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Original Article

Efficacy and safety of α-lipoic acid combined with prokinetic agents in the treatment of diabetic gastroparesis: a meta-analysis

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Abstract: Objective: Results of previous randomized trials have shown that interventions of Alpha-lipoic acid (ALA) combined with prokinetic agents can significantly reduce the gastric dyskinesia of Diabetic Gastroparesis (DGP) in a wide range of individuals. However, each separate trial has limited power to assess particular outcomes. The aims of this study were mainly to systematically review the effects and safety of ALA combined with prokinetic agents in treating DGP. Methods: PubMed, Cochrane Library, EMBASE, Web of Science, CNKI, CBM, VIP, WanFang, and clinicaltrials.gov were searched. Randomized controlled trials (RCTs) of ALA combined with prokinetic agents (experimental group) and prokinetic agents only (control group) in treating DGP were included. Data were searched from their inception untill February 11th 2019, using Stata 12.0 for Meta-analysis. Results: Thirteen RCTs were finally included with 1064 patients. Meta-analysis results showed that ALA combined with prokinetic agents can significantly improve the efficacy rate ($P<0.001$), regardless of the type of prokinetic agents (domperidone or clebopride or mosapride or itopride) combined with ALA or the length of treatment (<4 weeks or ≥4 weeks). Furthermore, the experimental group was able to significantly improve gastric emptying rate ($P<0.001$), serum motilin and gastrin level ($P<0.001$). No remarkable difference between the experimental group and control group in the incidence of adverse reactions was found ($P=0.868$). Conclusions: ALA combined with prokinetic agents can significantly improve the efficacy rate and gastric emptying rate with few adverse reactions, and reduce serum motilin and gastrin levels in DGP.

Keywords: Alpha-lipoic acid, prokinetic agents, diabetic gastroparesis, meta-analysis

Introduction

Diabetic gastroparesis (DGP) is a chronic gastric dyskinesia and a common chronic complication of diabetes which affects more than 5% of the diabetic patients [1]. It is characterized by delayed gastric emptying without any mechanical obstruction. With the improvement of our living conditions and increased life expectancy of the population, the incidence of diabetes is on the rise, and it is expected to keep rising in the next 20 years; particularly in China where there are more than 200 million diagnosed with prediabetes and diabetes [2]. DGP affects intestinal absorption and the metabolism of hypoglycemic agents and nutrients, and increases glucose variability. The common adverse consequence is a severe hypoglycemic reaction in an unpredicted time period, which can have a series of negative impacts on blood glucose control and the quality of life of the patients [3].

The pathogenesis of DGP has not been fully elucidated yet. The mechanisms that are known include oxidative stress, polyol pathway flux, protein kinase C activation, and advanced glycation end products. All of these can lead to microvascular disease and neurological dysfunction [4]. Currently, there is no specific therapy for the treatment of DGP in clinical practice. Antiemetic drugs and prokinetic agents are commonly used to alleviate the symptoms of DGP, but there are many problems including long-term adverse reactions with these drugs, and high recurrence rate post drug withdrawal.

Alpha-lipoic acid (ALA) is a medium-chain fatty acid [5]. Evidence suggests that ALA can pro-

tect nerve tissue through the following mechanisms: regains glutathione levels, increases blood flow, prevents lipid peroxidation and augments antioxidant enzymes' activity, helps glucose uptake, and improves metabolism in peripheral nerves with nerve conduction velocity [6-8]. Thus, it seems that ALA is an ideal substance for treatment of oxidative neural disorders, i.e. DGP.

For the past few years, a number of randomized controlled trials (RCTs) have been conducted on the effects and safety of ALA combined with prokinetic agents in treating DGP, but the results of these RCTs are not completely consistent, and the sample size of a single study is limited. Therefore, this meta-analysis was conducted to systematically assess the effects and safety of ALA combined with prokinetic agents in the treatment of DGP, with a view to explore new therapeutic directions for DGP.

Materials and methods

Search strategy

Eight databases were searched including PubMed, the Cochrane Library, EMBASE, Web of Science, China National Knowledge Infrastructure (CNKI), VIP Database for Chinese Technical Periodicals, Chinese Biomedical Literature Database (CBM) and WanFang Data from their inception untill February 11th 2019. Searching terms were as follows: (diabet*) AND (gastroparesis OR gastroparalysis OR "gastric rhythm disorder" OR "gastric retention" OR "gastric emptying disorder" OR "delayed gastric emptying" OR DGP) AND ("α-lipoic acid" OR "Alpha-lipoic acid" OR "thioctic Acid" OR "poic acid"). The ClinicalTrials.gov registry was also searched for unpublished trials and the authors were contacted for any additional information if necessary. Relevant references from the included studies were sought to retrieve additional eligible studies. No limits were set on language, publication year or type of publication.

Inclusion and exclusion criteria

Inclusion criteria: 1) RCTs, double or single-blind or open-label. Follow-up time and sample size were not limited. 2) Participants: (1) participants had a diagnosis of diabetes based on the WHO diagnostic criteria in 1999. (2) Participants had one or more GDP symptoms, including early fullness/fullness, loss of appetite, belching, nausea/vomiting, epigastric discomfort/epigastric pain, persisting for more than 2 weeks; (3) X-ray barium meal examination suggested the presence of gastric emptying delays; (4) Endoscopic examination ruled out ulcers, tumors, and other organic lesions; ultrasound examination excluded organic lesions of the liver, gallbladder, spleen, and pancreas. (5) Participants with other systemic diseases that may cause the above symptoms were excluded; (6) Age, gender and other general conditions were not limited. 3) Intervention: on the basis of the control of blood glucose, the experimental group was given ALA combined with prokinetic drugs, and the control group was given prokinetic drugs alone. 4) Outcomes: total efficacy rate, adverse reactions, gastric emptying rate, serum motilin, serum gastrin.

Exclusion criteria: A study that included any of the following: (1) traisl: non-randomized controlled trials (NRCTs), animal experiments, review articles; (2) participants: children or participants with other diseases; (3) interventions: studies involving other interventions; (4) outcomes: outcome measures were not appropriate, relevant data could not be obtained from the original author; (5) repeated published literature.

Literature search and data extraction

Literature search and data extraction were performed by two researchers (J.Y. and Y.G.) independently, and the third researcher (B.P.) was involved in discussions for any disagreements. The following information of eligible articles was extracted to a data extraction form: author, publication year, sample size, intervention, dosage, duration, mean age, mean course of the disease, fasting blood glucose (FBG), and outcomes. If relevant details were insufficiently reported in studies, authors were contacted by email, and the ClinicalTrials.gov register was searched for further information.

Quality assessment

According to the Cochrane collaboration's update tool for assessing the risk of bias (Version 5.1.0, updated March 2011) [9], two

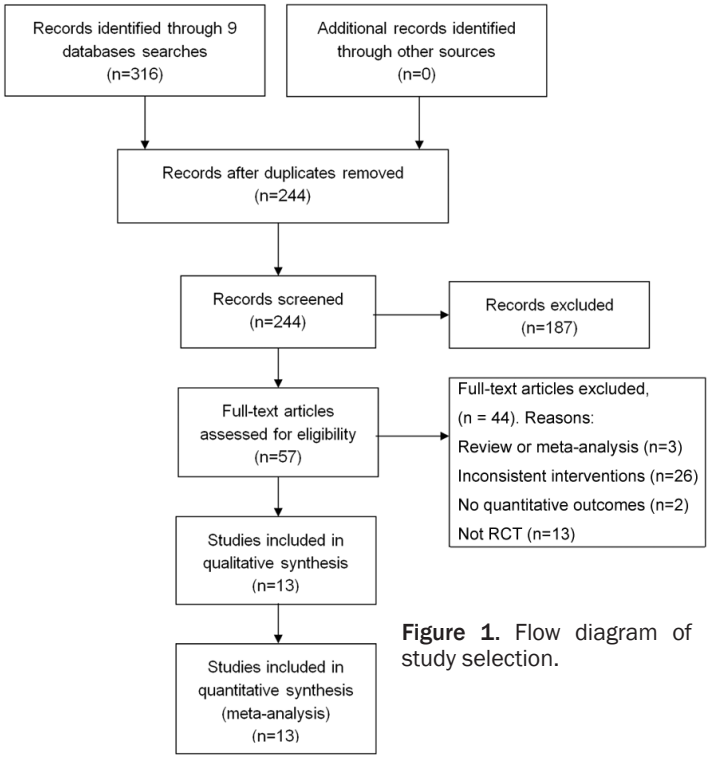

Figure 1. Flow diagram of study selection.

reviewers (J.Y. and Y.G.) assessed the quality of the included studies independently, and the third reviewer (X.S.) was consulted for any disagreements. The risks of bias were classified as high, unclear, or low by assessing the 7 components as random sequence generation, allocation concealment, blinding of outcome assessment, blinding of participants and personnel, incomplete outcome data, selective outcome reporting, and other biases. If necessary, we tried to contact the authors by e-mail for further information.

Statistical analysis

Stata software (Version 12.0; Stata Corp, College Station, TX, USA) was used for statistical analysis. Dichotomous data were expressed as relative risk (RR) with 95% confidence interval (CI), and continuous data as standardized mean difference (SMD) with 95% CI. Heterogeneity was tested by χ^2-based Cochran Q statistic (*P* values <0.10 indicates statistically significant heterogeneity) and I^2 statistic. If I^2<50% and P>0.1, using a fixed-effects model to pool the estimations across studies. If I^2≥50% or P≤0.1, after excluding clinical heterogeneity between studies, the random-effects model was used. We used sensitivity analysis to observe changes in the pooled effect size and heterogeneity between included studies, so as to assess the reliability and stability of the pooled results. Subgroup analyses were carried out according to the factors including the type of prokinetic agents and duration of the included studies. We used a funnel plot and Egger's and Begg's test to judge publication bias, and the trim and fill method was used to correct the funnel asymmetry caused by publication bias. P<0.05 was considered a statistically significant value.

Results

Search results

As displayed in **Figure 1**, in total, we identified 316 citations with 72 duplicates. After preliminary screening of the titles and abstracts, 57 studies were selected for full-text review, and then 44 studies were excluded since 3 of them were reviews or meta-analysis, 13 of them were Not RCTs, 2 studies included research providing no quantitative outcomes, and the rest were those with undesirable interventions. Ultimately, 13 RCTs [10-22] were determined to be used in this meta-analysis.

Study characteristics

Thirteen studies involving 1064 subjects were included in the meta-analysis. The sample size ranged from 50 to 110 participants, duration varied from 2 to 4 weeks, mean age ranged from 47.8 to 68.1 years, mean course of disease varied from 6.3 to 11.8 years, FBG ranged from 6.8 to 9.23 mmol/L (**Table 1**).

Quality assessment

As shown in **Table 2**, randomization was categorized as low risk in eight studies with appropriate use of random sequence generation. One study was categorized as high risk by applying the order of registration. The remaining four studies did not provide details about the method of randomization and were categorized as unclear risk. Allocation concealment

Table 1. Basic characteristics of included studies

First author, year of publication	Group	Sample size	Intervention	dosage	Period of treatment (week)	Mean age (year)	Mean course of the disease (year)	FBG (mmol/L)
Chen, 2015 [10]	Treatment group	25	α-lipoic acid + domperidone	0.45 g qd 10 mg tid	4 w	50.32±2.35	10.85±2.23	7.12±2.11
	Control group	25	domperidone	10 mg tid		51.36±2.47	10.26±2.68	7.23±2.65
Gao, 2015 [11]	Treatment group	30	α-lipoic acid + clebopride	0.6 g qd 0.68 mg bid	4 w	52.70±13.80	-	
	Control group	30	clebopride	0.68 mg bid		52.70±12.63	-	
Jiang, 2018 [12]	Treatment group	46	α-lipoic acid + mosapride	0.6 g qd 5 mg tid	2 w	57.19±6.24	9.64±2.05	9.16±10.98
	Control group	46	mosapride	5 mg tid		58.01±6.31	9.82±2.16	9.23±11.06
Li, 2014 [13]	Treatment group	45	α-lipoic acid + domperidone	24 mg qd 10 mg tid	4 w	68.1±4.2	-	7.55±1.39
	Control group	45	domperidone	10 mg tid		67.0±4.5	-	7.57±1.32
Liang, 2017 [14]	Treatment group	35	α-lipoic acid + mosapride	0.6 g qd 5 mg tid	2 w	48.2±9.1	11.8±8.5	-
	Control group	35	mosapride	5 mg tid		47.8±8.9	11.5±8.9	-
Liu, 2018 [15]	Treatment group	45	α-lipoic acid + mosapride	0.6 g qd 5 mg tid	2 w	56.34±6.46	-	-
	Control group	45	mosapride	5 mg tid		57.19±5.86	-	-
Luo, 2017 [16]	Treatment group	30	α-lipoic acid + itopride	0.6 g qd 50 mg tid	2 w	56.34±2.61	-	-
	Control group	30	itopride	50 mg tid		57.35±2.42	-	-
Ma, 2015 [17]	Treatment group	60	α-lipoic acid + itopride	0.6 g qd 5 mg tid	2 w	56.7±6.8	6.8±1.6	6.8±1.6
	Control group	50	itopride	5 mg tid		58.4±7.5	6.3±2.2	6.9±0.8
Pan, 2015 [18]	Treatment group	54	α-lipoic acid + mosapride	0.6 g qd 5 mg tid	2 w	56.3±15.2	7.8±4.1	7.6±0.6
	Control group	54	mosapride	5 mg tid		58.1±14.6	8.2±5.0	7.8±0.8
Tang, 2016 [19]	Treatment group	47	α-lipoic acid + mosapride	0.6 g qd 5 mg tid	2 w	49.85±10.37	6.57±1.28	7.39±0.96
	Control group	47	mosapride	5 mg tid		48.33±10.72	6.38±1.35	7.25±0.92
Wu, 2014 [20]	Treatment group	40	α-lipoic acid + mosapride	0.6 g qd 5 mg tid	2 w	57.8±4.5	-	-
	Control group	40	mosapride	5 mg tid		59.5±6.4	-	-
Yang, 2012 [21]	Treatment group	41	α-lipoic acid + domperidone	0.6 g qd 10 mg tid	4 w	19~72	-	-
	Control group	39	domperidone	10 mg tid		21~73	-	-
Zhao, 2015 [22]	Treatment group	43	α-lipoic acid + mosapride	0.6 g qd 5 mg tid	2 w	-	-	-
	Control group	43	mosapride	5 mg tid		-	-	-

Table 2. The risk of bias of randomized trials

Criteria study	Random sequence generation	Allocation concealment	Blinding of outcome assessment	Blinding of participants and personnel	Incomplete outcome data	Selective outcome reporting	Other bias
Chen (2015) [10]	L	U	U	H	L	U	L
Gao (2015) [11]	U	U	U	H	L	U	U
Jiang (2018) [12]	L	U	U	H	L	U	L
Li (2014) [13]	H	U	U	H	L	U	U
Liang (2017) [14]	L	U	U	H	L	U	L
Liu (2018) [15]	U	U	U	H	L	U	U
Luo (2017) [16]	U	U	U	H	L	U	U
Ma (2015) [17]	L	U	U	H	L	U	L
Pan (2015) [18]	L	U	U	H	L	U	L
Tang (2016) [19]	L	U	U	H	L	U	L
Wu (2014) [20]	U	U	U	H	L	U	U
Yang (2012) [21]	L	U	U	H	L	U	L
Zhao (2015) [22]	L	U	U	H	L	U	L

Legends: H: high risk; L: low risk; U: unclear risk.

was categorized as unclear risk in 13 studies because of the lack of relevant descriptions. Without describing the blinding status of participants and personnel in 13 studies, drugs were administered in different ways in experimental and control groups (ALA iv VS Prokinetics po), blinding was easy to be broken, so all studies were categorized as high risk. Blinding of outcome assessment was categorized as unclear risk in 13 studies because of the lack of relevant descriptions. Incomplete outcome data were categorized as low risk in 13 studies with no loss to follow-up. As for selective reporting, 13 studies were classified as unclear risk. Lastly, 8 studies were judged as low risk and the remaining 4 studies were estimated as unclear in other bias.

Pooled analysis

The efficacy rate of ALA combined with prokinetics in the treatment of DGP: Thirteen RCTs reported results on efficacy rate, and no heterogeneity was observed (P=0.517; I^2=0%), pooled results with the fixed-effects model showed that the efficacy rate was significantly improved in the experimental group over that in the control group (RR=1.27, 95% CI: 1.20-1.35, P<0.001) (**Figure 2**). Sensitivity analysis was performed by eliminating the 13 included studies one by one, and the results indicated that no significant change was seen in the final combined effect size and heterogeneity, indicating that the result was robust. Results of subgroup analyses with respect to types of prokinetic agents were shown in **Figure 2**: subgroup one included 3 studies with the interventions of the experimental group (ALA combined with domperidone) versus control group (domperidone alone), pooled results showed that the efficacy rate was markedly higher in the experimental group (RR=1.26, 95% CI: 1.10-1.45, P=0.001); subgroup two only included 1 study with the interventions of the experimental group (ALA combined with clebopride) versus control group (clebopride alone), results also showed that efficacy rate of the experimental group was higher (RR=2.08, 95% CI: 1.36-3.18, P=0.001); subgroup three included 7 studies with the interventions of the experimental group (ALA combined with mosapride) versus control group (mosapride alone), results showed that the efficacy rate was remarkably higher in the experimental group (RR=1.25, 95% CI: 1.16-1.34, P<0.001); subgroup four included 2 studies with the interventions of experimental group (ALA combined with itopride) versus control group (itopride alone), results indicated that efficacy rate of the experimental group was observably higher (RR=1.23, 95% CI: 1.07-1.41, P<0.001). A further subgroup analysis was performed based on the therapeutic duration (<4 weeks or ≥4 weeks). The results demonstrated that the efficacy rate was significantly higher in the experimental group in both the long-duration subgroup (RR=1.38, 95% CI: 1.20-1.58, P<0.001) and short duration sub-

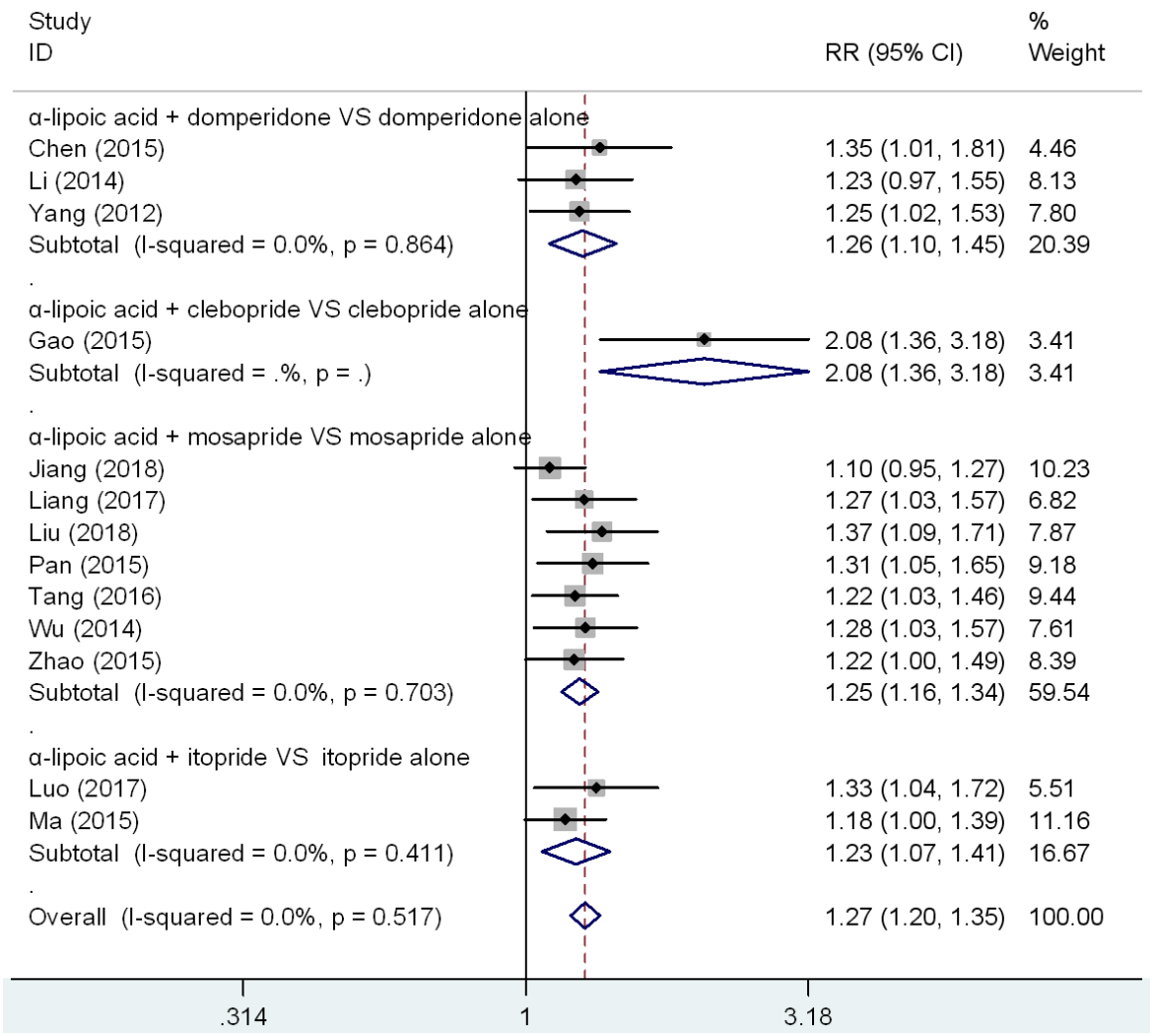

Figure 2. Forest figure and subgroup analysis (the type of prokinetic agents) of the efficacy rate of α-lipoic acid combined with prokinetics on DGP.

group (RR=1.24, 95% CI: 1.16-1.33, P<0.001) (**Figure 3**).

Adverse effects rate of ALA combined with prokinetics in the treatment of DGP: Pooled results from 7 studies did not demonstrate any large difference in the adverse effects rate between the experimental and control groups (OR=1.06, 95% CI: 0.55-2.05, P=0.868) with small heterogeneity (P=0.523; I^2=0%) (**Figure 4**).

Gastric emptying rate of ALA combined with prokinetics in the treatment of DGP: Eight RCTs reported results on gastric emptying rate, and clear heterogeneity was observed (P<0.001; I^2=82.7%). Pooled results with the random-effects model showed that ALA combined with prokinetics can significantly improve gastric emptying rate compared to the control group (SMD=1.74, 95% CI: 1.32-2.17, P<0.001) (**Table 3**).

Effect of ALA combined with prokinetics on motilin in the treatment of DGP: Eight RCTs reported results on motilin, and clear heterogeneity was observed (P<0.001; I^2=97.2%). Pooled results with the random-effects model showed that ALA combined with prokinetics can significantly decrease serum motilin (SMD=-3.00, 95% CI: -4.26--1.74, P<0.001) (**Table 3**).

Effect of ALA combined with prokinetics on gastrin in the treatment of DGP: Five RCTs reported results on gastrin, and no heterogeneity was observed (P=0.681; I^2=0%). Pooled

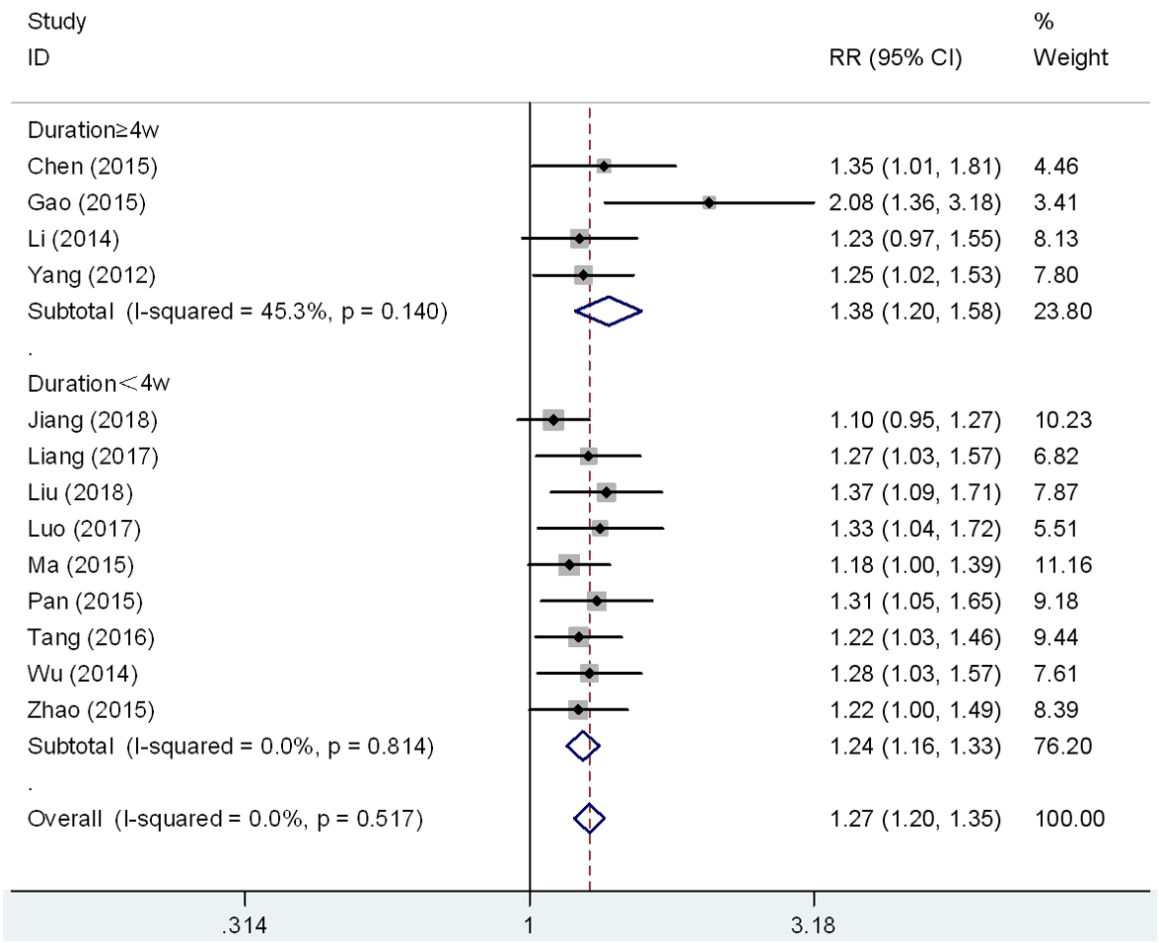

Figure 3. Results of subgroup analysis with respect to the duration of the efficacy rate of α-lipoic acid combined with prokinetics on DGP.

results with the fixed-effects model showed that ALA combined with prokinetics can significantly decrease serum gastrin (SMD=-0.85, 95% CI: -1.04--0.66, P<0.001) (**Table 3**).

Publication bias

Publication bias analysis was conducted on the results of the efficacy rate. The funnel plot was not completely symmetrical, the partial scatter points were outside the confidence limit, and the *p* values of both Begg's and Egger's test were less than 0.001. Therefore, the results indicated that publication bias existed. Whereas after the trim and fill method was applied to estimate the cause of asymmetry and correct it, results showed that there were 5 studies added to minimize the publication bias. After imputation adjustment, the pooled results remained statistically significant (RR=1.20, 95% CI: 1.14-1.26) (**Figure 5**).

Discussion

Pooled results of this meta-analysis indicated that ALA combined with prokinetic agents was effective in increasing the total efficacy rate and gastric emptying rate, and decreasing serum motilin and gastrin with few adverse reactions. Subgroup analyses results showed that the increase of total efficacy rate was independent of the type of prokinetic agents (domperidone or clebopride or mosapride or itopride) and the length of treatment (<4 w or ≥4 w).

Though the exact pathogenesis of DGP is not fully elucidated, lots of contributing factors have been put forward, including vagal dysfunction, hyperglycemia, absence of neural nitric oxide synthase expression in the myenteric plexus, disturbances in the interstitial cells of Cajal (ICC) network, dysfunction of underlying

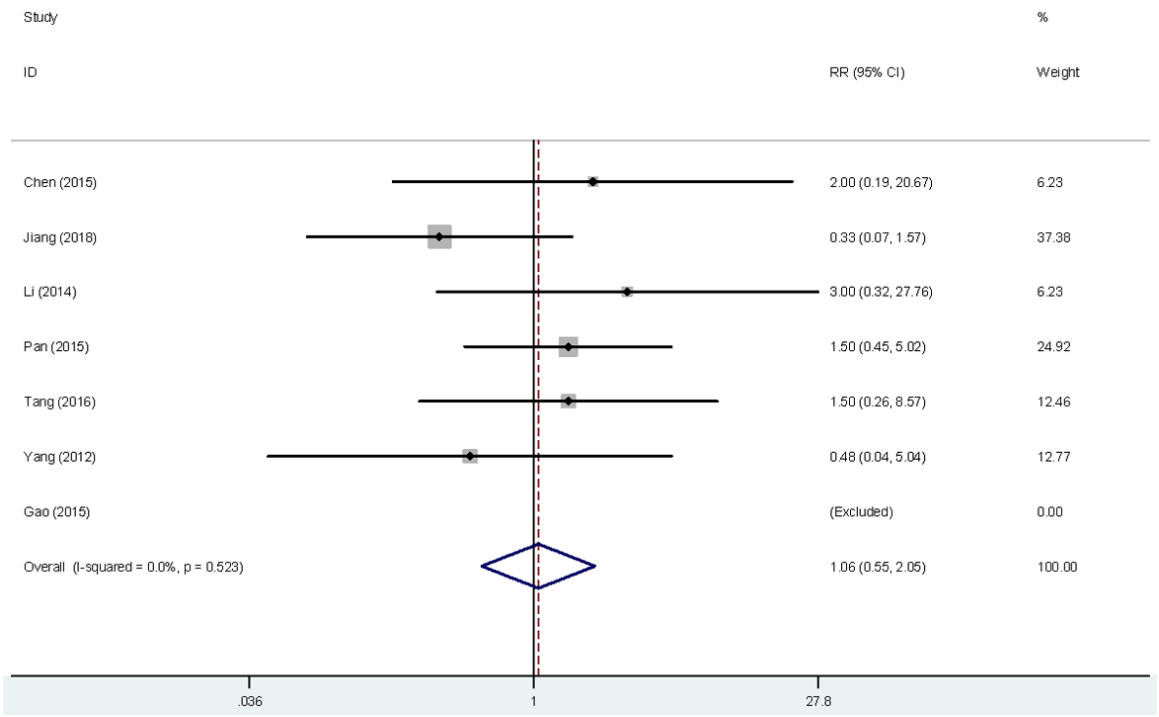

Figure 4. Forest plot of adverse reactions of α-lipoic acid combined with prokinetics on DGP.

Table 3. Summary statistics of secondary results

Secondary outcomes	Model for meta-analysis	No. of trials	No. of participants	Effect size (95% CI)	*P*-value	I^2 (%)	Q-statistics (P)
GER	RE	8	696	1.74 [1.32, 2.17]	P=0.000	82.7	P=0.000
MTL	RE	8	696	-3.00 [-4.26, -1.74]	P=0.000	97.2	P=0.000
GAS	FE	5	452	-0.85 [-1.04, -0.66]	P=0.000	0.0	P=0.681

Legends: GER: gastric emptying rate; MTL: motilin; GAS: gastrin; RE: random-effects model; FE: Fixed-effects model.

smooth muscle, helicobacter pylori infection and oxidative stress [23-25]. Oxidative stress is a factor for potential loss of autonomic nervous function, for it is known that diabetes leads to a high oxidative stress states that multiple tissues respond to. Oxidative stress can be caused by increased reactive oxygen species and loss of antioxidant protection such as heme-oxygenase-1 (HO-1), while increased oxidative stress due to loss of macrophage HO-1 was associated with loss of ICC and caused delayed gastric emptying [26]. Research indicates that gastric emptying is slower during hyperglycemia when comparing euglycemia and hypoglycemia. The blood glucose concentration may influence the response to prokinetic drugs [27]. Furthermore, studies have shown [17, 28] that reactive oxygen species and lipid peroxidation can not only cause damage to the enteric nervous system and vascular endothelial cells but also induce apoptosis of ICC and gastrointestinal smooth muscle cells, leading to gastric motility disorders and delayed gastric emptying in DGP patients.

Currently, there is no specific treatment for DGP in clinical practice. Considering the adverse effects of long-term drug use and recurrence after drug withdrawal, the commonly used prokinetic drugs have some limitations. DGP's occurrence and development are closely related to oxidative stress. This study systematically evaluated the effects and safety of ALA combined with prokinetic agents in treating DGP. Pooled results indicated that ALA combined with prokinetic agents can improve the total efficacy rate markedly with few adverse reactions.

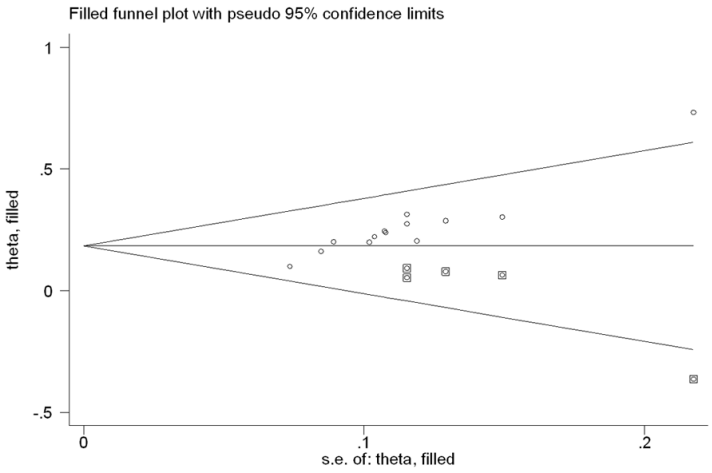

Figure 5. Begg's funnel plot of publication bias with respect to the efficacy rate of α-lipoic acid combined with prokinetics on DGP.

Possible mechanisms of ALA in the treatment of diabetic gastroparesis can be listed as follows: (1) ALA enters the body and is diffused into the cells, where it is involved in the scavenging process of oxygen free radicals, which can protect the function of islet cells, regulate blood glucose and improve the high-glucose environment in the body. (2) ALA's antioxidant effect can effectively protect the vascular endothelium, improve blood circulation, increase gastrointestinal blood flow, and improve the effect of prokinetic drugs on gastric peristalsis. (3) ALA can protect the autonomic nervous system, accelerate nerve conduction speed and effectively reduce diabetic neuropathy. (4) The antioxidant effects of ALA can reduce the damage of ICC and digestive tract smooth muscle cells under oxidative stress, promote gastric peristalsis and accelerate gastric emptying. (5) Otherwise, ALA can also promote the regeneration of other endogenous antioxidants, such as vitamin E and vitamin C, and further produce a synergistic antioxidant effect.

The limitations of this study are as follows. First, the quality of the included literature could be better (none of the studies described allocation and concealment; none of the studies were registered on clinicaltrials.gov, and their original trial protocols were not known, etc.). Secondly, the types of prokinetic agents, duration and baseline blood glucose were not completely consistent among these studies, which may be a source of heterogeneity of some of the outcomes. Thirdly, the treatment course was short in these studies and lacked long-term efficacy of drug observation. For all of these reasons listed above, the results derived from this meta-analysis should be interpreted with these considerations in mind.

Conclusion

The pooled results of this meta-analysis indicated that ALA combined with prokinetic agents can significantly improve the efficacy rate and gastric emptying rate, reduce serum motilin and gastrin levels, while having few adverse reactions. The above conclusions need to be further verified by more high-quality RCTs.

Disclosure of conflict of interest

None.

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