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Safety and efficacy of glibenclamide on cerebral oedema following aneurysmal subarachnoid haemorrhage: a randomised, double-blind, placebo-controlled clinical trial

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ABSTRACT

Background Glibenclamide has garnered attention due to its multifaceted neuroprotective effects in cases of acute central nervous system injury. We initiated a trial to explore the effectiveness and safety of a high dose of glibenclamide in the management of cerebral oedema following aneurysmal subarachnoid haemorrhage (aSAH).

Methods This trial constituted a single-centre, randomised clinical study. Half of the 56 patients assigned to the glibenclamide group received 15 mg of glibenclamide tablets daily for 10 days (5 mg, three times/day). The primary outcome was the proportion of patients achieving the subarachnoid haemorrhage early brain oedema score dichotomy (defined as Subarachnoid Haemorrhage Early Brain Oedema Score 0–2) at the 10-day postmedication. The secondary outcome of cerebral oedema was the concentration of sulfonylurea receptor 1-transient receptor potential melastatin 4 (SUR1-TRPM4) in the plasma and cerebrospinal fluid.

Results We enrolled 56 patients diagnosed with aSAH, who were admitted to the neurosurgery intensive care unit between 22 August 2021 and 25 April 2023. The primary outcome revealed that the glibenclamide group exhibited a notably higher proportion of mild cerebral oedema in comparison to the placebo group (60.7% vs 42.9%, adjusted OR: 4.66, 95% CI 1.14 to 19.10, p=0.032). Furthermore, the concentration of SUR1-TRPM4 in the cerebrospinal fluid of the glibenclamide group was significantly higher than the placebo group (p=0.0002; p=0.026), while the plasma TRPM4 concentration in the glibenclamide group was significantly lower than the placebo group (p=0.001).

Conclusion Oral administration of high-dose glibenclamide notably reduced radiological assessment of cerebral oedema after 10 days of medication. Significant alterations were also observed in the concentration of SUR1-TRPM4 in plasma and cerebrospinal fluid. However, it is worth noting that glibenclamide was associated with a higher incidence of hypoglycaemia. Larger trials are warranted to evaluate the potential benefits of glibenclamide in mitigating swelling and then improving neurological function.

Trial registration number ChiCTR2100049908.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Glibenclamide has potential neuroprotective effects.
⇒ Glibenclamide acts on SUR1-TRPM4 channel.

WHAT THIS STUDY ADDS

⇒ Efficacy and safety of high-dose oral glibenclamide following aneurysmal subarachnoid haemorrhage (aSAH).
⇒ Evaluate cerebral oedema using Subarachnoid Haemorrhage Early Brain Oedema Score and monitoring sulfonylurea receptor 1-transient receptor potential melastatin 4 indicators.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ A potential role for glibenclamide in the pathogenesis of brain swelling following aSAH.
⇒ Advocate for further investigating larger-scale studies.

INTRODUCTION

Stroke is the second leading cause of death and the third leading cause of disability worldwide.[1] Subarachnoid haemorrhage (SAH), a form of haemorrhagic stroke, accounts for 5% of all haemorrhagic strokes, with approximately 85% resulting from intracranial aneurysm rupture.[2 3] While early repair of ruptured aneurysms and diligent postoperative management can enhance overall outcomes, aneurysmal SAH (aSAH) remains a deadly condition with a 44% mortality rate.[4 5] Cerebral oedema arising as a secondary complication of SAH can elevate intracranial pressure, which is an ominous prognostic indicator. A prospective trial revealed a significant association between global cerebral oedema and increased mortality in aSAH patients (OR=1.8, 95% CI 1.1 to 2.9, p=0.02).[6] Another study identified global cerebral oedema as one of the few secondary factors predicting poor cognitive function. Timely and effective

management of global cerebral oedema holds promise for substantially enhancing aSAH prognosis.[7] Nonetheless, malignant cerebral oedema subsequent to SAH remains a pressing concern. Two meta-analyses have suggested that decompressive craniectomy in SAH patients has limited long-term prognostic benefits.[8 9] Clinical drug therapies for SAH have generally demonstrated limited effectiveness. Notably, the selective calcium channel blocker nimodipine remains the sole evidence-based choice for SAH treatment, although with limited efficacy.[10]

Glibenclamide has garnered attention for its multifaceted neuroprotective effects in acute central nervous system injuries, achieved by blocking the sulfonylurea receptor 1-transient receptor potential melastatin 4 (SUR1-TRPM4) channel.[11–15] An experimental study in a rodent model of SAH demonstrated that glibenclamide can inhibit cerebral oedema, microglial activation and the excessive release of inflammatory cytokines.[16] However, a trial conducted by Costa *et al*[17] assessed the use of glibenclamide in aSAH. Patients were randomly assigned to receive 5 mg of oral glibenclamide or placebo for 21 days. The results, however, did not demonstrate a significant improvement in 6-month mortality, the incidence of delayed cerebral ischaemia or functional outcomes. To address these discrepancies between preclinical and clinical findings, we have designed a glibenclamide trial with varying doses and administration durations, aiming to provide multidimensional and comprehensive evidence regarding the efficacy and safety of higher doses of glibenclamide.

METHODS

Study design and participants

This trial evaluating glibenclamide's effectiveness in treating cerebral oedema following aSAH was conducted at a single-centre in China. Prior to study participation, participants or their legally authorised representatives provided written consent.

Participants

Recruitment took place from 22 August 2021 to 25 April 2023, involving patients admitted to the neurosurgery intensive care unit. Inclusion criteria encompassed radiological evidence of aSAH (confirmed by CT/CTA/MRI/MRA/DSA), age 18 or older, surgery performed within 72 hours of admission, and a Hunt-Hess grade of 2 or higher. Patients with a Hunt-Hess grading of 2 but an estimated hospitalisation of less than 10 days were excluded. Additionally, exclusion criteria were as follows: (1) hypoglycaemia (fasting <3.9 mmol/L) or prior hypoglycaemic episodes at admission; (2) pregnancy; (3) known kidney or liver disease; (4) patients not fully independent before the bleeding event; (5) substance abuse or alcohol dependency; (6) use of warfarin drugs; (7) suspicion of other life-threatening conditions. To establish baseline measurements of SUR1-TRPM4 in humans, eight patients with hydrocephalus and normal intracranial pressure (excluding those caused by aSAH or cerebral trauma complications) were included.

Randomisation and masking

Eligible participants were randomly assigned to receive either glibenclamide or a placebo in a 1:1 ratio using a computer-generated sequence. Sealed envelopes were used to conceal allocation. Clinical physicians recruited and screened patients. Both treatment groups received bottles and tablets with identical appearances; however, clinical physicians were not blinded to drug-related adverse events. Participants and intervention administrators were unaware of group assignments. Those assessing outcomes and analysing data were blinded to clinical variables, interventions, and functional outcomes, conducting impartial and objective evaluations of clinical results across trial groups.

Procedures

Patients who were randomly assigned to the glibenclamide group were administered 15 mg of glibenclamide tablets daily for a continuous period of 10 days following enrolment. These tablets, each containing 2.5 mg of glibenclamide, were sourced from (Shanxi Fenhe Pharmaceutical Co, China; per tablet (2.5 mg)). Conversely, patients assigned to the placebo group received a vitamin B1 sourced from Shanxi Hengruida Pharmaceutical Co, China. All patients received medication either through nasogastric feeding tubes or orally at specific intervals (08:00, 12:00, 16:00), three times a day, with two tablets administered simultaneously. Both groups received standard care in accordance with expert consensus guidelines.[18] For patients exhibiting radiological evidence of oedema, we used the Subarachnoid Haemorrhage Early Brain Oedema Score (SEBES), as proposed by Claassen *et al*[19] for SAH. The treatment of cerebral oedema usually recommended dehydration treatment and, if deemed necessary, performed decompressive craniectomy. Plasma and cerebrospinal fluid samples underwent centrifugation at the basic laboratory of neurosurgery at Xuanwu Hospital, Beijing, China, followed by analysis using a commercial ELISA kit (Human ABCC/TRPM4 ELISA, Neobioscience, Beijing, China) for the measurement of SUR1-TRPM4 levels. The description of other data information and blood glucose related adverse events will be detailed in online supplemental materials.

Outcomes

The primary efficacy outcome assessed the proportion of patients achieving the SEBES dichotomy (defined as 0–2) at 10 days after medication. Secondary efficacy indicators included radiological and clinical scores for different time periods. For radiological evaluation, we not only observed cerebral oedema but also observed the bleeding volume, and observed the modified Fisher scale after 10 days of administration. For clinical evaluation, we recorded the modified Rankin Scale (mRS) score at discharge, as well as the mRS score for long-term telephone follow-up in

3 and 6 months. Blood glucose-related adverse events and others were also documented. Any complications that occurred during hospitalisation in both two groups of patients would be recorded, including death, cerebral hernia, cerebral infarction, hydrocephalus, pulmonary infection, liver and kidney dysfunction, vasospasm, proportion of patients who underwent decompressive craniectomy after 10 days of medication, and length of hospital stay. Additionally, monitoring of SUR1-TRPM4 levels in plasma and cerebrospinal fluid was performed at two intervals during the medication period. Additionally, blood glucose-related adverse events and others were also documented.

Statistical analysis

Based on the literature review, the proportion of mild cerebral oedema in the placebo group was 20.0%, whereas in the glibenclamide group, it was 55.0%.[20] To detect a 35.0% improvement in efficacy for the glibenclamide group compared with the placebo group regarding the main outcome, which was the proportion of patients achieving the SEBES dichotomy (defined as 0–2), a two-sided hypothesis test with α=0.05 and 80% power was employed. Using PASS V.15 software, a sample size of 27 cases was calculated for two groups. Considering a 5% loss rate due to follow-up and non-adherence to the treatment protocol, a minimum of 28 patients were required for both the glibenclamide and placebo groups.

All analyses were performed on the intention-to-treat population. Categorical variables were presented as frequency and percentage and compared using either the χ^2 test or Fisher's exact test. Continuous variables were represented as mean±SD or median (IQR) and compared using the Student's t-test or Wilcoxon rank-sum test. Logistic regression was employed to estimate ORs along with their associated 95% CIs. The SUR1-TRPM4 indicator values in plasma and cerebrospinal fluid samples between the glibenclamide and placebo groups were compared using a two-way analysis of variance. In all tests, statistical significance was defined as two-sided p values <0.05. All statistical analyses were performed using SPSS (V.25.0, IBM Corp).

RESULTS

We enrolled 82 patients with aSAH who were admitted to the neurosurgery intensive care unit. After excluding 26 patients who did not meet the protocol criteria, the remaining patients were randomly assigned. Among the 28 patients allocated to the glibenclamide group, 4 patients still experienced severe and persistent hypoglycaemia despite adjustments to their glucose supplementation regimen and halving the dosage (figure 1). There

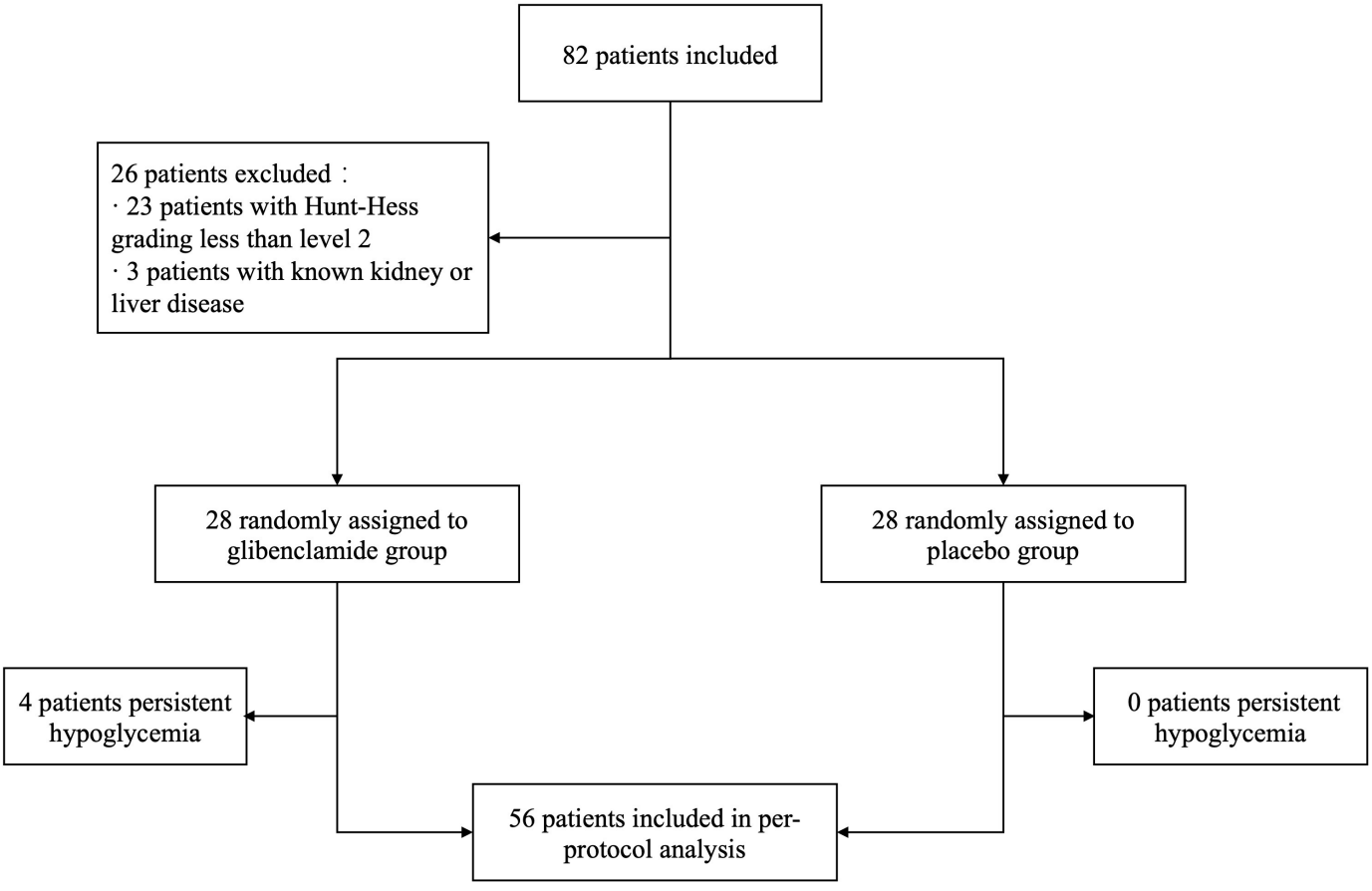

Figure 1 Consolidated Standards of Reporting Trials diagram.

Table 1 Patient characteristics and treatments based on allocated groups

Variable	Glibenclamide (n=28)	Placebo (n=28)	P value
Age (years)	61.8±11.6	59.1±12.6	0.412
Female	16 (57.1)	11 (39.3)	0.181
BMI (kg/m^2)	24.3±3.6	25.6±4.7	0.251
Systolic blood pressure (mm Hg)	147.2±34.3	150.7±31.4	0.692
Diastolic blood pressure (mm Hg)	86.1±13.5	85.2±18.7	0.832
Treatment			
Vascular embolisation	26 (92.9)	24 (85.7)	0.669
Osmotic therapy (more than 10 days)	15 (53.6)	14 (50.0)	0.789
Osmotic therapy (full volume)	3 (10.7)	7 (25.0)	0.163
Lumbar puncture	17 (60.7)	16 (57.1)	0.786
Cerebrospinal fluid shunt during medication	13 (46.4)	7 (25.0)	0.094
Decompressive craniectomy at admission	4 (14.3)	2 (7.1)	0.669
Location of aneurysm			0.705
Anterior circulation	23 (82.1)	25 (89.3)	
Posterior circulation	5 (17.9)	3 (10.7)	
Related grading			
Hunt-Hess grade	3 (3–4)	3 (3–4)	0.971
WFNS grade	5 (4–5)	4 (4–5)	0.999
Modified Fisher scale	4 (3–4)	4 (3–4)	0.279
SEBES	4 (3–4)	4 (2–4)	0.492
mRS	5 (4.3–5)	4 (2–5)	0.183
Medical history			
Hypertension	23 (82.1)	18 (64.3)	0.131
Diabetes	6 (21.4)	2 (7.1)	0.252
Coronary heart disease	4 (14.3)	7 (25.0)	0.313
Cerebral infarction	2 (7.1)	1 (3.6)	1.000
Subarachnoid haemorrhage	1 (3.6)	1 (3.6)	1.000

Data are presented as mean±SD, median (IQR) or number of patients (%).
BMI, body mass index; WFNS grade, World Federation of Neurosurgical Societies grade; mRS, modified Rankin Scale; SEBES, Subarachnoid Haemorrhage Early Brain Oedema Score.

were no significant differences in demographics and baseline characteristics between the two groups (table 1).

The primary outcome was that the glibenclamide group displayed a higher proportion of mild cerebral oedema, defined as 0–2 points in SEBES, compared with the placebo group at 10 days postmedication (tables 2 and 3). No significant differences were observed in the distribution of SEBES between the two groups (p=0.077; figure 2).

The secondary outcomes showed that the proportion of patients with mRS scores of 0–2 at discharge was higher in the placebo group (table 3). However, on 3-month and 6-month follow-ups, glibenclamide exhibited a significant advantage in long-term prognosis, with an increasing number of cases achieving good functional outcomes of 0–2 (table 3). No patients were lost to follow-up for the 3-month and 6-month mRS scores, and the distribution of mRS scores at different time periods can be seen in online supplemental figure S1. The long-term mortality rates were consistent in both groups (online supplemental figure S1). Similarly, from a radiological perspective, the modified Fisher scales at 10 days postmedication demonstrated a more significant improvement in the glibenclamide group, with a higher number of patients achieving scores of 0–2 (table 3).

Over the course of the 10-day medication period, there were no significant variance concentrations of SUR1 and TRPM4 in plasma and cerebrospinal fluid among the three groups within the first 7 days (p=0.499; p=0.116; p=0.148; p=0.072; figure 3). After 7 days of medication, the concentration of SUR1 in plasma of the glibenclamide group was similar to the placebo group (p=0.132; figure 3A). However, the concentration of SUR1 in the cerebrospinal fluid of the glibenclamide group significantly exceeded

Table 2 Primary and secondary outcomes of participants

Variable	Glibenclamide (n=28)	Placebo (n=28)	P value
Primary outcome			
SEBES (0–2) at 10 days after medication	17 (60.7)	12 (42.9)	0.181
Secondary outcomes			
mRS at discharge	4 (3–5)	3 (2–5)	0.744
mRS at 3 months	2.5 (1–5)	2.5 (1–5)	0.996
mRS at 6 months	2 (1–5)	3 (1–5)	0.890
Modified Fisher scale at 10 days after medication	2 (1.3–3)	2.5 (1–3.8)	0.244
Adverse events			
Hypoglycaemia	4 (14.3)	0 (0.0)	0.111
Death at discharge	3 (10.7)	2 (7.1)	1.000
Cerebral hernia	3 (10.7)	6 (21.4)	0.469
Cerebral infarction	6 (21.4)	8 (28.6)	0.537
Hydrocephalus	13 (46.4)	7 (25.0)	0.094
Pulmonary infection	22 (78.6)	16 (57.2)	0.086
Liver and kidney dysfunction	14 (50.0)	15 (53.6)	0.789
Vasospasm	16 (57.1)	11 (39.3)	0.362
Decompressive craniectomy at 10 days after medicine	1 (3.6)	2 (7.1)	1.000
Hospital staying (days)	17.5 (11.5–24.5)	20.0 (11.0–29.8)	0.806

Data are presented as mean±SD, median (IQR) or number of patients (%).
mRS, modified Rankin Scale; SEBES, Subarachnoid Haemorrhage Early Brain Oedema Score.

that of the placebo group (p=0.0002; figure 3B). Interestingly, the plasma TRPM4 concentration in the glibenclamide group was significantly lower than that in the placebo group after 7 days of medication (p=0.001; figure 3C). Furthermore, the concentration of cerebrospinal fluid TRPM4 in the glibenclamide group significantly surpassed that in the placebo group (p=0.026; figure 3D).

The incidence of hypoglycaemia in the glibenclamide group was notably high at 14.3%. Meanwhile, the proportion of other adverse complications were similar between the glibenclamide and placebo groups (tables 2 and 3). Additionally, we monitored intracranial pressure and observed that the average intracranial pressure in the glibenclamide group was significantly lower than that in the placebo group (p<0.0001; figure 4).

The radiological imaging of two typical patients of the glibenclamide and placebo groups were shown in figure 5. Both groups consisted of typical patients with Hunt-Hess grade, WFNS grade (World Federation of Neurosurgical Societies grade), and modified Fisher scale of 4, with a SEBES of 3 on the first day after surgery (figure 5A,B,E,F). However, after 10 days of medication, we observed that the modified Fisher scale in the placebo group remained at 3, indicating severe cerebral oedema with a SEBES of 4 (figure 5C,D). In contrast, the glibenclamide group reduced the modified Fisher scale by 2, achieving a SEBES of 2 (figure 5G,H). Furthermore, the glibenclamide group had an mRS of 3 at 6 months, while the placebo group scored 4.

DISCUSSION

Following an aSAH, it can cause substantial cerebral oedema, thereby elevating the mortality rate associated with aSAH.[6] This occurs due to early ischaemic brain injury and subsequent disruption of the blood-brain barrier, resulting in cellular swelling. The opening of the SUR1-TRPM4 channel may further contribute to cytotoxic brain oedema and vascular brain oedema.[21] Glibenclamide, functioning as an inhibitor of the SUR1 receptor, has demonstrated its potential to mitigate cerebral oedema and provide neuroprotective effects in various central nervous system injuries, including ischaemic conditions,[22–24] as well as haemorrhagic cerebrovascular diseases.[15 25 26] To the best of our knowledge, this is the first randomised controlled trial assessing the efficacy of high-dose oral glibenclamide in addressing cerebral oedema following aSAH. The primary outcome was SEBES, a composite assessment that incorporates clinical scores, radiological evaluations and monitoring parameters from both plasma and cerebrospinal fluid to predict and analyses functional outcomes subsequent to aSAH. Our study demonstrates that oral glibenclamide notably increases the proportion of cases characterised by

Table 3 Univariate and multivariate regression analyses of glibenclamide outcomes compared with placebo

Variable	Univariable regression analysis		Multivariable regression analysis	
	OR (95% CI)	P value	OR (95% CI)*	P value*
Primary outcome				
SEBES (0–2) at 10 days after medication	2.06 (0.71 to 5.98)	0.184	4.66 (1.14 to 19.10)	0.032†
Secondary outcomes				
mRS (0–2) at discharge	0.42 (0.13 to 1.37)	0.151	0.57 (0.16 to 2.07)	0.395
mRS (0–2) at 3 months	1.00 (0.35 to 2.85)	1.000	2.03 (0.53 to 7.71)	0.300
mRS (0–2) at 6 months	1.54 (0.54 to 4.42)	0.423	3.91 (0.92 to 16.56)	0.064
Modified Fisher scale (0–2) at 10 days after medication	2.50 (0.83 to 7.55)	0.104	3.94 (1.09 to 14.24)	0.037†
Adverse events				
Death at discharge	1.56 (0.24 to 10.14)	0.641	1.33 (0.17 to 10.74)	0.787
Cerebral hernia	0.44 (0.10 to 1.98)	0.283	0.24 (0.04 to 1.33)	0.103
Cerebral infarction	0.68 (0.20 to 2.31)	0.538	0.39 (0.09 to 1.63)	0.197
Hydrocephalus	2.60 (0.84 to 8.07)	0.098	1.88 (0.51 to 7.01)	0.346
Pulmonary infection	2.75 (0.85 to 8.88)	0.091	2.27 (0.67 to 7.67)	0.186
Liver and kidney dysfunction	0.87 (0.30 to 2.47)	0.789	0.57 (0.18 to 1.88)	0.357
Vasospasm	2.06 (0.71 to 5.98)	0.184	1.95 (0.65 to 5.79)	0.231
Decompressive craniectomy at 10 days after medicine	0.48 (0.04 to 5.64)	0.560	0.32 (0.03 to 4.23)	0.389

*Data were adjusted for cerebrospinal fluid shunt during medication.
†On behalf of p<0.05.
mRS, modified Rankin Scale; SEBES, Subarachnoid Haemorrhage Early Brain Oedema Score.

mild cerebral oedema as well as those showing favourable bleeding volume assessments defined by the modified Fisher scale, in comparison to the placebo group. It improves the SEBES distribution among aSAH patients. Furthermore, the treatment enhances the proportion of patients achieving a favourable long-term functional prognosis. However, it is associated with an increased risk of hypoglycaemia. Importantly, no significant differences in other adverse events were observed between the two groups. Moreover, the SUR1-TRPM4 indicators that we monitored exhibited distinct variations, corresponding to radiological findings, thereby underscoring the significant advantage of glibenclamide in ameliorating cerebral oedema.

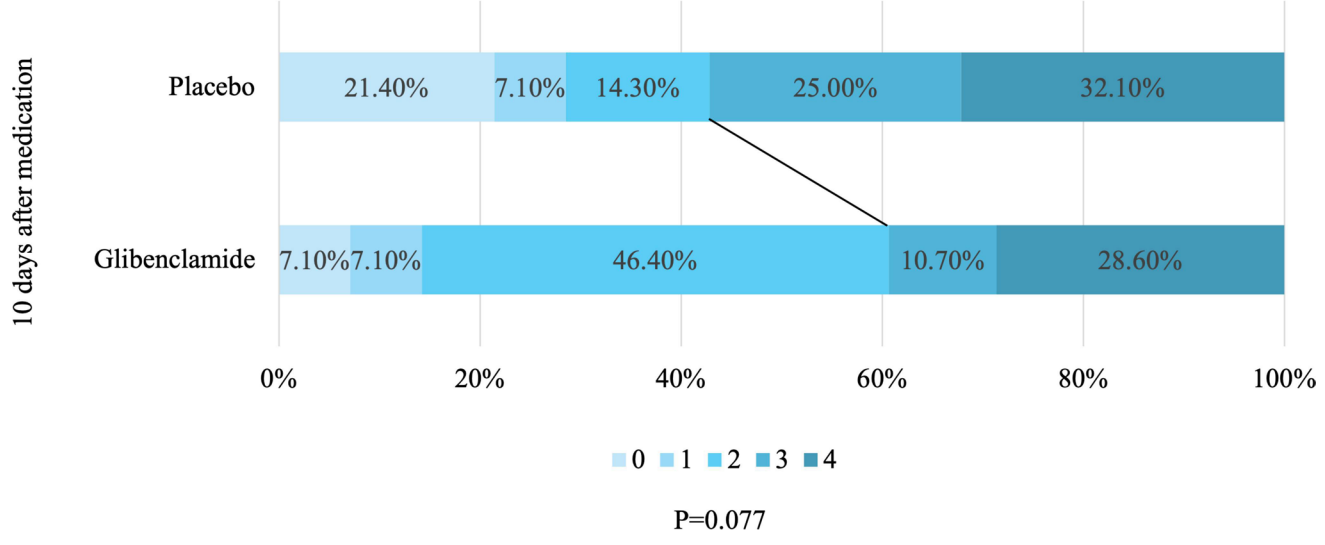

Figure 2 Distribution of Subarachnoid Haemorrhage Early Brain Oedema Score after 10 days of medication. Data are presented percentage of patients (%).

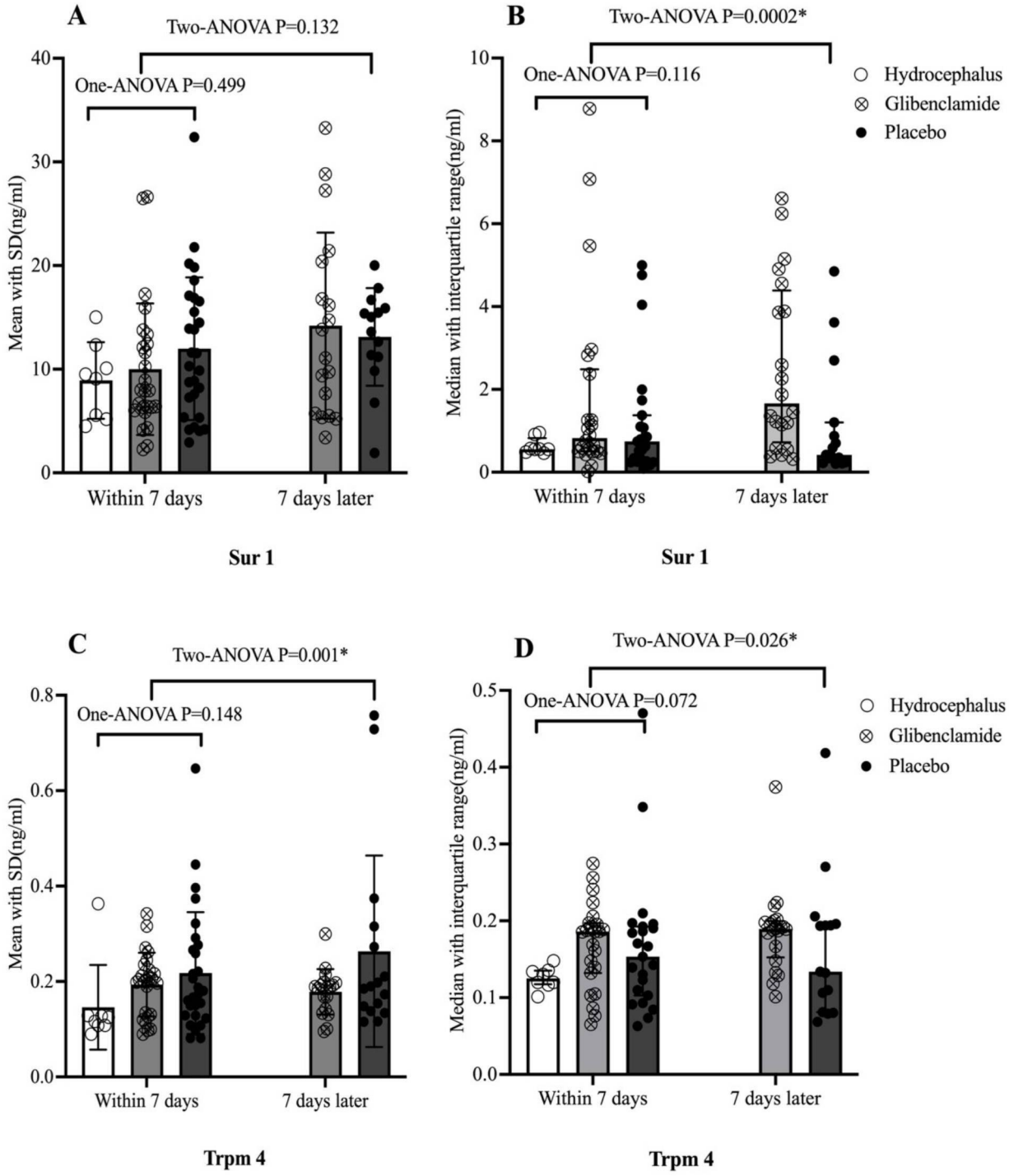

Figure 3 Secondary outcomes in the hydrocephalus, glibenclamide and placebo. (A) Comparison of plasma SUR1 between three groups. (B) Comparison of cerebrospinal fluid SUR1 between three groups. (C) Comparison of plasma TRPM4 between three groups. (D) Comparison of cerebrospinal fluid TRPM4 between three groups. *On behalf of p<0.05. ANOVA, analysis of variance; SUR1, sulfonylurea receptor 1; TRPM4, transient receptor potential melastatin 4.

This study introduces a novel treatment strategy, providing a comprehensive analysis of the efficacy and safety of higher doses of glibenclamide across various dimensions and supported by more extensive evidence.

Previous clinical studies have demonstrated that intravenous glibenclamide yielded suboptimal outcomes and did not exhibit significant effects when administered at dosages of 2.5 mg/day for traumatic brain injury,[27] 5 mg/day for acute ischaemic stroke[20] and 5 mg/day for aSAH.[17] However, for moderate and severe traumatic brain injury, a dosage of 10 mg/day was found to reduce contusion expansion rates.[28] In light of these findings, we determined that a daily

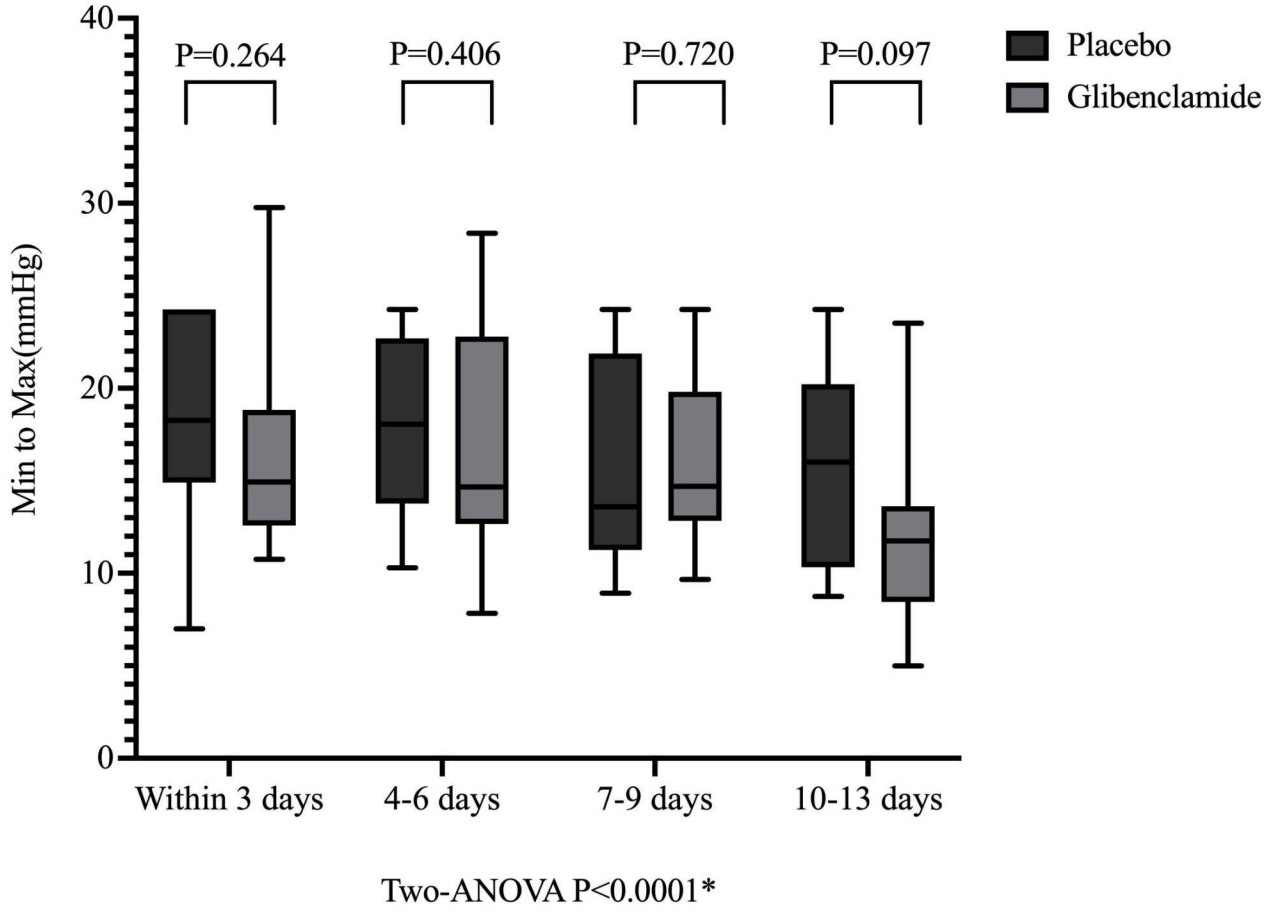

Figure 4 Comparison of intracranial pressure between two groups. *On behalf of p<0.05. ANOVA, analysis of variance.

dosage of 15 mg was appropriate. It is worth noting that previous reports have confirmed the safe administration of glibenclamide at various dosages, ranging from 2.5 mg/day to 20 mg/day, within clinical settings.[29]

The clinical interventions and long-term prognosis for patients with aSAH vary depending on the disease's severity and the occurrence of secondary brain injury. Our assessment of the clinical severity of aSAH patients on admission relied on the Hunt-Hess and WFNS grading systems. To provide robust radiological evidence, we favoured the use of head CT scans. These scans not only reveal the extent of cerebral oedema but also pinpoint the location and severity of bleeding, which is crucial for diagnosis. For assessing cerebral oedema, we employed the SEBES, which proved to be effective.[19] The modified Fisher scale was used to evaluate the extent of bleeding in aSAH cases, with higher scores correlating with an increased risk of cerebral vasospasm. This scoring system holds predictive value in anticipating cerebral vasospasm.[30] Importantly, we did not interfere with clinical physicians' decisions regarding treatment responses based on their assessment of the patients' condition. The probability of undergoing decompressive craniectomy surgery on admission was similar between the two groups of patients with cerebral oedema (14.3% vs 7.1%, p=0.669).

The primary outcome revealed a significant improvement in cerebral oedema in the glibenclamide group following medication. Notably, on admission, patients in the glibenclamide group exhibited more pronounced cerebral oedema compared with the placebo group, as evidenced by higher WFNS and mRS scores, as well as a greater likelihood of requiring decompressive craniectomy. However, after 10 days of medication, the incidence of patients in the glibenclamide group necessitating decompressive craniectomy was lower (3.6% vs 7.1%, p=1.000), with one patient in the placebo group undergoing bilateral decompressive craniectomy. Although not statistically significant, this analysis indirectly suggests the advantage of glibenclamide in ameliorating cerebral oedema and reducing the need for secondary procedures. Decompressive craniectomy is a recognised treatment for addressing cerebral oedema. However, a preclinical study demonstrated that in an ischaemia model, glibenclamide was as effective as decompressive craniectomy in preventing death from malignant cerebral oedema but outperformed it in preserving neurological function and the integrity of watershed cortex and deep white matter.[11] These findings align with the results of our trial.

The secondary outcomes reveal an interesting trend in the glibenclamide group, where the proportion of patients showing improved functionality increased over

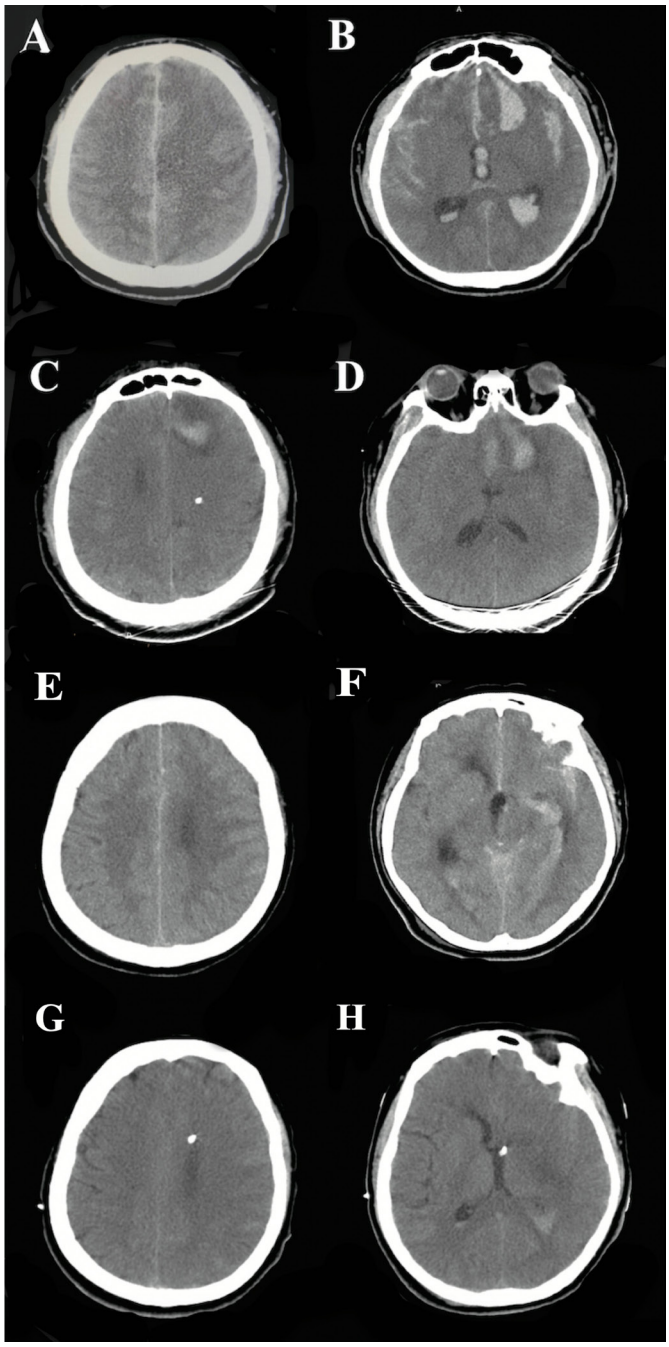

Figure 5 Typical cases presentation of two groups of patients. (A, B) Patients in the control group underwent cranial CT scan on first day after surgery. (C, D) Patients in the control group underwent cranial CT scan on 10th day after surgery. (E, F) Patients in the glibenclamide group underwent cranial CT scan on first day after surgery. (G, H) Patients in the glibenclamide group underwent cranial CT scan on 10th day after surgery.

time. This observation diverges somewhat from the findings of previous trials.[20 27 31] Those trials suggested that glibenclamide led to better functional outcomes at the time of discharge. In our trial, we did not observe significant improvement at discharge. Nevertheless, when considering long-term prognosis, our trial demonstrated a growing proportion of patients benefiting from glibenclamide. Analysis of the modified Fisher scale indicated that patients treated with glibenclamide experienced faster absorption of intracranial haemorrhage. However, the occurrence of adverse complications such as cerebral vasospasm did not exhibit significant differences when compared with the placebo group. This conclusion is in line with the results of a previous randomised controlled trial.[17] Additionally, glibenclamide did not elevate the incidence of other adverse events in patients, nor did it substantially prolong the length of hospital stays. Glibenclamide did not reduce the mortality rate in aSAH patients, which aligns with the results of previous studies.[17 24 26]

Active transportation relies on a continuous supply of ATP to provide energy, such as Na^+/K^+-ATPase and Ca^{2+}-ATPase. Although both K_{ATP} and SUR1-TRPM4 channels are regulated by SUR1, they have opposite functional effects in central nervous system injury. The opening of selective K_{ATP} channels causes cell hyperpolarisation and may have neuroprotective effects, while the opening of non-selective SUR1-TRPM4 channels causes cell depolarisation.[32] The opening of SUR1-TRPM4 channels is associated with excessive influx of Na^+, accompanied by the influx of Cl^- and H_2O, causing osmotic cell swelling (cytotoxic oedema). If severe, it leads to cell necrosis.[25] Pathological activation of the SUR1-TRPM4 channel can also mediate the disruption of the blood-brain barrier, disrupting the tight connections between cells and leading to vascular oedema.[15] Secondary injury ultimately leads to complete loss of capillary structure and enters the haemorrhagic transformation. After the rupture of an aneurysm, blood extravasation produces thrombin and methemoglobin at the injury site, which independently mediate delayed angiogenic oedema.[33] SUR1-TRPM4 channel leading to endothelial cell infiltrating death is also a factor in the formation of haemorrhagic transformation, leading to delayed vascular oedema.[22] Our results indicate that oral high-dose glibenclamide significantly reduces plasma TRPM4 levels, bringing the concentration as close as possible to normal intracranial pressure patients with hydrocephalus. Sheth KN[24] found similar results regarding the association between elevated MMP-9 levels and cerebral oedema after ischaemic stroke, with glibenclamide reducing the concentration of MMP-9 in plasma. This indicates that glibenclamide acts as an inhibitory channel in the blood, but its research fails to indicate intracranial conditions. We observe the concentration of SUR1-TRPM4 in the cerebrospinal fluid and find that patients with glibenclamide significantly increased, while the placebo group tended to approach patients with hydrocephalus. We also observed that patients in the glibenclamide group were more likely to require cerebrospinal fluid shunting within 7 days (46.4% vs 25.0%, p=0.094). We speculate that apoptotic processes are clearly enhanced after glibenclamide treatment in SUR1 cells,[34] and remains in the cerebrospinal fluid and accumulates in the ventricles, leading to ventricular enlargement in patients with glibenclamide. Clinicians then

perform cerebrospinal fluid shunt, but glibenclamide does not cause the occurrence of malignant hydrocephalus. AQP1 and $Na^+/K^+/Cl^-$ co-transporter have an important role in choroid plexus injury-induced cerebrospinal fluid hypersecretion and hydrocephalus after SAH,[35] which is different from the mechanism of glibenclamide and needs further investigation. Here, we consider that the levels of SUR1-TRPM4 in the plasma of patients with normal intracranial pressure hydrocephalus are close to those of normal individuals, while belonging to a pathological process in cerebrospinal fluid. Therefore, the concentration of SUR1-TRPM4 in cerebrospinal fluid is highly similar to that of the placebo group.

The limitations of this study primarily revolve around the small sample size. In order to enhance the radiological evaluation of cerebral oedema, additional indicators such as the measurement of haematoma volume should be incorporated. Future investigations into glibenclamide should aim to minimise the duration of administration, as these variables may potentially lead to an underestimation of glibenclamide's efficacy in terms of achieving positive functional outcomes at the 6-month mark. Furthermore, there is a notable absence of assessments pertaining to cognitive improvement. It is imperative to acknowledge that global cerebral oedema represents a crucial risk factor for cognitive dysfunction following SAH. Therefore, treatment strategies targeting brain swelling hold significant promise for ameliorating cognitive outcomes post-SAH.[7] It is important to note that high doses of oral glibenclamide carry the potential risk of inducing severe hypoglycaemia, and its usage is subject to considerable individual variation. Consequently, it is imperative to rigorously adhere to the designated treatment protocol, and it is strongly recommended to employ intravenous micropumps to regulate the infusion rate for enhanced safety.

In summary, the administration of oral high-dose glibenclamide yielded noteworthy reductions in the radiological assessment of cerebral oedema and bleeding following a 10-day medication regimen. Significant alterations were also observed in the concentrations of SUR1-TRPM4 in both plasma and cerebrospinal fluid. While glibenclamide may not exhibit a substantial impact on overall mortality rates, it does demonstrate the potential to influence the distribution of patients with a favourable functional prognosis. However, it is worth noting that the use of glibenclamide is associated with an elevated incidence of hypoglycaemia. These findings underscore a potential role for glibenclamide in the pathogenesis of brain swelling following aSAH and advocate for further investigation through larger-scale studies in this context.

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