Health and Quality of Life Outcomes

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Effect of ginkgo diterpene lactone meglumine on the quality of life in patients with acute ischemic stroke

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Abstract

Objective Ginkgo diterpene lactone meglumine (GDLM) could improve the functional outcome after acute ischemic stroke (AIS). This study aimed to investigate the efficacy of GDLM on the quality of life in patients with AIS in China.

Methods This is a post hoc analysis of Efficacy and Safety of Ginkgo Diterpene Lactone Meglumine in Acute Ischemic Stroke trial. The quality of life was measured using the EuroQoL questionnaire, including EQ-5D and EQ visual analogue scale (EQ-VAS). The primary outcomes were changes in EQ-5D and EQ-VAS from baseline to day 14 and day 90 after randomization.

Results A total of 3219 patients with completed data on outcomes were enrolled, with median age of 63 years (interquartile range, 55–70) and 2,067 (64.2%) men. GDLM was associated with a significant decrease in scores of ED-5Q components (from 0 [no problem] to 3[extreme problem]), the mean difference between GDLM and placebo group was -0.14 for mobility, -0.11 for usual activities and self-care, -0.09 for pain/discomfort, and -0.34 for anxiety/depression on day 14, respectively. Similar results were observed on day 90. Additionally, there was statistically significant difference of changes in EQ-VAS between the GDLM group and the placebo group from baseline to day 14 (mean difference, 1.70; 95% confidence interval [CI], 0.78–2.62; $P=0.0003$) and to day 90 after randomization (mean difference, 3.29; 95% CI, 2.37–4.22; $P<0.001$).

Conclusions In this analysis of Chinese patients with AIS, GDLM could improve the 14-day and 90-day quality of life compared with the placebo.

Trial registration URL: https://www.clinicaltrials.gov. Unique identifier: NCT02526225. Registration Date: 2016–02-01.

Keywords Acute ischemic stroke, Ginkgo diterpene lactone meglumine, Neuroprotective drugs, Quality of life

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Introduction

Health-related quality of life is a comprehensive measurement of physical, social, and mental function and has been proved to be useful in estimating the impact of diseases and treatments from the perspective of the patients [1, 2]. Stroke survivors have impaired or decreased quality of life on long-term basis even among those who have no post-stroke disability [3, 4]. It is estimated that nearly one quarter of ischemic stroke survivors have a poor or very poor quality of life 2 years after the stroke [5]. Quality of life after stroke is of vital concern for survivors, so exploring effective interventions is necessary to help stroke survivors.

Recently, brain cytoprotection, as proposed by STAIR (Stroke Treatment Academic Industry Roundtable), has the capability of reducing ischemic brain injury by antagonizing detrimental molecular events in all brain components [6, 7]. The potential therapeutic effects of brain cytoprotection have been proven in patients with acute ischemic stroke (AIS) [8–13]. As one of the brain cytoprotections, ginkgo diterpene lactone meglumine (GDLM), which is made of extracts from ginkgo biloba L, composing of active ingredient of ginkgolides A, B, and K and some other contents, has been widely used in the treatment of AIS in China [14–16]. The active ingredient in GDLM has been shown to have a variety of neuroprotective and reparative effects that can help maintain the blood–brain barrier, reduce brain edema, improve energy metabolism, help with antioxidation, anti-inflammation, and anti-apoptosis, and promote angiogenesis, which may be benefit in the recovery of AIS [15, 17–19]. Data from our previous randomized controlled trial has found that GDLM could improve the proportion of patients achieving good clinical outcomes at 90 days compared with placebo among patients with AIS [20]. However, whether GDLM could improve the quality of life in patients with AIS remains unclear.

Therefore, using data from the Efficacy and Safety of Ginkgo Diterpene Lactone Meglumine in Acute Ischemic Stroke trial [20], this post hoc analysis was aimed to investigate the efficacy of GDLM on quality of life in patients with AIS.

Study design

This study was a post hoc analysis of a multicenter, randomized, double-blinded, placebo-controlled, parallel group trial (NCT02526225, Registration Date: 2016–02-01), which was primarily designed to explore the efficacy and safety of GDLM in patients with AIS [20]. Patients were randomized if they (1) were aged 18–80 years, (2) had a clinical diagnosed AIS symptom within 48 h, (3) had a modified Rankin Scale (mRS) score ≤ 1 prior to onset, (4) had a National Institutes of Health Stroke Scale (NIHSS) score between 4 and 24, had a total score of upper and lower limbs on motor deficits ≥ 2, and (5) signed informed consent. Among 3452 randomized patients from 100 centers in China, we further excluded 233 patients who had missing data on EuroQol five-dimension scale (EQ-5D) at baseline, day 14, or day 90, leaving 3,219 patients in the analysis (Fig. 1). The trial design is in compliance with the Declaration of Helsinki and was approved by the ethics committee at Beijing Tiantan Hospital and at each participating site. Written informed consent for participation in the trial was provided by the patients or their legal representative.

Randomization and blinding

Within 48 h after symptom onset, eligible patients were randomly assigned in a 1:1 ratio to receive GDLM or placebo, according to the randomization number stimulated

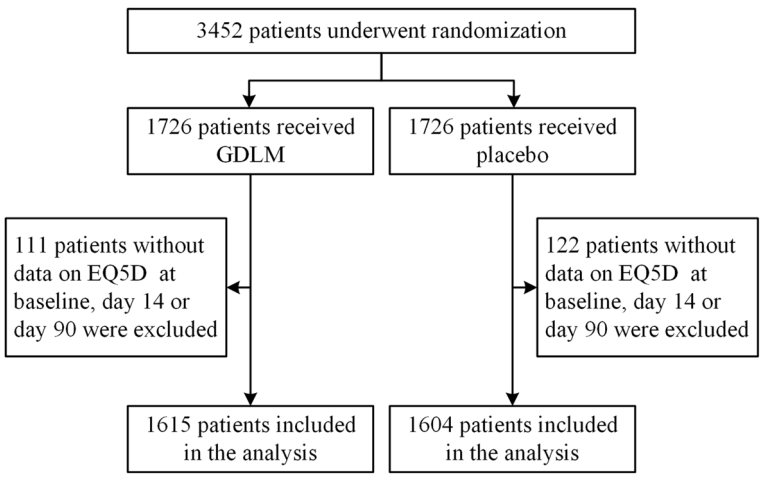

Fig. 1 The flowchart of the study. Abbreviations: EQ5D, EuroQol five dimension scale; GDLM, Ginkgo Diterpene Lactone Meglumine

centrally by an independent statistician. The two forms of drugs were visually identical and cannot be distinguishable in appearance. Both researchers and patients were blinded to the treatment.

Treatment

Patients in the GDLM group received GDLM injection 5 ml (GDLM 25 mg) once daily via intravenous infusion for 14 consecutive days. Patients in the placebo group received GDLM mimic injection (physiological saline) 5 ml once daily via intravenous infusion for 14 consecutive days. Both the GDLM and placebo were diluted in 250 mL of sterile 0.9% sodium chloride injection. Treatment was discontinued when the patients were discharged prior to 14 days. All the patients were followed up to day 90 after the randomization.

Outcomes

The primary outcome was changes in health-related quality of life from baseline to day 14 and day 90 after randomization. The health-related quality of life was assessed using the EuroQoL questionnaire, which consists of two parts: EQ-5D and EQ visual analogue scale (EQ-VAS). EQ-5D comprises of the following five dimensions: mobility, usual activities, self-care, pain/discomfort, and anxiety/ depression. Each dimension has three levels, no problems (1), some problems (2), and extreme problems (3) [21–23]. The EQ-VAS was carried out by patient as an assessment of self-well-being in the vertical and visual analogue scales. A value of 100 on this scale indicates a perfect score for health but a score of 0 means death. A single utility score can be calculated using the population-based preference weights for each dimension of EQ-5D [21–23]. We used the Chinese preference weights developed by Liu et al. [23] The EuroQoL scale was also completed by investigators through face-to-face interview. All investigators were trained and certified based on a shared standardized interview protocol. For those patients with dysarthria or disability caused by severe stroke, EuroQoL was completed by a proxy.

Statistical analysis

Participants were analyzed according to the treatment to which they were randomized using an intention-to-treat principal. Baseline data were expressed as mean with standard deviation or median with interquartile range (IQR) for categorical variables according to the distribution, and as frequency with proportion for categorical variables. Differences between treatment groups of changes in EQ-5D and EQ-VAS were be calculated as mean differences with 95% confidence intervals (CIs) by using a generalized linear model, with adjustment for study centers. The proportions of patients with no problem on EQ-5D and increased EQ-VAS were assessed with the use of a logistic regression, and odds ratios (ORs) and 95% CIs were reported. Additionally, the treatment effects on the primary outcomes were analyzed among several prespecified subgroups (age, sex, previous stroke, hypertension, diabetes mellitus, time from onset to treatment, and NIHSS). All the tests were 2 sided, and $P<0.05$ was considered statistically significant. Statistical analyses were performed with use of SAS software, version 9.4 (SAS Institute).

Results

Baseline characteristics

Among 3,452 patients randomized, 111 patients in the GDLM group and 122 patients in the placebo group had missing data on EuroQoL measurement at baseline, day 14, or day 90 were excluded, leaving 3,219 patients in the intention-to-treat analysis. A comparison in baseline characteristics between excluded and included patients was presented in Table S1. Most characteristics were well-balanced, except that excluded patients had a relatively lower prevalence of hypertension.

The median age of the enrolled patients was 63 years (IQR,55–70), 2,067 (64.2%) were men. The median baseline NIHSS score was 7 points (IQR, 6–9), median ESVAS was 52 (IQR, 40–63), median values for mobility, usual activities, self-care, pain/discomfort, and anxiety/depression were both 2 points. The characteristics of the patients between the two treatment groups at baseline were well balanced (Table 1).

Outcomes of changes in EQ-5D

The proportion of patients with no problem in mobility (OR, 1.58; 95% CI, 1.37–1.83), usual activities (OR, 1.41; 95% CI, 1.22–1.65), self-care (OR, 1.41; 95% CI, 1.21–1.64), pain/discomfort (OR, 1.48; 95% CI, 1.27–1.72), and anxiety/depression (OR, 1.42; 95% CI, 1.22–1.65) was higher in the GDLM group than that the placebo group at day 14 (Table 2).

In terms of changes in the five dimensions of EQ-5D, the results showed a significant difference in mobility (mean difference, -0.14; 95% CI, -0.17 to -0.10; $P<0.0001$), usual activities (mean difference, -0.11; 95% CI, -0.14 to -0.07; $P<0.0001$), self-care (mean difference, -0.11; 95% CI, -0.14 to -0.07; $P<0.0001$), pain/discomfort (mean difference, -0.09; 95% CI, -0.12 to -0.06; $P<0.0001$), and anxiety/depression (mean difference,

Table 1 Baseline Characteristics

Characteristics	GDLM group (*N* = 1615)	Placebo group (*N* = 1604)	*P* value
Age, years, median (IQR)	63(55–71)	63(54–70)	0.2850
Age categories			
< 65	869 (53.81)	892 (55.61)	0.3042
≥ 65	746 (46.19)	712 (44.39)	
Sex, n (%)			
Female	601 (37.21)	551 (34.35)	0.0903
Male	1014 (62.79)	1053 (65.65)	
Ethnics, n (%)			
Han Chinese ethnic group	1594 (98.70)	1584 (98.75)	0.8925
Non-Han Chinese ethnic group	21 (1.30)	20 (1.25)	
Body mass index, kg/m^2, median (IQR)	23.66(21.78–25.56)	23.81(21.97–25.71)	0.2721
Systolic blood pressure, mmHg, median (IQR)	146(132–160)	144(130–160)	0.0413
Diastolic blood pressure, mmHg, median (IQR)	86(80–96)	86(80–94)	0.1516
Medical history, n (%)			
Previous stroke	371 (22.97)	353 (22.01)	0.5122
Hypertension	998 (61.80)	993 (61.91)	0.9478
Diabetes mellitus	371 (22.97)	351 (21.88)	0.4588
Time from onset of stroke to treatment, hr, median (IQR)	24(10–31)	24(10–31)	0.6509
Time from onset of stroke to treatment categories, hr			
< 24	683 (42.29)	695 (43.33)	0.5517
≥ 24	932 (57.71)	909 (56.67)	
NIHSS score, median (IQR)	7(6–9)	7(6–9)	0.6389
NIHSS score categories, n (%)			
≤ 7	834 (51.64)	803 (50.06)	0.3704
> 7	781 (48.36)	801 (49.94)	
EQ-VAS, median (IQR)	51(40–64)	52(40–63)	0.8404
EQ-5D-3L, median (IQR)			
Mobility	2(2–2)	2(2–2)	0.5839
Usual activities	2(2–2)	2(2–2)	0.4488
Self-care	2(2–2)	2(2–2)	0.3960
Pain/discomfort	2(1–2)	2(1–2)	0.8823
Anxiety/depression	2(1–2)	2(1–2)	0.3215

Abbreviations: *GDLM* Ginkgo diterpene lactone meglumine, *IQR* interquartile range, *EQ-VAS* European Quality of Life Visual Analogue Scale, *EQ-5D-3L* 3-level European Quality of Life's 5-dimension, *NIHSS* National Institute of Health stroke scale

-0.08; 95% CI, -0.12 to -0.05; $P < 0.0001$) between the GDLM and placebo group from baseline to day 14 after randomization. The results remained for day 90 after randomization (Table 3).

Outcomes of changes in EQ-VAS

The EQ-VAS scores increased after randomization across treatment groups. There was statistically significant difference for changes in EQ-VAS scores from baseline to day 14 after randomization between the GDLM group (mean, 18.16; 95% CI, 17.51–18.81) and the placebo group (mean, 16.46; 95% CI, 15.81–17.11) (mean difference, 1.70; 95% CI, 0.78–2.62; $P = 0.0003$) (Fig. 2). Similar and stronger results were observed for changes in EQ-VAS scores from baseline to day 90 after randomization (mean difference, 3.29; 95% CI, 2.37–4.22; $P < 0.0001$) (Fig. 2).

Additionally, the proportion of patients with increased EQ-VAS on day 14 in the GDLM group was higher than that in the placebo group (1432 [88.7%] versus 1381 [86.1%]; OR, 1.26; 95% CI, 1.03–1.56; $P < 0.0001$). Similar and stronger results were observed for changes in EQ-VAS from baseline to day 90 after randomization (1502 [93.0%] versus 1440 [89.8%]; OR,

Table 2 Proportion of patients with no problem on EQ-5D from baseline to day 14 and day 90*

Items	From baseline to Day 14				From baseline to Day 90			
	GDLM group (*N* = 1615)	Placebo group (*N* = 1604)	Odds ratio (95% CI)	*P* value	GDLM group (*N* = 1615)	Placebo group (*N* = 1604)	Odds ratio (95% CI)	*P* value
Mobility	670 (41.5)	496 (30.9)	1.58 (1.37–1.83)	< 0.0001	1046 (64.8)	849 (52.9)	1.63 (1.42–1.88)	0.0190
Usual activities	543 (33.6)	423 (26.4)	1.41 (1.22–1.65)	< 0.0001	891 (55.2)	723 (45.1)	1.50 (1.31–1.72)	< 0.0001
Self-care	542 (33.6)	423 (26.4)	1.41 (1.21–1.64)	< 0.0001	890 (55.1)	722 (45.0)	1.50 (1.31–1.72)	< 0.0001
Pain/discomfort	1199 (74.2)	1060 (66.1)	1.48 (1.27–1.72)	< 0.0001	1377 (85.3)	1237 (77.1)	1.72 (1.43–2.06)	< 0.0001
Anxiety/depression	1189 (73.6)	1063 (66.3)	1.42 (1.22–1.65)	< 0.0001	1386 (85.8)	1235 (77.0)	1.81 (1.51–2.17)	< 0.0001

Abbreviations: *CI* confidence interval, *GDLM* Ginkgo diterpene lactone meglumine, *MoCA* Montreal Cognitive Assessment

The model was adjusted for the corresponding baseline MoCA component and clinical sites

Table 3 Changes in the components of EQ-5D from baseline to day 14 and day 90*

Items	From baseline to Day 14				From baseline to Day 90			
	GDLM group (*N* = 1615)	Placebo group (*N* = 1604)	Mean difference (95% CI)	*P* value	GDLM group (*N* = 1615)	Placebo group (*N* = 1604)	Mean difference (95% CI)	*P* value
Mobility	-0.52 (-0.54–0.49)	-0.38 (-0.40–0.35)	-0.14 (-0.17–0.10)	< 0.0001	-0.78 (-0.80–0.75)	-0.63 (-0.66–0.61)	-0.14 (-0.18–0.11)	< 0.0001
Usual activities	-0.46 (-0.49–0.44)	-0.36 (-0.38–0.33)	-0.11 (-0.14–0.07)	< 0.0001	-0.71 (-0.73–0.68)	-0.58 (-0.61–0.56)	-0.12 (-0.16–0.09)	< 0.0001
Self-care	-0.46 (-0.49–0.44)	-0.36 (-0.38–0.33)	-0.11 (-0.14–0.07)	< 0.0001	-0.71 (-0.73–0.68)	-0.58 (-0.61–0.56)	-0.12 (-0.16–0.09)	< 0.0001
Pain/discomfort	-0.41 (-0.43–0.39)	-0.32 (-0.34–0.30)	-0.09 (-0.12–0.06)	< 0.0001	-0.53 (-0.54–0.51)	-0.44 (-0.46–0.42)	-0.09 (-0.11–0.06)	< 0.0001
Anxiety/depression	-0.43 (-0.45–0.41)	-0.34 (-0.37–0.32)	-0.08 (-0.12–0.05)	< 0.0001	-0.55 (-0.57–0.53)	-0.46 (-0.48–0.44)	-0.10 (-0.12–0.07)	< 0.0001

Abbreviations: *CI* confidence interval, *GDLM* Ginkgo diterpene lactone meglumine, *MoCA* Montreal Cognitive Assessment

The model was adjusted for the corresponding baseline MoCA component and clinical sites

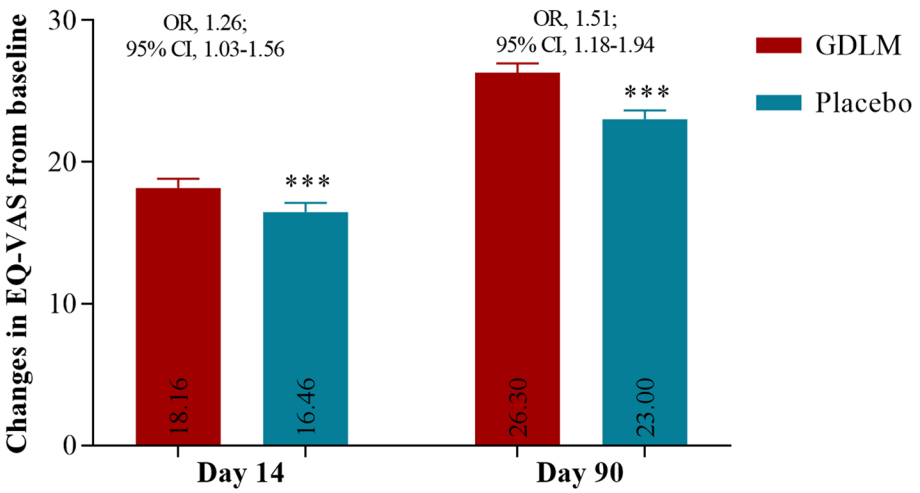

Fig. 2 Changes in EQ-VAS from baseline to day 14 and day 90 after randomization. Abbreviations: CI, confidence interval; EQ-VAS, EuroQol visual analogue scale; OR, odds ratio; GDLM, Ginkgo Diterpene Lactone Meglumine

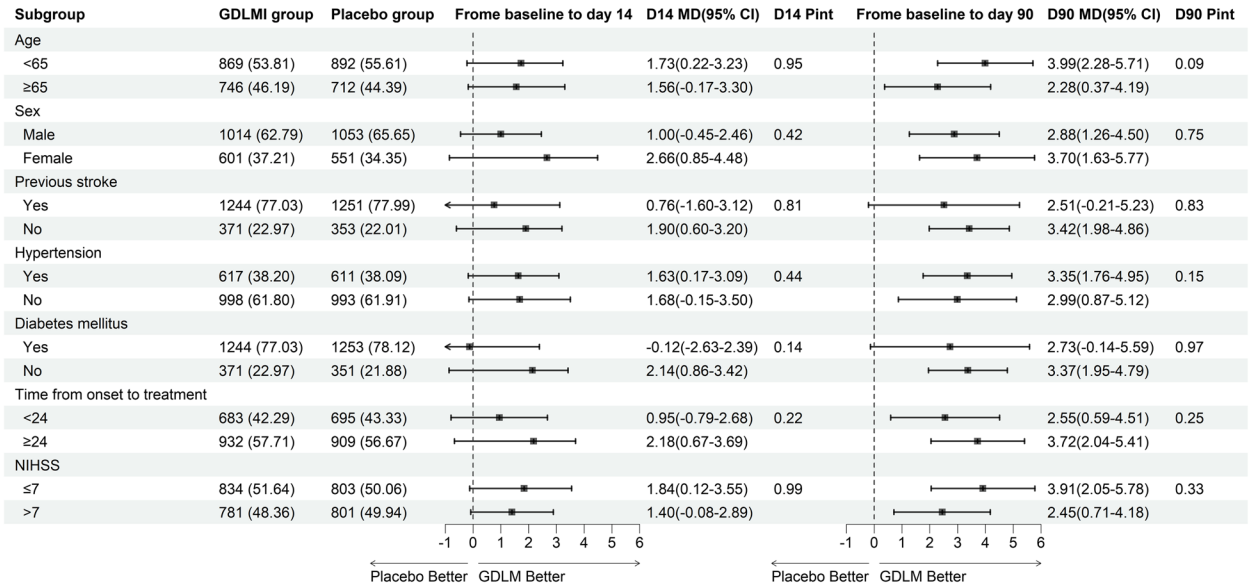

Fig. 3 Subgroup analyses for changes in EQ-VAS from baseline to day 14 and day 90 after randomization. Abbreviations: CI, confidence interval; GDLM, Ginkgo Diterpene Lactone Meglumine; MD, mean difference; NIHSS, National Institutes of Health Stroke Scale

1.51; 95% CI, 1.18–1.94; $P < 0.0001$) (Fig. 2). The results were consistent across subgroups (Fig. 3).

Discussion

This post hoc analysis found that GDLM could improve the quality of life measure by EQ-5D and EQ-VAS from baseline to day 14 and day 90, in comparison with placebo among patients with AIS within 48 h after symptom in China.

Ginkgo diterpene lactone raw material, as a raw material for ginkgo diterpene lactone meglumine injection, is extracted and purified from ginkgo leaf. Ginkgolide-related intravenous preparation is a class of multitargeted neuroprotectants widely used for the treatment of cardiocerebrovascular diseases in China, of which GDLM was approved for clinical use among patients with ischemic stroke in 2012 (national medicine permission number, Z20120024). The efficacy of GDLM in treatment of stroke has been widely investigated. A meta-analysis included 23 clinical trials found that ginkgo terpene lactone preparations have good therapeutic effects in improving clinical efficacy and neurological function on patients with IS [24]. For acute IS, GDLM injection could be used as a complementary therapy to improve the clinical efficacy of recombinant tissue plasminogen activator [24]. Another meta-analysis with 13 clinical trials showed that ginkgo biloba leaf preparations had a good therapeutic effect on patients with ischemic stroke and can improve their hemorheology indices [17]. Consistently, our previous study showed that among patients with AIS, GDLM improved the proportion of patients achieving favorable clinical outcomes on day 90 compared with placebo. However, whether the GDLM could improve the quality of life after stroke remained uninvestigated in these trials.

Indeed, evidence on the effect of GDLM on the quality of life was insufficient. One study showed that patients with acute cerebral infarction who treated with ginkgolide meglumine had a good quality of life than those treated with placebo [25]. Similarly, another study used Barthel index to reflect the quality of life, and the result showed that ginkgo ketone ester dropping pills combined with Xueshuantong on blood lipid could significantly improve quality of life in patients with acute cerebral infarction [26]. Similarly, and extensively, our study found that there was a significant increase in the EQ-VAS, and the proportion of patients with no problem on the five components of EQ-5D components (mobility, self-care, usual activities, pain/discomfort, and anxiety /depression). Our study added novelty evidence regarding the effect of GDLM on the quality of life.

The mechanisms underlying the effect of GDLM on the quality of life remained unclear, several possible reasons were proposed as follows. First, GDLM includes effective ingredients of ginkgolides A, B, and K, which has the advantages of high content of high content of active ingredients and low adverse reactions. It has been reported that the ingredients of ginkgolide B could inactive the NLRP3 inflammasome and reduce the level of

proinflammatory cytokines by promoting autophagy degradation in LPS-stimulated BV2 cells [27]. Additionally, animal models showed that ginkgolide B could significantly reduce the levels of RAGE and Bax protein and then improved neuroinflammation through the flora-gout-brain axis by rescuing the decrease in Lactobacillus abundance and the increase in Bacteroides abundance [28]. Additionally, previous studies showed that GDLM could enhance the expression of IkBa protein and reduce the expression of NF-kB p65 and Bax by inhibiting NF-kB to reduce the production of TNF and IL-1B [29]. GDLM has shown a multi-pathway neuroprotective and reparative effect, including blocking platelet-activating factor activity, anti-inflammatory and antioxidant activities, and regulating excitatory amino acid and brain cell energy metabolism [15, 17–19]. Through the mechanisms, GDLM could improve the prognosis after stroke and improve the quality of life in stroke survivors.

The limitations of our study needed to be addressed. First, it was an exploratory analysis rather than primary aim of the trial, so the results might be susceptible to type I error and need to be further confirmed in an independent trial. Second, our findings may not be externally generalizable to non-Chinese population. This analysis was based on data from a trial performed in Chinese patients. Health quality of life may be affected by patient's ethnicity and culture. Third, our study estimated health-related quality of life at 3 months after the onset of stroke, as done in previous trials [30, 31]. Previous population-based studies showed that health-related quality of life declined annually up to 5 years after stroke [32]. The results of our study require more verification. Finally, other significant factors that may impact health-related quality of life of patients, such as socioeconomic status, possible cognitive impairment, or depression, were not assessed in this trial, which needed to be considered in the future investigations.

Conclusions

This post hoc analysis showed that among Chinese patients with AIS treated within 48 h after onset, GDLM could significantly improve the quality of life at day 14 and day 90 compared with the placebo. The findings in the current study needed to be validated in other populations, especially those with more severe stroke. Our study provided evidence supporting the use of GDLM in the treatment of AIS.

Trial registration

NCT02526225 (https://www.clinicaltrials.gov, Registration Date: 2016–02-01).

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12955-024-02315-1.

Supplementary Material 1.

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Data sharing statement
Data are available to researchers on request for purposes of reproducing the results or replicating the procedure by directly contacting the corresponding author.

Consent to participate
Not applicable.

Authors' contributions
XZ, AW contributed to the study design and conception; XT wrote the manuscript. XT, QX, XX, YZ researched data and contributed to discussion. XT, AW contributed to the discussion and reviewed/edited the manuscript. All authors have read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The trial design is in compliance with the Declaration of Helsinki and was approved by the ethics committee at Beijing Tiantan Hospital and at each participating site.

Competing interests
The authors declare no competing interests.

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