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Review Article

Efficacy and Safety of Mecobalamin Combined with Prokinetic Agents in the Treatment of Diabetic Gastroparesis: A Meta-Analysis

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Abstract

Background: The aim of the present study was to systematically review the efficacy and safety of mecobalamin combined with prokinetic agents in diabetic gastroparesis (DGP).

Methods: A variety of databases were searched from inception to Nov 2, 2018. RCTs of mecobalamin combined with prokinetic agents group (experimental group) versus prokinetic agents only group (control group) in DGP were included. RevMan 5.3 and Stata 12.0 were used to perform the meta-analysis. Finally, 24 RCTs with 1,878 patients were included.

Results: The total efficacy rate was significantly higher in the experimental group (mecobalamin combined with prokinetic drugs) compared with the control group (prokinetic drugs alone) (P<0.001), and the improvement was observed regardless of the administration route. Furthermore, the treatment group exhibited a significantly improved gastric emption rate (P<0.001), motilin (P<0.001) and recurrence rate (P<0.001), and there was no statistical difference in the incidence of adverse reactions between two groups (P=0.49).

Conclusion: Mecobalamin combined with prokinetic agents can significantly improve total efficacy rate and gastric emptying rate, decrease serum motilin and the recurrence rate without increasing adverse reactions in DGP. Thus, mecobalamin may can be used as a new therapeutic option for DGP.

Keywords: Mecobalamin; Prokinetic agents; Diabetic gastroparesis; Meta-analysis

Introduction

Diabetic gastroparesis (DGP) is a chronic gastric dyskinesia and is characterized by delayed gastric emptying without any mechanical obstruction. Furthermore, DGP is also a common chronic complication of diabetes and may be present in up to 5% of diabetic patients (1). With the growth and aging of the population, the prevalence of diabetes and DGP continues to rise. DGP often impairs quality of life, and can also affect the absorption and metabolism of oral hypoglycemic agents and nutrients, increase the glucose variability, and cause serious problems with glycemic control. A common adverse consequence is a severe hypoglycemic reaction in an unpredicted period (2).

Unfortunately, there are few, if any, efficient treatments for this disease. Antiemetic drugs and prokinetic agents are commonly used to alleviate

the symptoms of DGP; however, long-term use is limited due to the side effects, and the recurrence rate is high following drug withdrawal. For example, metoclopramide can cause certain adverse reactions, such as depression and lethargy. While domperidone and cisapride are prone to relapse after drug discontinuation. Hence, there is a need for more effective and safer drugs for DGP. It is understood that autonomic neuropathy plays an important role in the pathogenesis of DGP. Thus, the nutrition of the degenerative gastrointestinal autonomic nerve may be a new therapeutic direction for DGP.

Mecobalamin is a common drug and for the past few years, a number of randomized controlled trials (RCTs) have been conducted on the efficacy and safety of mecobalamin combined with prokinetic agents in DGP. However, the results of these RCTs are not completely consistent, and the sample size of a single study is limited. Furthermore, a relevant meta-analysis is still lacking to date.

Thus, the aim of the present meta-analysis was to identify the efficacy and safety of mecobalamin combined with prokinetic agents in treating DGP, with a view to investigating a new therapeutic option for DGP.

Methods

The current systematic review and meta-analysis was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.

Literature search

Databases, including PubMed, the Cochrane Library, EMBASE, Web of Science, China National Knowledge Infrastructure, VIP Database for Chinese Technical Periodicals, Chinese Biomedical Literature Database, and WanFang Data, were searched from their inception to Nov 2, 2018. Search terms were as follows: (diabet*) AND (gastroparesis OR gastroparalysis OR retinopathy OR "gastric rhythm disorder" OR "gastric retention" OR "gastric emptying disorder" OR "delayed gastric emptying" OR DGP) AND (cobamides OR methylcobalamin OR mecobalamin OR "methyl vitamin B_{12}" OR cobamamide OR cyanocobalamin). The ClinicalTrials.gov registry was also searched for unpublished trials and the authors were contacted for additional information if necessary. Relevant references from included studies were sought to retrieve additional eligible studies. No limits were set on language, publication year, and type of publication.

Inclusion and exclusion criteria

The inclusion criteria were as follows: 1) RCTs with any follow-up duration and sample size. 2) Participants: participants should have a diagnosis of diabetes based on the WHO diagnostic criteria in 1999; participants had one or more DGP symptoms, including anorexia, bloating, early satiety, abdominal pain, and vomiting, persisting for >2 wk; X-ray barium meal examination showed an objective evidence for the presence of gastric emptying delay; endoscopic examination ruled out ulcers, tumors, and other organic lesions; and ultrasound examination excluded organic lesions of the liver, gallbladder, spleen, and pancreas; participants with other systemic diseases that may cause the above symptoms were excluded; and age, gender, and other general conditions are not limited. 3) Intervention: on the basis of the control of blood glucose, the experimental group was given mecobalamin combined with prokinetic drugs, the control group was given prokinetic drugs alone. 4) Outcomes: total efficacy rate, the recurrence rate, gastric emptying rate, serum motilin, and adverse reactions.

The exclusion criteria were as follows: 1) non-randomized controlled trials, animal experiments, and review articles; 2) participants: children or participants with other diseases; 3) interventions: studies involving other interventions; 4) outcome: outcome measures were not appropriate, relevant data could not be obtained from the original author; and 5) repeated published literature.

Data extraction

Literature search and data extraction were performed by two researchers (JY and BP) inde-

pendently, and the third researcher (XG) was involved in a discussion 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. When 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 updated tool for assessing the risk of bias (ver. 5.1.0; updated March 2011) (3), two reviewers (JY and BP) assessed the quality of the included studies independently, and the third reviewer (XS) was consulted for any disagreements. The risks of bias were classified as high, unclear, or low by assessing the seven 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, the authors were contacted by e-mail for further information.

Statistical analysis

RevMan 5.3 and Stata 12.0 software were used for statistical analysis. Dichotomous data are expressed as the odds ratio (OR) with a 95% confidence interval (CI), and continuous data are presented as the mean difference (MD) with 95% CI. Heterogeneity was tested by χ^2-based Cochran Q statistic (P<0.10 indicated statistically significant heterogeneity) and I^2 statistic. If I^2<50% and P>0.1, a fixed-effects model was used 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. Sensitivity analysis was used 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 analysis was performed according to the administration route of the included studies. The funnel plot and Egger's and Begg's test were used 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 to indicate a statistically significant result.

Results

The flow diagram of the study selection process is presented in Fig. 1.

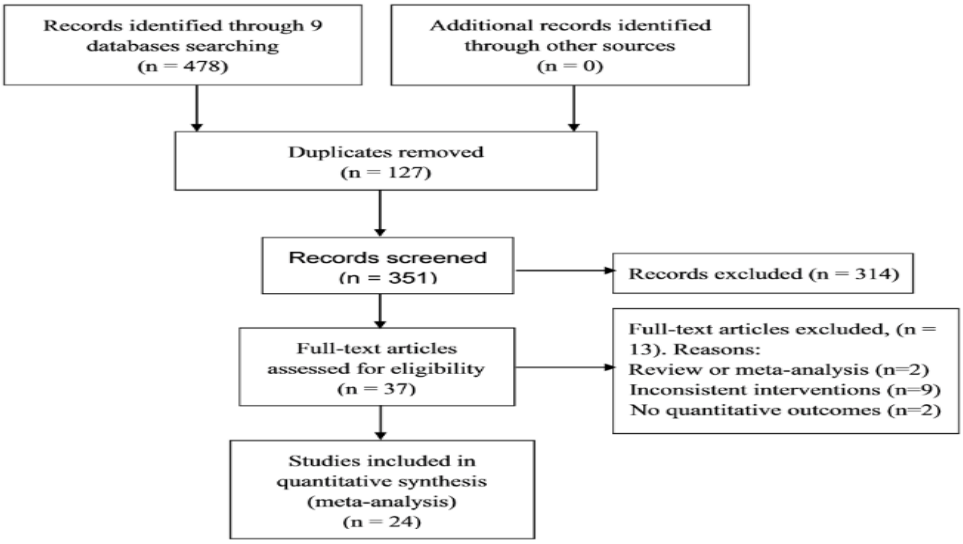

Fig. 1: Flow diagram of study selection

Overall, 478 citations with 127 duplicates were identified. After preliminary screening of the titles and abstracts, 37 studies were selected for full-text review, and 13 studies were excluded since two were reviews, two provided no quantitative outcomes, and the rest included undesirable interventions. Ultimately, 24 RCTs (4-27) were involved in the present meta-analysis.

As presented in Table 1, the characteristics of the included studies were summarized. Twenty-four studies involving 1,878 subjects were ultimately included. The sample size ranged between 32 and 144, the duration varied between 3 and 8 wk, the mean age ranged between 46.8 and 73.1 yr, the mean course of the disease varied between 0.5 and 17.1 yr, and the FBG ranged between 6.8 and 9.0 mmol/l.

Table 1: Characteristics of included studies

Author, Year	*Group*	*Sample size*	*Intervention*	*Duration (week)*	*Mean age (year)*	*Mean course of disease (year)*	*FBG (mmol/L)*	*Dosage*	*Administration route*
An 2018(4)	T	16	Mecobalamin + mosapride	4	73.1±8.2	4.5±1.6	-	0.5mg tid 5mg tid	Po
	C	16	Mosapride		72.8±8.0	4.7±2.0	-	5mg tid	Po
Du 2015(5)	T	50	Mecobalamin + domperidone	4	58.3±5.9	-	-	0.5mg tid 10mg tid	Po
	C	50	Domperidone		59.1±5.8	-	-	10mg tid	Po
Gu 2015(6)	T	34	Mecobalamin + mosapride	8	70.1±6.9	3.7±0.9	6.8±1.0	0.5mg tid 5mg tid	Po
	C	36	Mosapride		69.8±6.9	3.8±0.8	6.8±0.9	5mg tid	Po
Guan 2013(7)	T	41	Mecobalamin + mosapride	4	-	-	-	0.5mg qd 5mg tid	Im Po
	C	44	Mosapride		-	-	-	5mg tid	Po
Guo 2017(8)	T	50	Mecobalamin + domperidone	4	51.7±3.6	-	-	0.5mg tid 10mg tid	Po
	C	50	Domperidone		52.1±3.5	-	-	10mg tid	Po
Huang 2012(9)	T	34	Mecobalamin+ mosapride	4	46.8±10.9	10.2±6.8	-	0.5mg tid 10mg tid	Po
	C	36	Mosapride		47.1±10.5	10.5±6.9	-	10mg tid	Po
Jin 2015(10)	T	37	Mecobalamin+ mosapride	6	71.0	5.1±1.7	-	0.5mg tid 5mg tid	Po
	C	37	Mosapride		71.0	4.9±1.6	-	5mg tid	Po
Li 2013(11)	T	28	Mecobalamin + cisapride	3	-	-	-	0.5mg qd 5mg tid	Im Po
	C	28	Cisapride		-	-	-	5mg tid	Po
Li 2012(12)	T	36	Mecobalamin + mosapride	4	53.7	-	-	500mg qd 10mg tid	Im Po
	C	36	Mosapride		54.3	-	-	10mg tid	Po
Li 2012(13)	T	52	Mecobalamin + etopril	4	-	-	-	0.5mg tid 50mg tid	Po
	C	44	Etopril		-	-	-	50mg tid	Po
Liu	T	30	Mecobalamin +	4	-	-	-	0.5mg qd	Im

2009(14)			mosapride					5mg tid	Po
	C	28	Mosapride		-	-	-	5mg tid	Po
Mao 2017(15)	T	42	Mecobalamin + mosapride	6	68.4±4.7	-	-	0.5mg tid 5mg tid	Po
	C	42	Mosapride		65.4±3.6	-	-	5mg tid	Po
Qiao 2009(16)	T	38	Mecobalamin + cisapride	4	56.0±8.5	8.2±2.1	8.7±3.2	0.5mg qd 10mg tid	Im Po
	C	34	Cisapride		54.0±8.9	8.5±2.6	9.0±3.3	10mg tid	Po
Ren 2010(17)	T	24	Mecobalamin + mosapride	4	56.0±8.4	-	-	0.5mg qd 10mg tid	Im Po
	C	21	Mosapride		54.0±8.6	-	-	10mg tid	Po
Shi 2018(18)	T	43	Mecobalamin + mosapride	6	66.4±5.6	1.9±0.4	6.9±0.9	0.5mg tid 5mg tid	Po
	C	43	Mosapride		65.9±6.1	1.9±0.4	7.1±1.1	5mg tid	Po
Sun 2011(19)	T	36	Mecobalamin + etopril	4	59.4±14.3	17.1±2.1	7.6±0.8	0.5mg qd 50mg tid	Im Po
	C	39	Etopril		65.0±13.0	15.1±2.5	6.9±0.6	50mg tid	Po
Tian 2006(20)	T	45	Mecobalamin + cisapride	4	-	-	-	0.5mg qd 10mg tid	Im Po
	C	30	Cisapride		-	-	-	10mg tid	Po
Wang 2013(21)	T	72	Mecobalamin + domperidone	4	62.3±6.1	10.6±1.1	-	0.5mg qd 10mg tid	Im Po
	C	72	Domperidone		62.3±6.1	10.5±1.1	-	10mg tid	Po
Wu 2009(22)	T	48	Mecobalamin + mosapride	4	53.0	0.6	-	0.5mg qod 5mg tid	Im Po
	C	24	Mosapride		50.0	0.5	-	5mg tid	Po
Wu 2016(23)	T	51	Mecobalamin + mosapride	6	57.3±5.5	9.4±4.2	-	0.5mg tid 5mg tid	Po
	C	51	Mosapride		59.3±3.7	8.8±4.8	-	5mg tid	Po
Zhai 2008(24)	T	36	Mecobalamin + mosapride	4	-	-	-	0.5mg tid 5mg tid	Po
	C	36	Mosapride		-	-	-	5mg tid	Po
Zhao 2016(25)	T	37	Mecobalamin + mosapride	4	-	-	-	0.5mg tid 5mg tid	Po
	C	37	Mosapride		-	-	-	5mg tid	Po
Zhao 2016(26)	T	36	Mecobalamin + mosapride	6	70.1±3.3	7.5±2.4	-	0.5mg tid 5mg tid	Po
	C	36	Mosapride		69.5±3.1	8.3±2.0	-	5mg tid	Po
Zhu 2018(27)	T	46	Mecobalamin + trimebutin maleate	4	59.3±7.9	-	-	0.5mg tid 200mg tid	Po
	C	46	Trimebutin maleate		60.1±6.4	-	-	200mg tid	Po

T, treatment group; C, control group; d, day; w, week; po, oral; im, intramuscular injection; -, not available

Risk of bias data for the included RCTs is presented in Table 2. Randomization was categorized as low risk in three studies with appropriate use of random sequence generation. Eight studies were categorized as high risk using the order of registration or treatment method to randomize.

The remaining 13 studies did not provide details about the method of randomization and were categorized as unclear risk. Totally, 24 studies did not describe any information regarding allocation concealment, blinding of participants, personnel, and outcome assessment. Furthermore, drugs were administered in different ways in the treatment and control groups (mecobalamin im vs. prokinetics po) in 10 studies, and blinding was easily broken; therefore, these 10 studies were categorized as high risk. The remaining 14 studies were categorized as unclear risk. Incomplete outcome data was categorized as low risk in 24 studies with no loss to follow-up. As for selective reporting, 24 studies were classified as unclear risk. Finally, three studies were classed as low risk and the remaining 21 studies were estimated as unclear risk in other bias.

Table 2: Risk of bias assessment in the included studies

Study (yr)	*Random sequence generation*	*Allocation concealment*	*Blinding of participants and personnel*	*Blinding of outcome assessment*	*Incomplete outcome data*	*Selective reporting*	*Other bias*
An (2018)(4)	H	U	U	U	L	U	U
Du (2015)(5)	H	U	U	U	L	U	U
Gu (2015)(6)	H	U	U	U	L	U	U
Guan (2013)(7)	L	H	H	H	L	U	L
Guo (2017)(8)	H	U	U	U	L	U	U
Huang (2012)(9)	H	U	U	U	L	U	U
Jin (2015)(10)	U	U	U	U	L	U	U
Li (2013)(11)	U	H	H	H	L	U	U
Li (2012)(12)	U	H	H	H	L	U	U
Li (2012)(13)	U	U	U	U	L	U	U
Liu (2009)(14)	U	H	H	H	L	U	U
Mao (2017)(15)	L	U	U	U	L	U	L
Qiao (2009)(16)	U	H	H	H	L	U	U
Ren (2010)(17)	H	H	H	H	L	U	U
Shi (2018)(18)	H	U	U	U	L	U	U
Sun (2011)(19)	U	H	H	H	L	U	U
Tian (2006)(20)	U	H	H	H	L	U	U
Wang (2013)(21)	L	H	H	H	L	U	L
Wu (2009)(22)	H	H	H	H	L	U	U
Wu (2016)(23)	U	U	U	U	L	U	U
Zhai (2008)(24)	U	U	U	U	L	U	U
Zhao (2016)(25)	U	U	U	U	L	U	U
Zhao (2016)(26)	U	U	U	U	L	U	U
Zhu (2018)(27)	U	U	U	U	L	U	U

H, high risk; L, low risk; U, unclear risk.

Twenty-four RCTs (4-27) reported total effective rate as an outcome measure, and no heterogeneity was observed (P=1.00; I^2=0%). Pooled results with a fixed-effects model showed that the experimental group (mecobalamin combined with prokinetics) exhibited a significantly improved total effective rate compared with the control group (prokinetics only) (OR, 4.09; 95%CI, 3.09-5.42; P<0.001; Fig. 2). The result of subgroup analysis indicated that the total effective rate was markedly improved regardless of the administration route (intramuscular injection or oral administration) (Table 3).

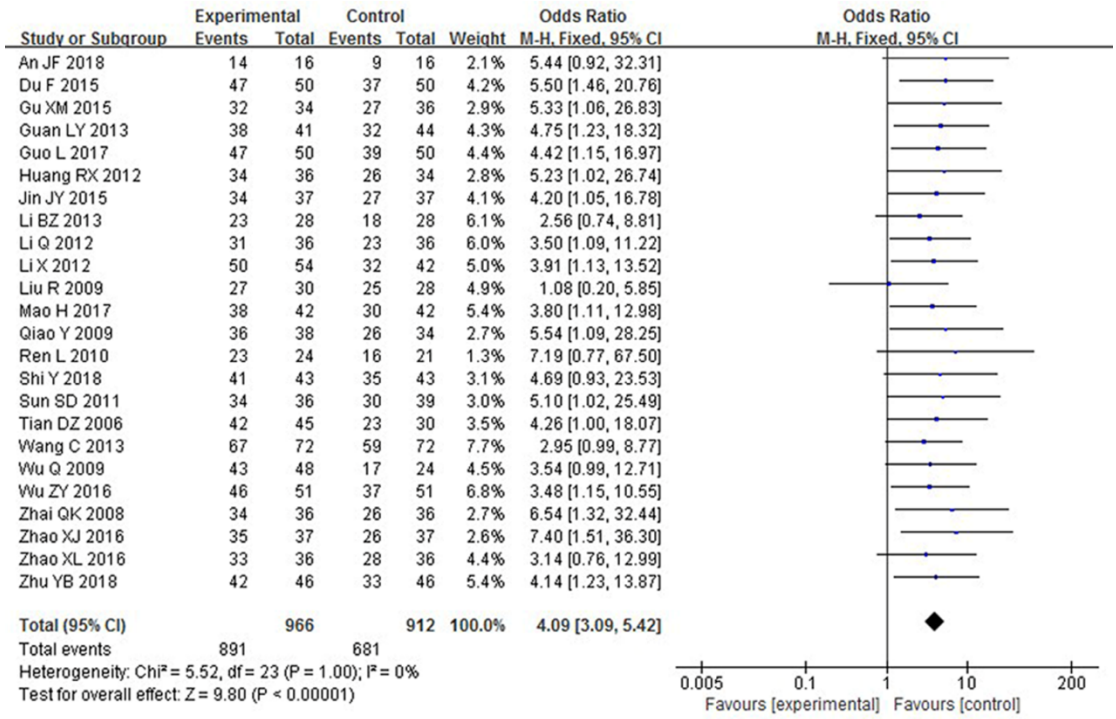

Fig. 2: Forest figure of the total efficacy rate of mecobalamin combined with prokinetics in DGP

Table 3: Subgroup meta-analysis of the administration route with respect to the total efficacy rate of mecobalamin in DGP

Subgroup	*Model for meta-analysis*	*No. of trials*	*Effect size (95%CI)*	P-*value*	I^2 *(%)*	*Q-statistics (P)*
mecobalamin im	FE	10	3.54 (2.29-5.46)	<0.001	0	0.95
mecobalamin po		14	5.24 (3.62-7.59)	<0.001	0	0.94

po, oral; im, intramuscular injection; FE, fixed-effects model.

Twelve RCTs (4,6,7,9,11,13,14,16,18-20,25) reported results on the recurrence rate, and significant heterogeneity was identified (P=0.008; I^2=56%). Pooled results with a random-effects model showed that mecobalamin combined with prokinetics can markedly decrease the recurrence rate (OR, 0.17; 95%CI, 0.10-0.31; P<0.001) (Table 4).

Table 4: Summary of the results of other outcome measures

Outcome indicator	*No. of trial*	*P; I^2*	*Model for meta-analysis*	*Effect size*	*95%CI*	P
Recurrence rate	12	P=0.008; I^2=56%	RE	OR=0.17	0.10-0.31	<0.001
Gastric emptying rate	7	P=0.03; I^2=57%	RE	MD=11.97	9.90-14.03	<0.001
Motilin	2	P<0.001; I^2=96%	RE	MD=-93.94	-142.34- -45.53	<0.001
Adverse effects rate	3	P=0.49; I^2=0%	FE	OR=1.74	0.36-8.48	=0.49

RE, random-effects model; FE, fixed-effects model; OR, odds ratio; MD, mean difference.

Seven RCTs (4,10,15,21,23,25,27) reported the outcome measure of gastric emptying rate, and significant heterogeneity was observed (P=0.03; I^2=57%). Pooled results with a random-effects model showed that mecobalamin combined with prokinetics can significantly improve gastric emptying rate compared with the control group (MD, 11.97; 95% CI, 9.90-14.03; P<0.001) (Table 4).

Two RCTs (23,27) reported motilin as an outcome measure, and obvious heterogeneity was observed (P<0.001; I^2=96%). Pooled results with a random-effects model showed that mecobalamin combined with prokinetics can significantly decrease serum motilin (MD, -93.94; 95% CI, -142.34- -45.53; P<0.001) (Table 4).

Pooled results from three studies (16,17,19) did not demonstrate a significant difference in the adverse effects rate between the two groups (OR, 1.74, 95% CI, 0.36-8.48; P=0.49) with no heterogeneity (P=0.49; I^2=0%) (Table 4).

Publication bias analysis was conducted on the outcome of the total efficacy rate. The funnel plot was symmetrical, all scatter points were inside the confidence limit, and the P-value of Egger's test was 0.056 (Fig. 3). There was a small possibility of publication bias, the results of total efficacy rate of mecobalamin combined with prokinetics in DGP were reliable.

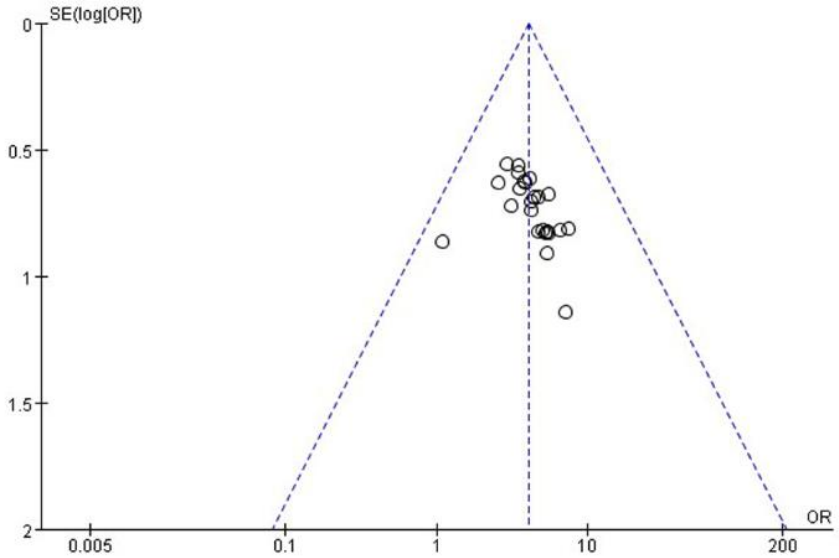

Fig. 3: Funnel plots of publication bias with respect to the total efficacy rate of mecobalamin combined with prokinetics in DGP

Discussion

The aim of the present study was to assess the efficacy and safety of mecobalamin combined with prokinetics in DGP by a meta-analysis. Collectively, pooled results demonstrated that mecobalamin combined with prokinetic agents is effective in improving the total efficacy rate and gastric emptying rate, and decreasing serum motilin and the recurrence rate, without increasing adverse reactions compared with the control group. Subgroup analysis results showed that the effective rate was markedly improved regardless of the administration route.

Autonomic neuropathy plays an important role in the pathogenesis of DGP. Perennial hyperglycemia can lead to the degeneration of autonomic nerve cells and axonal demyelination (27). Elevated glycosylated hemoglobin can lead to narrowing of the vascular cavity. This pathological basis can lead to pathological changes of the gastrointestinal nervous system, which can inhibit the release of acetylcholine, slow down the spread of basic gastric electric rhythm, weaken

the contraction of gastric fundus tension, cause a decline of gastric peristalsis and secretion function, and ultimately lead to the delay of gastric emptying. In recent years, using neurotrophic drugs to treat DGP has attracted increasing attention. The present meta-analysis first evaluated the efficacy and safety of mecobalamin combined with prokinetic agents in treating DGP. Pooled results indicated that mecobalamin combined with prokinetic agents can markedly improve the total efficacy rate and gastric emptying rate. Possible mechanisms may be related to the following aspects: ectogenic mecobalamin entering into the organelles of the neurons, which promotes the metabolism of the three major nutrients and the transformation of homocysteine to methionine by methyl conversion reaction, which participates in the synthesis process of thymine bases, accelerating the synthesis of protein and nucleic acid, which facilitates neural axon regeneration and the formation of the myelin sheath, and therefore repairs the damaged gastrointestinal nerve tissue. In addition, in patients with diabetic gastroparesis, motilin levels have been found to be elevated due to gastric dyskinesia (28). The present study found that serum motilin was markedly reduced in the treatment group, suggesting that the effect of mecobalamin on improving gastric dyskinesia in DGP may be related to the regulation of inordinate gastrointestinal hormones. Moreover, prokinetic agents are commonly used to alleviate the symptoms of DGP; however, the recurrence rate is high after drug withdrawal. The present pooled results showed that mecobalamin combined with prokinetics can markedly decrease the recurrence rate compared with prokinetics alone. Mecobalamin may be used as a new therapeutic option for DGP, and this needs to be tested further by more high-quality RCTs.

The strengths of the present meta-analysis are that this is the first meta-analysis with respect to the efficacy and safety of mecobalamin combined with prokinetic agents in the treatment of DGP. Furthermore, the present study represents a comprehensive overview of the evidence and risk of bias assessment and includes only RCTs. There are also limitations of the current analysis taken into consideration. Firstly, some RCTs were of poor quality and, for example, had a questionable design, were single-center with short duration, and enrolled few participants. Secondly, obvious heterogeneity was observed in some outcome measures, such as recurrence rate, gastric emptying rate, and motilin. The statistically significant results could have been influenced by heterogeneity. Thirdly, the treatment courses were short in the included studies and lacking of long-term efficacy of drug observation. For all of these reasons, the results derived from the present meta-analysis should be treated with considerable caution, and more high-quality RCTs are required for further clarification.

Conclusion

Mecobalamin combined with prokinetic agents can significantly improve the total effective rate and gastric emptying rate, and reduce serum motilin and the recurrence rate without increasing adverse reactions. Mecobalamin may be used as a new therapeutic option for DGP. These results need to be treated cautiously due to the limitations of the included studies and need to be further verified by larger and better-designed studies.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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Conflict of interest

The authors declare that there is no conflict of interest.

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