Efficacy and safety of glibenclamide therapy after intracerebral haemorrhage (GATE-ICH): A multicentre, prospective, randomised, controlled, open-label, blinded-endpoint, phase 2 clinical trial

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Summary

Background Glibenclamide is a promising agent for treating brain oedema, but whether it improves clinical outcomes in patients with intracerebral haemorrhage (ICH) remains unclear. In this study, we aimed to explore the efficacy and safety of glibenclamide treatment in patients with acute ICH.

Methods The Glibenclamide Advantage in Treating Oedema after Intracerebral Haemorrhage (GATE-ICH) study was a randomised controlled phase 2 clinical trial conducted in 26 hospitals in the northwest of China, recruiting patients with acute ganglia ICH no more than 72 h after onset from Dec 12, 2018 to Sept 23, 2020. During the first 7 days after enrolment, patients randomly assigned to the glibenclamide group were given glibenclamide orally (1.25 mg, 3/day) and standard care, while patients randomly assigned to the control group were given standard care alone. The computer-generated randomisation sequence was prepared by a statistician not involved in the rest of the study. Randomisation was computer-generated with a block size of four. The allocation results were unblinded to participants and investigators. The primary outcome was the percentage of patients with poor outcome (defined as modified Rankin Scale [mRS] score of ≥3) at day 90. The trial was registered at ClinicalTrials.gov (NCT03741530).

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Abbreviations: ICH, Intracerebral haemorrhage; PHE, Perihemaetomal oedema

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Findings 220 participants were randomised and 200 participants (mean [standard deviation] age, 56 [11] years; sex, 128 [64.0%] male and 72 [36.0%] female) were included in the final analysis, with 101 participants randomly assigned to the control group and 99 to the glibenclamide group. The incidence of poor outcome at day 90 was 20/99 (20.2%) in glibenclamide group and 30/101 (29.7%) in control group (absolute difference, 9.5%; 95% confidence interval [CI], -3.2%−21.8%; $P = 0.121$) with adjusted odds ratios of 0.54 (95% CI, 0.24−1.20; $P = 0.129$). No significant difference was found in the overall rates of adverse events or serious adverse events between groups. However, the incidence of asymptomatic hypoglycaemia was significantly higher in glibenclamide group than control group (15/99 [15.2%] vs 0/101 [0.0%]; absolute difference, 15.2%; 95% CI, 7.5%−24.1%; $P < 0.001$).

Interpretation Our study provides no evidence that glibenclamide (1.25 mg, 3/day) significantly reduces the proportion of poor outcome at day 90 after ICH. In addition, glibenclamide could result in higher incidence of hypoglycaemia. Larger trials of glibenclamide with optimised medication regimen are warranted.

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Keywords: Intracerebral haemorrhage; Perihemaetomal oedema; Glibenclamide; Prognosis

Research in context

Evidence before this study

Preclinical studies have shown that glibenclamide plays an important role in mitigating both cytotoxic and vasogenic oedema by blocking sulfonylurea receptor 1-transient receptor potential melastatin 4 (SUR1−TRPM4) channels, but whether it improves clinical outcomes in patients with intracerebral haemorrhage (ICH) remains unclear. We did a PubMed search using the terms "glibenclamide" AND ("intracerebral haemorrhage" OR "ICH") AND ("randomised controlled trial" OR "clinical trial" OR "meta-analyses") for studies without language or publication date restrictions on June 1, 2022. Three relevant studies, including two protocols and one randomised controlled trial (RCT), were identified. The RCT enrolled 78 patients with aneurysmal subarachnoid haemorrhage and found that glibenclamide was not associated with better functional outcomes after aneurysmal subarachnoid haemorrhage. These results were unable to provide evidence for the use of glibenclamide in patients with ICH.

Added value of this study

The GATE-ICH trial, to our knowledge, is the first multicentre RCT to assess the benefit of glibenclamide in patients with ICH. Glibenclamide did not decrease the incidence of 90-day poor outcome (mRS ≥ 3) and resulted in higher incidence of hypoglycaemia. However, the treatment of glibenclamide significantly shifted the mRS distribution towards lower values and reduced the brain oedema.

Implications of all the available evidence

Current studies did not justify the routine use of glibenclamide in patients with acute ICH. Larger trials are needed to verify the definite effect of glibenclamide with optimised medication regimen.

Introduction

Intracerebral haemorrhage (ICH) accounts for 10% to 15% of all stroke subtypes.[1] The mortality of ICH is 47% to 64% at 1 year after onset, and only 20% to 30% of the survivors regain functional independence.[2−4] Perihaematomal oedema (PHE) is an important contributor to secondary brain injury after ICH, which makes it a potential target for ICH treatment.[5,6]

Glibenclamide is one of the anti-diabetic second-generation sulfonylurea (SFU) derivatives.[7] Preclinical studies have shown that glibenclamide plays an important role in mitigating both cytotoxic and vasogenic oedema by blocking sulfonylurea receptor 1-transient receptor potential melastatin 4 (SUR1−TRPM4) channels.[8,9] A prospective randomised controlled clinical trial which enrolled patients with ischaemic stroke found that intravenous glibenclamide significantly reduced the midline shift,[10] and improved survival in patients aged ≤70 years.[11] Several retrospective studies also suggested that pre-treatment of oral SFU such as glibenclamide was associated with less PHE and better functional outcomes in ICH patients with medical history of type 2 diabetes.[12−14] Our pilot study indicated that oral glibenclamide significantly decreased the volume of PHE and brought improvement in the neurological function of patients with acute ICH.[15] This evidence suggests that glibenclamide is a promising option for reducing PHE and improving clinical outcomes in patients with ICH. Therefore, we designed a multicentre,

randomised, controlled clinical trial to evaluate whether treatment with glibenclamide could reduce the PHE and further improve the functional outcomes in patients with acute ICH.

Methods

Trial design and oversight

This Glibenclamide Advantage in Treating Oedema after Intracerebral Haemorrhage (GATE-ICH) study was a multicentre, prospective, randomised, controlled, open-label, blinded-endpoint phase 2 clinical trial including patients with primary ICH in 26 hospitals in the northwest of China. The participating trial sites are listed in eTable 1. The study design and protocol were approved by ethics committee at Xijing Hospital. The protocol was published elsewhere and displayed in supplementary file 1.[15] The written consents were provided by participants or their legally authorised representatives before study entry and the patients were enrolled from Dec 12, 2018 to Sept 23, 2020, with final follow-up in December 2020. All procedures in the present study were in accordance with the recommendation of Good Clinical Practice (GCP) guidelines and the Declaration of Helsinki.

Patients

Patients eligible for inclusion in the GATE-ICH trial were 18 years or older, had primary basal ganglia haemorrhage of 5 to 30 mL with initial Glasgow Coma Scale (GCS) score of 6 or more, and had symptom onset less than 72 hours prior to admission. Patients with one of the following criteria were excluded from the study: (1) planned evacuation of a large haematoma; (2) prior significant disability (modified Rankin Scale [mRS] $\geq$ 3); (3) severe renal disease, severe liver disorder, or severe heart disease; (4) blood glucose <3.1 mmol/L at admission, or with history of hypoglycaemia. The details of inclusion and exclusion criteria were shown in eTable 3.

Randomisation and masking

Patients were randomly assigned in a 1:1 ratio to glibenclamide group or control group through a web-based randomisation process. The randomisation sequence was computer-generated (SAS Statistical Package, version 9.2) with a block size of 4 and was prepared by a statistician who did not directly participate in the recruitment and enrolment. The research coordinators at each trial site had the access to the randomisation results. The grouping results were unblinded to participants and researchers excluding those who assessed outcome and conducted analysis. All the imaging evaluations were conducted by investigators who were blinded to clinical variables, interventions, and functional outcomes. There was one investigator who was blinded to the allocation and intervention, assessing the functional outcomes at day 90. The statistical analysis was conducted by blinded independent biostatisticians.

Intervention

Patients randomly assigned to the glibenclamide group were prescribed glibenclamide tablets (Yun Peng Pharmaceutical Co., Shanxi, China; each tablet [2.5 mg]) 1.25 mg, 3 times daily and standard care for 7 consecutive days after enrolment. The glibenclamide was orally taken within 30 min before 3 meals. For patients with enteral nutrition, glibenclamide was given at regular timepoints (8:00, 12:00, 16:00) through nasogastric feeding tube. Patients randomly assigned to the control group were prescribed with standard care alone.

Both groups in the trial received standard care following guidelines.[16,17] For patients presenting with elevated BP, systolic blood pressure (SBP) was aimed to maintain lower than 140 mmHg. Osmotherapy was recommended for patients who showed clinical deterioration with radiological evidence of mass effect. Clinical seizures and electrographic seizures on electroencephalogram should be treated with antiseizure drugs.

Patient safety

For the safety of patients assigned to the glibenclamide group, the dose of glibenclamide should be reduced to 1.25mg twice daily if any of the following conditions was present: (1) laboratory-confirmed blood glucose level <3.1 mmol/L; (2) three laboratory-confirmed blood glucose levels <3.9 mmol/L within 12 hours. Glibenclamide should be discontinued if either of the above conditions occurred twice. In patients with blood glucose lower than 3.9 mmol/L, 50% glucose was suggested to use: the supplementation volume of 50% glucose = (100 − lab confirmed blood glucose [mg/dL]) × 0.4ml. Other glucose solutions with the same amount of sugar were also permitted.

Data collection

At the time of baseline screening, demographics, medical history (ischaemic stroke, ICH, coronary events, diabetes mellitus, and hypertension), results of physical examinations, vital signs, laboratory tests, electrocardiography (ECG), clinical scores (National Institutes of Health Stroke Scale [NIHSS], GCS, ICH score, Barthel index, mRS), and head CT results were recorded. During the first 7 days after enrolment, point-of-care blood glucose was monitored 3 times a day. The routine laboratory tests, ECG, clinical scores (NIHSS, GCS, ICH score, Barthel index, mRS), and head CT were repeated on days 3 and day 7. During the hospitalisation, concomitant treatments, adverse events (AEs), and serious AEs (SAEs) were documented. At 90 days after enrolment, a telephone follow-up about the mRS and Barthel index was performed.

The 3D Slicer software package (version 4.10.2; National Institutes of Health, Bethesda, MD, USA) was used to evaluate the imaging data. The volumes of ICH and PHE were measured using a semiautomatic volumetric algorithm and an edge-detection algorithm as previously described.[18,19] The brain oedema was depicted using five parameters as follows: (1) Absolute PHE:the volumes of PHE calculated by 3D slicer; (2) Relative PHE (rPHE): PHE volumes divided by ICH volumes; (3) Oedema extension distance (EED): $\sqrt[3]{\frac{\text{PHE volume} + \text{ICH volume}}{\frac{4}{3}\pi}} - \sqrt[3]{\frac{\text{ICH volume}}{\frac{4}{3}\pi}}$; (4) Peak PHE: the largest PHE volumes of the three CT scans; (5) Rate of PHE growth: the increase of PHE divided by the time intervals.

Outcomes

The primary efficacy outcome was the percentage of poor outcome (mRS ≥3) at 90 days after enrolment. The secondary efficacy outcomes were haematoma volumes, oedema parameters (absolute PHE, rPHE, EED, peak PHE, rate of PHE growth), and clinical scores (GCS and NIHSS) at day 3, and day 7, as well as clinical scores (Barthel index and mRS) at day 90. The changes of haematoma volumes, oedema parameters, and clinical scores from baseline to follow-up were also observed. The safety outcomes included the asymptomatic hypoglycaemia, symptomatic hypoglycaemia, incidence of cardiac AEs/SAEs or a QT interval of > 500 ms, incidence of all-cause mortality, and other AEs/SAEs.

Statistical analysis

We recruited 220 participants and continued their follow-up for 90 days in order to verify the improvements of the functional outcomes from our pilot study.[15] In our pilot study, the proportion of patients with mRS ≥ 3 at day 90 was 33.3% in control and 10.0% in glibenclamide group. The rate of non-adherence to the treatment protocol and overall loss to follow-up was assumed to be 15%. The sample size of 220 was calculated to provide at least 80% power (1-β) to detect an 23.3% absolute risk reduction in the proportion of patients with mRS ≥ 3 in the glibenclamide group compared with the control group, using a two-sided significance of 5% type I error (α).

Patients in our study were analysed according to the principle of modified intention-to-treat (mITT). The analysis for per-protocol (PP) population was repeated to assess the robustness of our conclusion. The outcomes were compared between patients in the glibenclamide group and the control group using the Chi-square test or Fisher's exact tests, and Student's *t* test or Wilcoxon rank-sum test. The binary logistic regression or general linear regression were used to estimate the odds ratios (OR) or β and associated 95% confidence intervals (CI). The shift of mRS at day 90 toward a better functional outcome was evaluated with ordinal logistic regression, and a common OR with 95% CI was derived after validation of the proportional odds assumption. The effects of glibenclamide were further adjusted for age, sex, time from onset to randomisation more than 24 hours, baseline NIHSS, baseline volumes of haematoma and PHE, osmotherapy and haemostatic agents during hospitalisation. We further compared the proportion of patients with poor outcome at day 90 using logistic regression in subgroups as follows: age, time to randomisation, baseline SBP, baseline ICH volume, baseline GCS, and with history of diabetes or not. The changes over time between groups were compared using generalised estimating equations. Two-sided *P* values < 0.05 were considered significant in all tests. The statistical analysis was performed with SPSS 25.0 software (SPSS Inc., Chicago, IL, USA).

Role of the funding source

The study sponsors played no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication. All authors had access to all the data in the study and were responsible for the decision to submit for publication.

Results

From Dec 12, 2018 to Sept 23, 2020, 1537 patients with ICH were screened, of whom 220 patients underwent randomisation. After excluding 20 patients who withdrew their consents or were not eligible for the GATE-ICH trial after randomisation, 200 patients were included in the final mITT analysis, consisting of 99 patients in glibenclamide group and 101 patients in control group (Figure 1). The geographic regions where the ICH patients were recruited from are shown in eTable 2 and eFigure 1. The baseline characteristics of mITT population (Table 1) and per-protocol (PP) population (eTable 4) did not differ significantly between two groups, including demographics, time from stroke onset to enrolment, stroke severity, vital signs, imaging characteristics, blood glucose, medical history, and previous antiplatelet therapy. The concomitant medical treatments of participants were similar between two groups, including osmotherapy, BP lowering treatment, statins, edaravone, and haemostatic agents (eTable 5).

The median time from onset to randomisation was 24 hours in control group, 22 hours in glibenclamide group (Table 1). The blood glucose changes in the first 7 days after enrolment are shown in Figure 2 and eTable 6. The baseline blood glucose was 6.6 (5.6 − 7.3) mmol/L in glibenclamide group and 6.3 (5.3 − 7.3) mmol/L in control group (*P* = 0.510) (eTable 6). Two hours after enrolment, blood glucose was

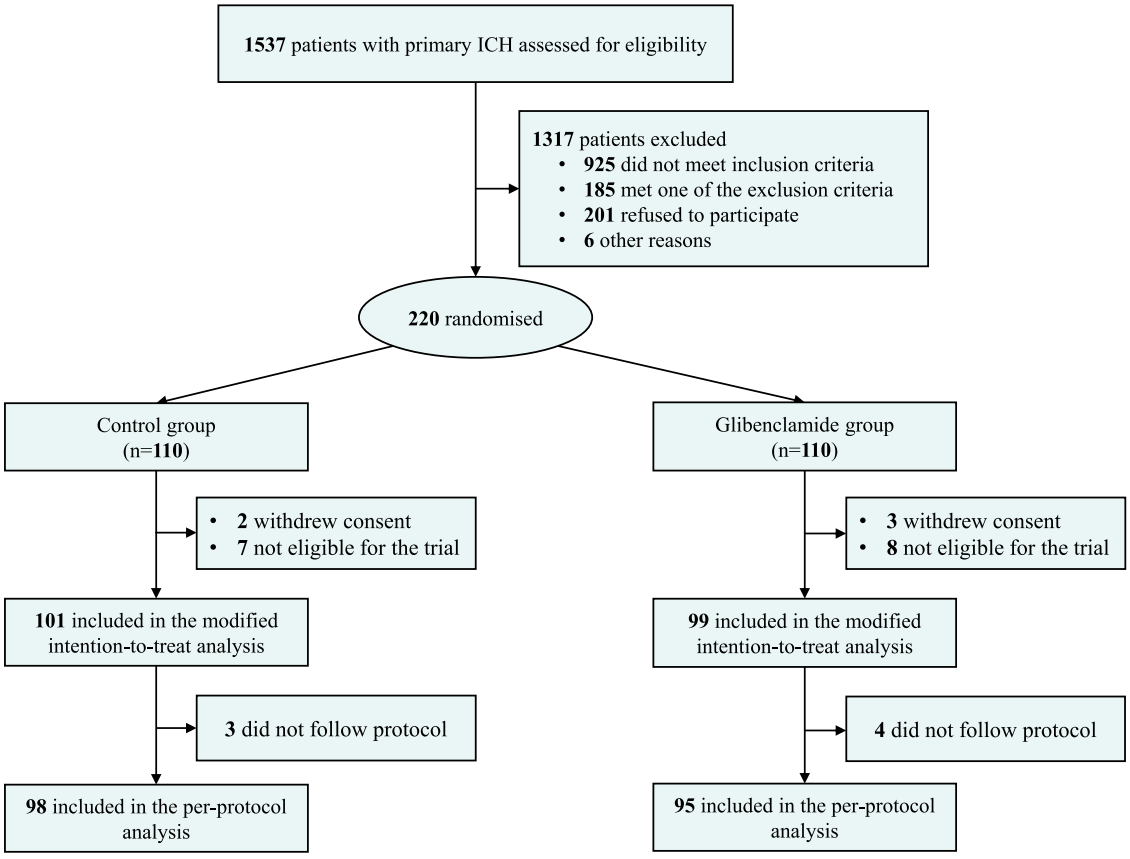

Figure 1. CONSORT Diagram.

6.7 mmol/L (1.5% higher than baseline) in glibenclamide group and 7.1 mmol/L in control group (12.7% higher than baseline) (P = 0.082) (eTable 6). During the following 6 days, the median blood glucose in glibenclamide group was between 6.6–7.6 mmol/L, while that in control group fluctuated between 6.8–8.1 mmol/L (Figure 2 and eTable 6). Compared with control group, glibenclamide group showed significantly lower blood glucose over time (P = 0.001 for between-group difference) (Figure 2). The SBP over time was similar between glibenclamide group and control group (P = 0.692 for between-group difference) (eFigure 2).

As shown in Table 2, the incidence of 90-day poor outcome (mRS ≥ 3) in glibenclamide group was slightly lower than that in control group (20/99 [20.2%] vs 30/101 [29.7%], absolute difference: 9.5%, 95% confidence interval [CI]: -3.2%–21.8%; P = 0.121). The adjusted analysis indicated that the application of glibenclamide did not significantly reduce the risk of 90-day poor outcome (adjusted OR: 0.54, 95% CI: 0.24–1.20; P = 0.129). The sensitivity analysis of the primary outcome in PP population was consistent with the mITT analysis (eTable 7). The poor outcome at day 90 was similar between groups in different grades of hospitals (eTable 8). The eFigure 3 showed no significant difference in the 90-day poor outcome in terms of each subgroup between glibenclamide group and control group. Distributions of mRS at day 90 are detailed in Figure 3, which demonstrated that the ordinal shift of mRS at day 90 generally favoured the glibenclamide group in both mITT population (adjusted common OR: 0.57, 95% CI: 0.34–0.98, P = 0.043) and PP population (adjusted common OR: 0.54, 95% CI: 0.31–0.94, P = 0.028). Other clinical secondary outcomes were displayed in Table 2, eTable 7, and eTable 10.

The baseline ICH volumes, PHE volumes, rPHE, and EED were similar between glibenclamide group and control group (Table 1). After adjustment of the confounders, glibenclamide treatment significantly reduced the PHE volume (β: -4.16, 95% CI:-7.09 – -1.23, P = 0.006) and EED (β: -0.06, 95% CI:-0.12 – -0.01, P = 0.026) at day 7 in mITT population (Table 2). The growth rate of PHE from day 1 to day 7 (β: -0.60, 95% CI: -1.01 – -0.18, P = 0.006) and peak PHE (β: -2.88, 95% CI: -5.34 – -0.42, P = 0.022) in glibenclamide group were also significantly decreased compared with control group in mITT population (Table 2). The effects of glibenclamide on oedema were more remarkable in patients enrolled <24 h from onset to randomisation than those ≥24 h (eTable 9). Similar results of PHE

	Control group (*N* = 101)	Glibenclamide group (*N* = 99)
Demographics		
Age (years), mean (SD)	56 (±10)	56 (±11)
Sex		
Male, N (%)	61 (60.4%)	67 (67.7%)
Female, N (%)	40 (39.6%)	32 (32.3%)
Time from onset to enrolment (h), median (IQR)	24 (13–38)	22 (11–32)
Severity		
NIHSS, median (IQR)	8.0 (4.0–12.0)	7.0 (5.0–10.0)
GCS, median (IQR)	15.0 (13.0–15.0)	15.0 (14.0–15.0)
mRS, median (IQR)	4 (2–4)	4 (3–4)
Vital Signs		
SBP (mm Hg), median (IQR)	160 (140–175)	154 (140–173)
DBP (mm Hg), median (IQR)	95 (81–106)	96 (88–102)
Heart rate (beats per min), median (IQR)	75 (69–82)	78 (70–82)
Body temperature (°C), median (IQR)	36.5 (36.3–36.7)	36.5 (36.3–36.8)
Baseline imaging characteristic		
Haematoma volume, mL, median (IQR)	9.2 (6.0–13.2)	8.7 (6.0–13.9)
PHE volume, mL, median (IQR)	12.4 (7.6–18.6)	12.0 (7.8–19.7)
rPHE, median (IQR)	1.3 (1.0–1.8)	1.3 (0.9–1.7)
EED, cm, median (IQR)	0.4 (0.3–0.6)	0.4 (0.3–0.5)
Baseline blood glucose, mmol/L, median (IQR)	6.3 (5.3–7.3)	6.6 (5.6–7.3)
Medical history		
Ischaemic stroke, N (%)	12 (11.9%)	10 (10.1%)
Haemorrhagic stroke, N (%)	7 (6.9%)	7 (7.1%)
Coronary artery disease, N (%)	11 (10.9%)	6 (6.1%)
Diabetes, N (%)	9 (8.9%)	4 (4.0%)
Hypertension, N (%)	87 (86.1%)	81 (81.8%)
Atrial fibrillation, N (%)	2 (2.0%)	1 (1.0%)
Previous antiplatelet therapy, N (%)	7 (6.9%)	3 (3.0%)

***Table 1*: Baseline characteristics of the participants, modified intention-to-treat population.**
Abbreviations: NIHSS, National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale; SBP, systolic blood pressure; DBP, diastolic blood pressure; EED, oedema extension distance; mRS, modified Rankin Scale; SD, standard deviation; IQR, interquartile range; PHE, perihaematomal oedema; rPHE, relative perihaematomal oedema.

volume and EED at day 7, peak PHE, and growth rate of PHE from day 1 to day 7 were detected in PP population (eTable 7). The changes of PHE in mITT population and PP population during the intervention period were shown in eFigure 4. Other imaging data were detailed in eTable 10.

As shown in Table 2, any AE or any SAE showed a non-significant difference between glibenclamide group and control group (any AE: 73/99 [73.7%] vs 65/101 [64.4%], adjusted OR: 1.86, 95% CI: 0.97–3.58, $P = 0.062$; any SAE: 24/99 [24.2%] vs 24/101 [23.8%], adjusted OR: 1.05, 95% CI: 0.52–2.15, $P = 0.889$). The detailed AEs and SAEs were displayed in Table 3. The proportion of asymptomatic hypoglycaemia events in glibenclamide group was significantly higher than that in control group (15/99 [15.2%] vs. 0/101 [0.0%], $P < 0.001$) (Table 3). There were 3 (3.0%) patients in glibenclamide group presented with symptomatic hypoglycaemia but none (0.0%) in control group ($P = 0.119$) (Table 3). No significant difference was observed in other safety events between glibenclamide group and control group (Table 3).

Discussion

This randomised controlled clinical trial showed that glibenclamide decreased PHE and improved distributions of 90-day mRS; however, it did not significantly reduce the risk of poor outcome at day 90 after acute primary ICH. The incidences of any AE or SAE were not significantly different, but glibenclamide increased the occurrence of hypoglycaemia.

Treatment of PHE is a promising target to improve outcomes in patients with acute ICH.[5,6] Although osmotic agents, anti-adrenergic agents, statins, celecoxib, and deferoxamine mesylate have been introduced as potential therapies to reduce the PHE, their benefits to the functional outcomes remain controversial.[20–25] Fu Y and colleagues conducted a study including 23 patients with primary ICH and found that fingolimod

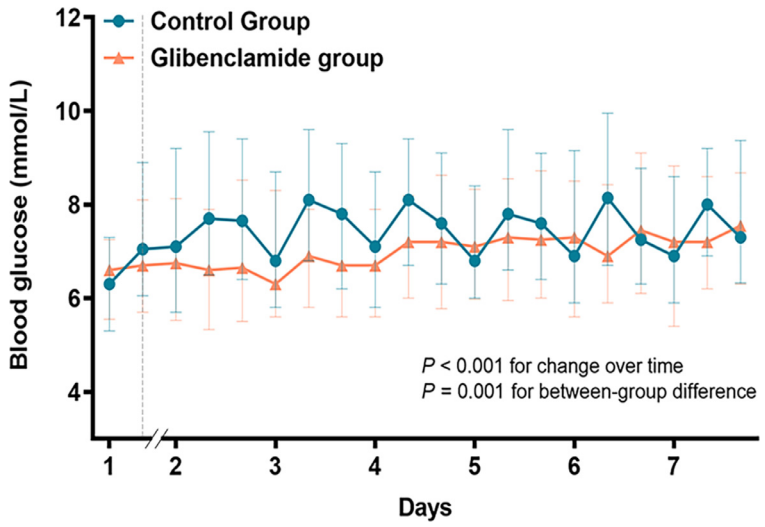

Figure 2. Blood glucose during the intervention period.

Median blood glucose over the 7-day trial period, expressed in mmol/L (mean difference: glibenclamide group vs. control group, -0.641 [-1.027– -0.256], $P = 0.001$. Time, 0.034 [0.022-0.046], $P < 0.001$). The dashed vertical line indicates 2 h after enrolment, and error bars indicate interquartile range.

reduced PHE and improved the 90-day functional outcomes.[26] However, the small sample size in the study restricted the generalisation of the conclusion. In GATE-ICH trial, glibenclamide reduced PHE at day 7 and improved the distributions of mRS at day 90, but failed to reduce the proportion of mRS ≥3 at day 90. The negative results of primary outcome in our study might be attributed to relatively small haematoma volume of the enrolled patients, which usually resulted in milder neurologic deficits and more favourable clinical outcomes. Therefore, whether patients with larger haematoma volume could benefit more from glibenclamide is worth exploring in future studies.

Several other factors may also influence the clinical outcomes in patients with supratentorial ICH, including lesion location and BP level.[1,27–31] In order to minimise the diversity of lesion location, we enrolled adults with primary basal ganglia haemorrhage. For purpose of avoiding large differences of BP, the SBP was reduced to <140mmHg in patients with elevated SBP without contraindication to BP-lowering treatment.[16] Furthermore, we have selected multiple parameters, including absolute PHE, rPHE, PHE peak, PHE growth rate and EED, to describe PHE to diminish the influence of haematoma volume on PHE. Thus, results of the GATE-ICH trial credibly demonstrated that glibenclamide treatment significantly reduced the brain oedema in ICH patients after adjustment for confounders.

The dosage of glibenclamide in our study was selected based on previous results and our pilot study. Huang K et al. treated acute hemispheric infarction with oral glibenclamide (a loading dose of 1.25 mg, followed by 0.625 mg every 8 hours) and found that it could prevent brain oedema without causing significant safety concerns.[32] Moreover, Zafardoost P et al. and Khalili H et al. applied oral glibenclamide of 2.5 to 10 mg per day to treat patients with moderate and severe traumatic brain injuries.[33,34] In GATE-ICH trial, the dosage of oral glibenclamide was 1.25 mg, 3 times daily from our pilot study,[15] in which the plasma concentration of glibenclamide increased gradually and achieved a steady state of 26.7 ng/mL at 72 h after first dose, close to the concentration of intravenous glibenclamide (28.3 ng/mL) in GAMES-RP study.[10,35] Apart from the dosage of glibenclamide, the timing of glibenclamide administration is another important consideration. In the current study, we found that the efficacy of glibenclamide on oedema (PHE volume at day 7, EED at day 7, and rate of PHE growth from day 1 to day 7) was significant in patients enrolled < 24h from onset to randomisation, rather than those ≥ 24h. This suggests that glibenclamide might need to be administered early to achieve better therapeutic effect on brain oedema in patients with ICH.

As for glucose management after ICH, guidelines recommended that both hyperglycaemia and hypoglycaemia should be avoided due to increased risks of mortality and poor outcomes.[16,36] In GATE-ICH trial, 5% or 10% glucose was suggested to prevent hypoglycaemia, and hyperosmotic glucose was suggested to treat patients with hypoglycaemia. Even so, we found that glibenclamide of 1.25 mg, 3 times per day significantly increased hypoglycaemia events compared with control group (18.2% vs. 0.0%). Similar problem was also found in previous studies on patients without diabetes

	Control group (N = 101)	Glibenclamide group (N = 99)	Absolute difference (95% CI)	*P*	Unadjusted analysis		Adjusted analysis[b]	
					OR/β (95% CI)	*P*	OR/β (95% CI)	*P*
Primary outcome								
Poor outcome at day 90, N (%)[a]	30 (29.7%)	20 (20.2%)	9.5% (−3.2%−21.8%)	0.121	0.60 (0.31−1.15)	0.123	0.54 (0.24−1.20)	0.129
Secondary outcomes								
Barthel index at day 90, median (IQR)	90 (75−100)	95 (79−100)	0 (−5−0)	0.091	5.02 (−1.22−11.26)	0.114	3.85 (−1.87−9.56)	0.186
mRS score at day 90, median (IQR)	2 (1−3)	1 (1−2)	0 (0−1)	0.052	−0.34 (−0.71−0.03)	0.071	−0.30 (−0.63−0.03)	0.077
Imaging outcomes, median (IQR)								
Haematoma volume at day 7, mL	6.7 (4.0−10.1)	6.1 (3.7−10.5)	0.1 (−1.2−1.5)	0.833	−0.26 (−1.99−1.46)	0.763	−0.62 (−1.78−0.54)	0.296
PHE volume at day 7, mL	25.0 (16.4−38.0)	20.3 (13.0−31.4)	3.4 (−0.7−7.7)	0.103	−3.38 (−7.61−0.86)	0.117	−4.16 (−7.09− −1.23)	**0.006**
rPHE at day 7	3.6 (2.5−5.6)	3.4 (2.2−5.0)	0.4 (−0.2−0.9)	0.172	−0.82 (−1.70−0.06)	0.067	−0.75 (−1.61−0.10)	0.083
EED at day 7, cm	0.8 (0.6−0.9)	0.8 (0.6−0.9)	0.1 (0−0.1)	0.116	−0.06 (−0.12−0.01)	0.073	−0.06 (−0.12− −0.01)	**0.026**
PHE peak, mL	25.0 (16.6−37.8)	21.7 (13.8−33.7)	2.1 (−1.8−6.1)	0.287	−0.08 (−0.22−0.07)	0.285	−2.88 (−5.34−−0.42)	**0.022**
Rate of PHE growth from day 1 to day 7, mL/day	1.56 (0.73−2.72)	1.02 (0.40−2.26)	0.4 (0.1−0.9)	**0.026**	−0.46 (−0.93−0.01)	0.054	−0.60 (−1.01− −0.18)	**0.006**
Safety outcomes								
Any AE, N (%)	65 (64.4%)	73 (73.7%)	9.4% (−4.1%−22.4%)	0.152	1.56 (0.85−2.85)	0.153	1.86 (0.97−3.58)	0.062
Any SAE, N (%)	24 (23.8%)	24 (24.2%)	0.5% (−12.0%−13.0%)	0.937	1.03 (0.54−1.97)	0.937	1.05 (0.52−2.15)	0.889

***Table 2*: Outcomes of the participants, modified intention-to-treat population.**

[a] Poor outcome was defined as mRS ranging from 3 to 6.

[b] The analysis was adjusted for age, sex, time from onset to randomisation more than 24 hours, baseline NIHSS, baseline volume of haematoma and PHE, osmotherapy and haemostatic agents during hospitalisation. Intervention effects on outcomes were examined by binary logistic regression or linear regression. Abbreviations: AE, adverse events; CI, confidence interval; EED, oedema extension distance; GCS, Glasgow Coma Scale; IQR, interquartile range; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; OR, odds ratio; PHE, perihaematomal oedema; rPHE, relative perihaematomal oedema; SAE, serious adverse event.

	Control group (n = 101)	Glibenclamide group (n = 99)	*P* value
Any AE, n/N (%)	65 (64.4%)	73 (73.7%)	0.152
Heart disease, n/N (%)	17 (16.8%)	10 (10.1%)	0.164
Pneumonia, n/N (%)	26 (25.7%)	26 (26.3%)	0.933
Liver disease, n/N (%)	4 (4.0%)	3 (3.0%)	1.000
Renal disease, n/N (%)	4 (4.0%)	0 (0.0%)	0.121
Electrolyte disturbances, n/N (%)	11 (10.9%)	15 (15.2%)	0.370
Venous thrombosis, n/N (%)	4 (4.0%)	3 (3.0%)	1.000
Urinary infection, n/N (%)	4 (4.0%)	4 (4.0%)	1.000
Hypoproteinaemia and/or anaemia, n/N (%)	5 (5.0%)	5 (5.1%)	1.000
Asymptomatic hypoglycaemia, N (%)	0 (0.0%)	15 (15.2%)	<0.001
Stress ulcer, n/N (%)	1 (1.0%)	0 (0.0%)	1.000
Other AEs, n/N (%)	12 (11.9%)	13 (13.1%)	0.789
Any SAE, n/N (%)	24 (23.8%)	24 (24.2%)	0.937
Heart disease, n/N (%)	3 (3.0%)	2 (2.0%)	1.000
Pneumonia, n/N (%)	14 (13.9%)	7 (7.1%)	0.177
Pulmonary embolism, n/N (%)	0 (0.0%)	1 (1.0%)	0.495
Respiratory failure, n/N (%)	1 (1.0%)	0 (0.0%)	1.000
Encephalitis, n/N (%)	0 (0.0%)	1 (1.0%)	0.495
Symptomatic hypoglycaemia, N (%)	0 (0.0%)	3 (3.0%)	0.119
Death, n/N (%)	2 (2.0%)	2 (2.0%)	1.000
Other SAEs, n/N (%)	12 (11.9%)	10 (11.0%)	0.687

***Table 3*: Adverse events of the participants, modified intention-to-treat population.**
Abbreviations: AEs, adverse events; SAEs, serious adverse events.

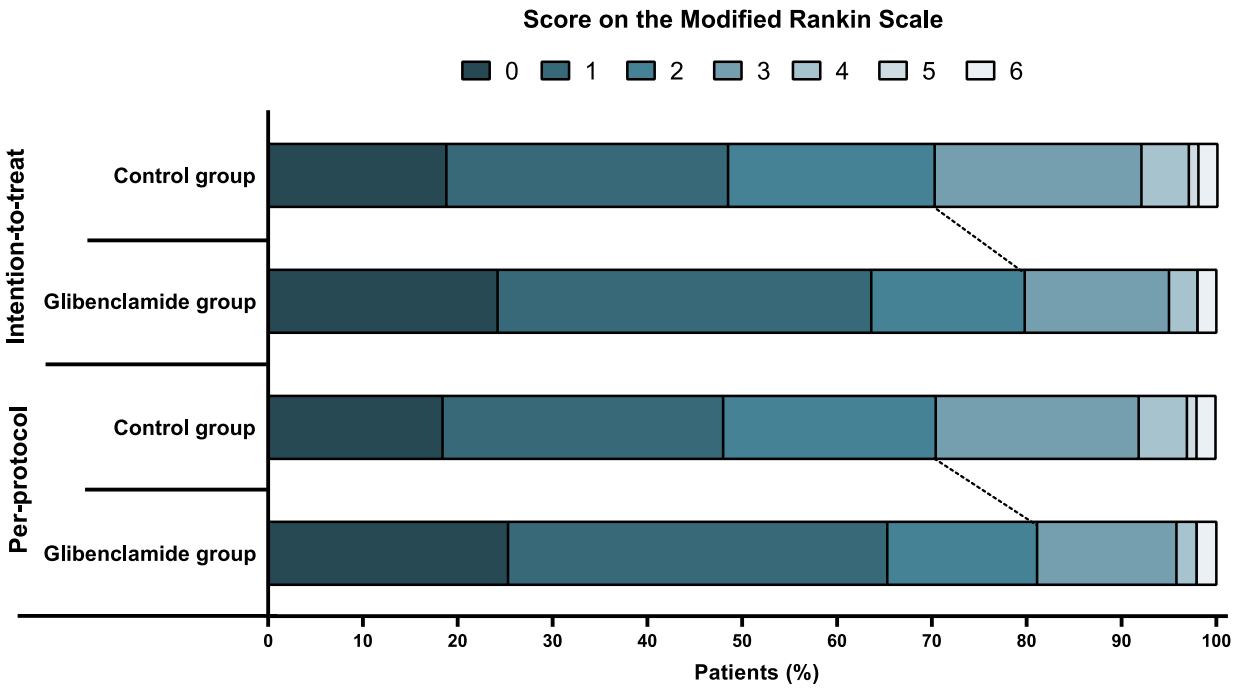

Figure 3. Outcomes at day 90 according to the Scores on mRS.

Distribution of 90-day scores on mRS for mITT population and PP population. 200 patients in the mITT analysis, including 101 patients in control group and 99 patients in glibenclamide group. 193 patients in the PP analysis, including 98 patients in control group and 95 patients in glibenclamide group. Abbreviations: mITT, modified intention-to-treat; mRS, modified Rankin Scale; PP, per-protocol.

mellitus. Results of GAMES-RP study showed that 20% (9/44) of patients in glibenclamide group had asymptomatic hypoglycaemia.[15] In another trial enrolling patients with moderate or severe traumatic brain injuries,[34] a higher dosage of oral glibenclamide (10 mg per day) induced 6.3% (2/32) of patients to discontinue medications because of symptomatic hypoglycaemia. Taken together, the above results suggest that in patients treated with glibenclamide, more cautious blood glucose management is deserved.

There are several limitations in this trial. First, the relatively small haematoma volume in enrolled patients (9.0 [6.0–13.6] ml) led to more favourable clinical outcomes, which might result in an underestimated efficacy of glibenclamide on the percentage of poor 90-day outcome. Patients with larger haematoma volume should be included in future studies. Second, the time frame for enrolment from onset was 72 hours. This may result in oedema already formed in some patients before the initiation of glibenclamide treatment, which may also contribute to the underestimation of the efficacy of glibenclamide on 90-day outcome. Third, the plasma concentration of oral glibenclamide achieved a steady state until 72 h after first dose. Thus, the effect of glibenclamide might be compromised during the early stage after enrolment due to insufficient plasma concentration. Fourth, oral glibenclamide of 1.25 mg, 3 times per day resulted in hypoglycaemia events occurred in 18.2% of participants, which might be a confounder to our results. Therefore, lower dose or more precise titration of glibenclamide may have more application potentials. Last but not least, 200 patients included in this study achieved a reduction in the incidence of poor outcomes by 9.5%, lower than 23.3% used in the sample size calculation. Therefore, a larger sample size is needed in further research to draw a definite conclusion.

In conclusion, glibenclamide did not significantly reduce the risk of poor outcome at day 90. Glibenclamide-related hypoglycaemia events should also be cautioned. Future larger studies are needed to explore the benefits of glibenclamide with more reasonable medication regimen in acute ICH.

Contributors

WJ conceived and designed the study. WJ and FY provided the main administrative, technical, and material support. JZ and FY were the trial managers, contributing to the promotion of the study, the training of personnel, and acquisition and interpretation of data. DeL, XYa, LY, KW, JW, XFW, DoL, BZ, BL, JG, WF, FF, XG, JQ, JL, XYu, QL, JC, XCW, YL, DW were the regional principal investigators who contributed to study design, technical and material support, enrolment of patients, data collection, and integrity of the data at each site. All of the authors had access to all the data in the study. WJ, JZ, FY and LS verified the data. CS, LW and LS gave support of statistical analysis and interpretation of the data. JZ, FY, CS, and WJ drafted the manuscript with input from all the authors and with no external writing assistance. All authors have approved the final version of the manuscript to be released. All authors have consented to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data sharing statement

Data will be available for non-commercial purpose and after approval of a study proposal by the executive committee 12 months after publication. Please email the corresponding authors for more information.

Declaration of interests

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.eclinm.2022.101666.

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