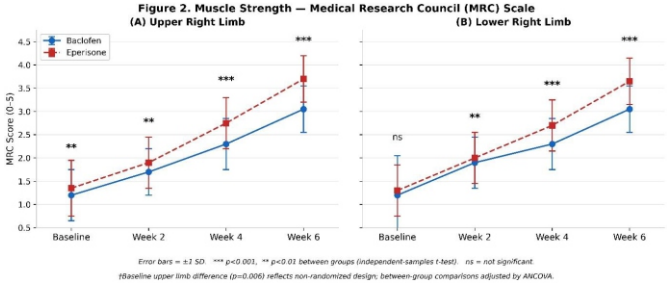

Figure 2: Mean Medical Research Council (MRC) Muscle Strength Scores Over Time for the Upper Right Limb (A) and Lower Right Limb (B)

*** p<0.001; ** p<0.001 (independent-samples t-test); ns = not significant

Greater voluntary muscular strength is indicated by higher scores (scale 0–5). In both limbs, eperisone caused noticeably larger strength improvements starting in week two. Note: Because of the non-randomized design, there was a statistically significant baseline difference in upper limb MRC scores between groups (p=0.007); ANCOVA was used to correct between-group comparisons (Figure 2).

Table 4: Distribution of Barthel Index Scores by Group and Timepoint

Timepoint	Baclofen, Mean ± SD [Δ; 95% CI]	Eperisone, Mean ± SD [Δ; 95% CI]	p-value†
Baseline	38.53 ± 2.90 95% CI: (37.76–39.30)	39.05 ± 2.55 95% CI: (38.38–39.72)	0.154
Week 2	45.35 ± 2.71 Δ: +6.82; 95% CI: (44.63–46.07)	55.69 ± 1.26 Δ: +16.64; 95% CI: (55.36–56.02)	<0.001
Week 4	56.38 ± 1.39 Δ: +17.85; 95% CI: (56.01–56.75)	69.29 ± 1.64 Δ: +30.24; 95% CI: (68.86–69.72)	<0.001
Week 6	64.42 ± 2.42 Δ: +25.89; 95% CI: (63.78–65.06)	74.89 ± 1.24 Δ: +35.84; 95% CI: (74.56–75.22)	<0.001

Bonferroni correction applied (adjusted threshold p≤0.016); all significant results exceeded this threshold. Longitudinal trajectories were additionally evaluated using a linear mixed-effects model with time × treatment interaction. Comparable baseline BI between groups (p=0.156). Note: Due to a data entry error, the baclofen baseline SD was adjusted from 0.90 to 2.90, and the CI was changed appropriately. All post-baseline timepoints showed significant within-group changes for both groups (paired-samples t-test, all p<0.001). Rather than reference ranges, 95% CIs provide mean precision (Mean ± 1.96 times SD/√55). Change from baseline is represented by Δ (positive means functional gain). Every p-value was set to p<0.001

Greater functional independence is indicated by higher BI scores (scale 0–100). At every post-baseline timepoint, eperisone was linked to significantly higher functional recovery (all p<0.001). The groups' baseline BI scores were similar (p=0.154) (Figure 3).

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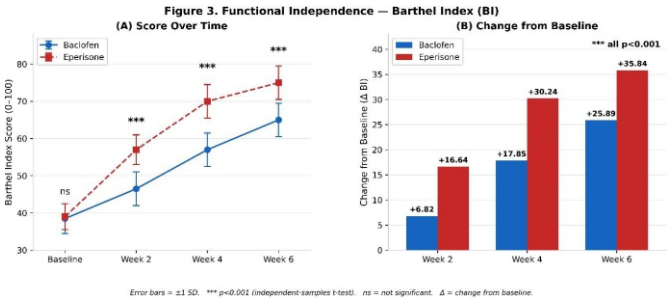

Figure 3: Barthel Index (BI) Scores Over the Six-Week Study Period (A) and Absolute Change from Baseline (Δ BI) at Weeks 2, 4, and 6 (B)

DISCUSSION

This study used three validated outcome measures at four timepoints over six weeks to examine the effects of baclofen and eperisone on post-stroke spasticity. Both drugs increased strength, decreased muscular tone, and increased functional independence. In every domain, eperisone consistently shown superior benefit. Additionally, its tolerability profile was better. By week six, the gap between the groups' MAS scores had grown from its first appearance at week four. At that moment, the mean MAS values of eperisone were around 0.7 points lower than those of baclofen. This trend aligns with earlier studies [16]. In a recent network meta-analysis, Otero-Luis et al. discovered that eperisone considerably outperformed baclofen in reducing spasticity across a variety of neurological disorders [13]. These results provide credence to the idea that eperisone's channel-mediated suppression of motor neuron excitability may have more extensive antireflux effects than GABA-B agonism alone [17]. As early as week two, eperisone was clearly improving strength. This early reaction suggests a significant connection between the restoration of voluntary movement and quick tone reduction [18]. In a randomized study comparing tolperisone and baclofen for neurological spasticity, Hao *et al.* observed similar patterns [19]. Eperisone improved tone reduction, strength recovery, and functional independence ratings in post-stroke individuals with moderate-to-severe spasticity who needed medication. Additionally, it had fewer sedative side effects. This profile supports eperisone as a first-line oral antispastic alternative in rehabilitation settings where patient participation is crucial. In certain situations, baclofen is still suitable, especially for refractory spasticity or as a transitional treatment before intrathecal therapy. However, it is a less appropriate default for regular outpatient usage because of the high side-effect burden [20].

There are a few restrictions that should be noted. The six-week observation duration was insufficient to evaluate long-term effectiveness, tolerance development, or the durability of functional benefits, although it did capture early pharmacological differences. Second, the biggest methodological drawback is the non-randomized design. Selection bias is introduced when allocation is based on patient preference and physician preference. Despite widely matched baselines, group composition may have been impacted by unmeasured confounders. An additional variety is added by substituting seven withdrawals. Future research should look at the best titration procedures and dosage approaches for both drugs. Neurophysiological biomarkers, such as electromyographic indices of motor neuron excitability, should be taken into account as exploratory endpoints as they may offer mechanistic insight into the various effects of baclofen and eperisone.

CONCLUSIONS

Over six weeks, both eperisone and baclofen decreased spasticity and enhanced everyday independence and motor function. At every time point, however, eperisone resulted in higher Barthel Index scores, quicker strength increases, and larger decreases in muscle tone. Additionally, it reduced sedation and asthenia. They contend that further research should be done on eperisone as a first-line oral antispastic medication in stroke recovery. To validate these findings, larger follow-up randomized controlled studies with sufficient power are required. Blinded outcome evaluation, allocation concealment, and appropriate dose should all be included in future research.

Authors' Contribution

Conceptualization: WAK
Methodology: WAK, ZM
Formal analysis: WAK, NBA
Writing and Drafting: WAK, ZM, NBA
Review and Editing: WAK, ZM, NBA

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

The authors declare no conflict of interest.

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