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ARTICLE

Effectiveness of Lactulose for Colonoscopy Preparation in Adults: A Meta-Analysis

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Abstract

Objective: To evaluate the effects of lactulose for bowel preparation prior to colonoscopy in adults. **Methods:** By searching for literature pertaining to RCT (randomized controlled trial) of bowel preparation with lactulose in adults up to 10th of July, 2021. The experimental group utilizes lactulose oral solution as the solution of choice for bowel preparation while the control group uses the standard bowel preparation solution. Literature selection and data extraction were completed independently by 2 researchers, including literature quality control. Data analysis was completed using the software RevMan5.2. **Results:** 11 RCT was included for data analysis. Meta-analysis showed that the lactulose group had a lower incidence of adverse effects [OR=13.58, 95CI% (6.10, 30.24), p<0.0001] and better tolerability [OR=13.58, 95CI% (6.10,30.24), p<0.0001] when compared with the control group. However, the bowel cleanliness was statistically insignificant between the two groups [WMD=0.2695%CI (-0.310.82), p=0.38]. **Conclusion:** according to current evidences, as a solution for bower preparation, lactulose has a lower incidence of adverse effects such as emesis or diarrhea, while effectively increasing tolerability, however it is not a superior solution for bowel preparation in terms of bowel cleanliness when compared with other standard choices. More high quality researches will be required to support its use.

Keywords: Lactulose; bowel preparation; colonoscopy; meta-analysis.

INTRODUCTION

Colonoscope is a fiber endoscope commonly used in clinical practice to visually identify lesions in the large intestine by inserting it retrogradely through the anus. It bears important clinical significance for the detection of lesions in the colon. It goes without saying that

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adequate intestinal preparations prior to the colonoscopy examination can significantly impact the visibility of point of interests during the examination. If bowel preparation was inadequate, feces in the intestines can cover the mucosal lesions, affecting diagnosis and consequently, the final treatment plan. Patients may encounter severe complications such as intestinal perforation and bleeding due to unclear visuals hence unknown direction of the intestinal cavity. At present, the commonly used oral medications for bowel preparation in clinical practice include polyethylene glycol electrolyte (PGE), magnesium sulfate, sodium phosphate, etc., but these drugs have their disadvantages: for example, patients taking polyethylene glycol electrolyte must consume a large amount of fluids orally, along with its common complaint of poor flavor, culminating to about 5% 15% of patients unable to complete said bowel preparation[1, 2] . Magnesium sulfate, on the other hand, when its concentration is too high, it brings a risk of dehydration, which can cause intestinal mucosal inflammation, ulceration, and the possibility of mucosal morphology changes; sodium phosphate can cause bloating, nausea, abdominal pain and other adverse reactions, and patients currently taking antihypertensive drugs, diuretics, and non-steroidal anti-inflammatory drugs are at risk of acute phosphate nephropathy and renal function damage. As such, the recommendation strength for these bowel cleansing agents is weak recommendation, with moderate quality of evidence as per the Chinese Guideline for Bowel Preparation for Colonoscopy [3] .

Lactulose is a widely used osmotic laxative in the treatment of adult constipation[4]. Numerous clinical reports have also found that lactulose has a good effect on intestinal preparation for colonoscopy in adults. The patients self-reported that they experienced better taste during consumption, high compliance or tolerability, low intestinal irritation, and found that lactulose is suitable for a wide range of people, among other benefits.

METHODS AND MATERIALS

Inclusion and exclusion criteria

The selected literature comprised of randomized controlled trial (RCT); with research subjects being patients of over 18 years of age who have been prescribed with colonoscopy; the experimental group uses lactulose for bowel preparation, and the control group uses other oral solutions for bowel preparation. Exclusion criteria: irrelevant research content; repetitive reports; animal-based mechanism research, conference abstracts, reviews, case reports, and others; literature with incomplete data.

Outcome indicators

Primary outcome indicators: bowel cleanliness score, and the incidence of adverse reactions; secondary outcome indicators: tolerability. The control group used conventional laxatives (for example: polyethylene glycol, magnesium sulfate, etc.). All results must be measured objectively, using recognized and effective measurement tools.

Literature search

"Lactulose" AND "Colonoscopy" OR "Bowel Preparation" was used as the search query in PubMed, Web of Science and other English databases; "Lactulose" AND “colonoscopy”

OR "intestinal preparation" was used as the search query in China National Knowledge Infrastructure (CNKI), Wanfang Data, Cqvip (www.cqvip.com), and Sinomed. Manual retrieval of relevant research references was employed to ensure a complete recall rate. The search time of the Chinese and English databases is from the establishment of the database to July 10, 2021.

Literature screening, data extraction and quality evaluation

Two researchers (Jiapeng Zhang, Weiwen Shi) independently completed literature screening and data extraction. The extracted information included the name of the first author, publication year, country, sample size, age of the research subjects, intervention measures, intervention time, outcome indicators, etc. In RevMan 5.2 software, the Cochrane systematic review manual was used to evaluate the quality of the included studies, mainly from seven aspects: whether it was RCT; whether it used allocation concealment; whether it was a double-blind study; whether it used blinded assessment; whether the outcome indicators were complete; whether they were selectively reported; whether there were other biases.

Evaluation of outcome indicators

GRADEpro was used to assess the quality of evidence included in the meta-analysis. It is currently adopted by renowned institutions such as the World Health Organization and the Cochrane Collaboration. The 8 evaluation indicators of this tool include risk bias, lack of consistency, simplicity, imprecision, other biases, effect size, evidence quality, and importance. The level of evidence is divided into 4 levels: high, medium, low, and very low grade [5].

Statistical methods

RevMan5.3 software was used for statistical analysis. The measurement data uses standardized mean difference (SMD) or mean difference (MD) as the effect indicator, and the count data uses relative risk (RR) as the effect indicator. The effect size is calculated as a point estimate and 95% confidence interval (CI). First, a heterogeneity test was performed, then the included studies were analyzed in tandem with its I2 quantification to test for homogeneity. If the included studies have good homogeneity ($P>0.05$ or $I2<50\%$), then the fixed effects model was used for analysis, else the random effects model was used. The difference is considered statistically significant at $P<0.05$.

RESULTS

Literature search results

initial search yielded 226 related articles, including 86 English articles and 140 Chinese articles; after deduplicating, evaluating titles, abstracts and downloading the full text, screening according to the inclusion and exclusion criteria, among them the original data from the research by Menacho et al.[6] cannot be obtained, and after receiving no response from the author, 11 RCTs were finally included. The literature screening process is shown in Figure 1.

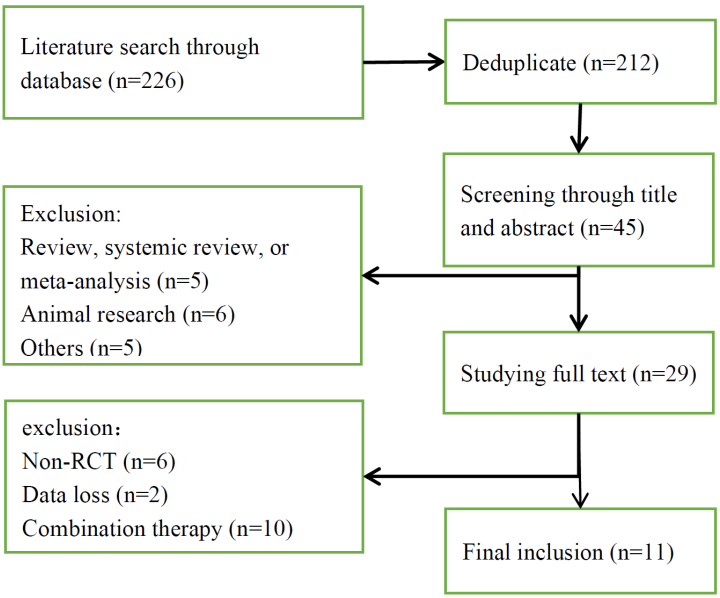

Figure 1. Literature screening process

Characteristics of the included literature

11 RCT articles were included, of which 9 were Chinese articles[7-15], 2 were English articles[16, 17], and the publication time was between 2013 and 2021. The study country was mainly China, laxative of choice for the experimental group was lactulose, and the intervention of choice of the control group were mainly polyethylene glycol electrolyte and oral magnesium sulfate. The complete details can be found in Table 1.

Methodological quality assessment of the included literature

There is a certain risk of bias in all of the included literature. In terms of random allocation: 8 out of 11 included studies stated that the random allocation method was used[8, 10-14, 16, 17], the other 3 did not state their allocation method[7, 9, 15], with 4 of the studies[10-13] not explicitly stating their choice of random allocation method. 4 studies[8, 14, 16, 17]specified that they used the random number table method; among them, the research by Li[16] and Jagdeep[17] have the highest quality, having used the single-blind method within the group, with a low risk of bias; the rest of the literature was not blinded; and the selective reporting of trial results and other risk indicators of bias were not reported in the literature due to their uniqueness, however, the overall quality of the literature is moderate. The methodological quality of the literature is shown in Figure 2.

Quality of evidence classification for the primary outcome indicators of the included literature

The 11 included studies have a total of 3 evaluation indicators. For the primary outcome indicator, bowel cleanliness, it is measured via 2 different data types, hence they were

Table 1 . Characteristics of the included literature

Author	Year	Country	Sample size		Subject age		Intervention		Time of intervention	Outcome indicator
			③EG	④CG	③EG	④CG	③EG	④CG		
Li CX[16]	2019	China	88	88	50.15±10.66	49.63±11.98	⑨LAT 200mL + water 2L	PGE 2L	2 days	Bowel cleanliness / colonoscopy outcomes / patient or physician satisfaction / tolerability
Jagdeep [17]	2021	India	20	20	36.30±8.986	34.35±10.155	⑨LAT 300mL + water 700mL	PGE 2L + water 1L	2 days	quality of bowel preparation / palatability / discomfort / electrolyte levels
Huang Y[8]	2020	China	①B:40 ②C:40	40	① B:51.51±7.75 ② C:51.07±7.31	52.27±7.12	*B*: ⑨LAT 30mL 1 day prior to examination, t.i.d. *C*: ⑨LAT 15mL 2 days prior to examination, t.i.d.	240mL of PGE+ water 4000mL	3 days	Incidence of adverse reaction / indicators of bowel cleanliness / quality of bowel preparation
Wang XQ[7]	2021	China	48	SLG: 48 PGE: 48	3.82±0.42	⑤ SLG:3.81±0.42 PGE: 3.83±0.42	LAT 5~15mL/d 3 days prior to examination; 9pm day before and 6am on the day of examination: 40-70mL of LAT + 250~450mL of water	⑤SLG: 20-100mL of boiling water + SLG 2-10g ⑥PGE: 60mL of PGE + cool water 1000mL	4 days	Bowel cleanliness / incidence of adverse reaction / successful recognition of ileocecal junction via colonoscopy
Su R[9]	2019	China	100	100	≥60 years old	≥60 years old	⑨LAT 45mL +water 1200mL	Group A: 25% ⑦MS 100mL + water 2000mL Group B: 60mL of PGE + water 1000mL, repeat 2 hours later	3 days	Bowel cleanliness / adverse reaction
Gao HL[10]	2015	China	100	100	45.3±2.5	44.1±3.5	⑨ LAT 200mL + water 1000mL	50%⑦MS + water 2000mL	2 days	Adverse reaction / bowel cleanliness
Su YB[11]	2015	China	60	60	72.3±3.5	72.1±4.5	2-3d prior to examination: LAT oral solution 10-30 mL t.i.d. for 3 days 6h prior to examination: ⑨ LAT 100-200mL + water 500-1000 mL	6h prior to examination: PGE 120mL + water 2000 mL	3-4days	Adverse reaction / bowel cleanliness / tolerability
Xu XJ[12]	2015	China	57	60	64.0±14.1	60.5±15.0	⑨LAT oral solution 200mL	120mL of ⑥PGE	2 days	Bowel cleanliness / patient's degree of completeness / incidence of adverse reaction / taste / tolerability / contraindications
Nian YY[13]	2020	China	78	72	49.72±13.87	52.61±10.76	Night before examination: 100 mL ⑨LAT + 1 000 mL water 6 hours prior to examination: 200 mL ⑨LAT + 2000 mL water	Night before examination: 60mL of ⑥ PGE + 1000mL of water 6 hours prior to examination: 120mL of ⑥PGE + 2000mL water + ⑧SP:30~50mL + 100mL water	2 days	Patient basic information / comfort level of bowel preparation / bowel cleanliness / scoring of colonic bubble
Zhang JM[14]	2018	China	20	22	No obvious difference	No obvious difference	120mL of ⑨LAT + 1000-1500mL of warm water at 8pm the night before and 5am on the day of examination	30mL of⑥ PGE+ 1500-2000mL of water at 8pm the night before and 5am on the day of examination	2 days	Bowel cleanliness / safety / adverse reaction
Bai L[15]	2013	China	140	⑦ MS: 140	67.8±10.1	⑦ MS: 65.9±9.7	10-30mL⑨ LAT t.i.d. for 3-4d before examination. 6h prior to examination: 200~300mL ⑨ LAT+2000~3000mL water	⑦MS group: 50% MS 50mL+ water 2500-3000mL	2 days	Safety / tolerability / acceptance/adverse reaction/complication rate

Notation：①B: oral lactulose was prescribed 1 day prior to colonoscopy；②C: oral lactulose was prescribed 2 days prior to colonoscopy; ③EG: Experimental Group; ④CG: Control Group; ⑤SLG: Senna leaf group; ⑥PGE: Polyethylene glycol electrolyte group;⑦MS: Magnesium sulphate group; ⑧SP: Simethicone Powder; ⑨LAT: lactulose

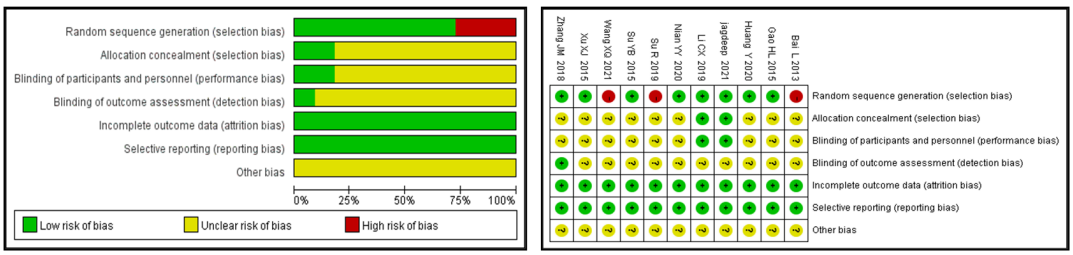

Figure 2. Methodological quality of included literature

displayed with 2 forest plots. The GRADE tool was used to evaluate the quality of each outcome index, and the results showed that 2 indexes were middle grade, and the other 2 outcome indexes were low grade. Details can be found in Table 2.

META-ANALYSIS RESULTS

The effect of lactulose on bowel cleanliness in adults prior to colonoscopy

A total of 11 literatures analyzed the bowel cleanliness score of lactulose. Since there are differences between the 2 evaluation scales, with 4 of the studies using binary variables, and the other 4 using continuous variables, the results are shown in the figure below in a forest plot. In the studies using binary variables, the heterogeneity among the studies is small

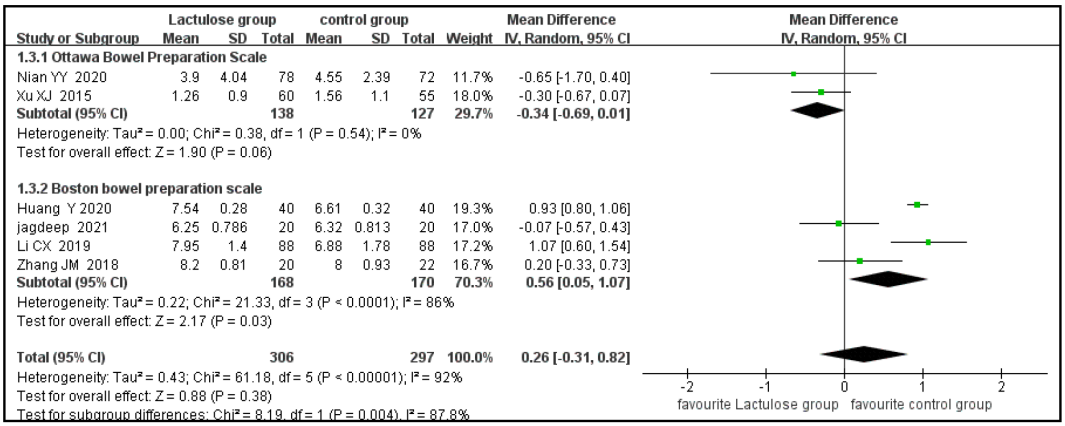

Figure 3. Forest chart comparing bowel cleanliness between the lactulose group and the control group (mean difference)

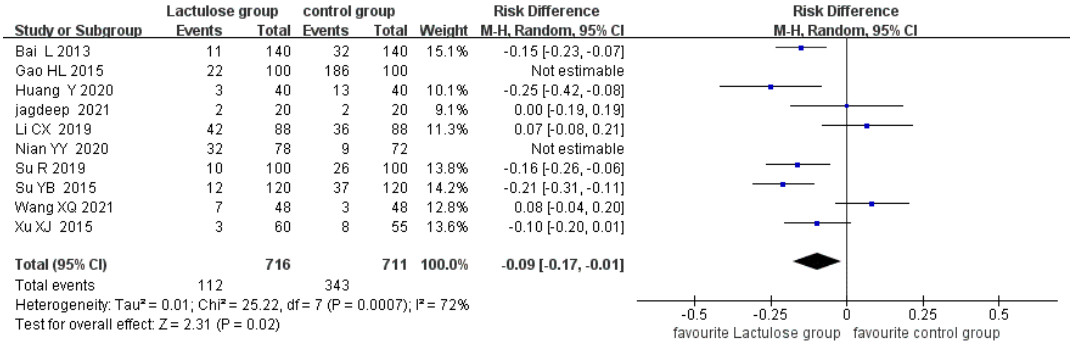

Figure 4. Forest plot comparing the incidence of adverse intestinal reactions between the lactulose group and the control group (risk difference)

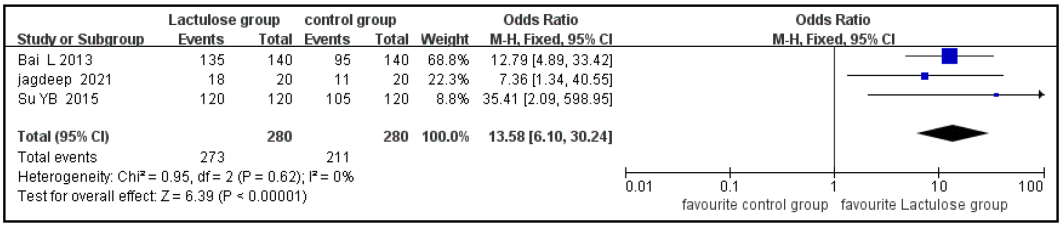

Figure 5. Forest plot comparing the patient tolerability between the lactulose group and the control group (odds ratio)

(2=3.87, P=0.28, I2=23%), and due to that (I2<50%), we used the fixed effects model, and found that the bowel cleanliness score in the lactulose group was better than that of the control groups using other oral solutions, with statistically significant differences [OR=5.86, 95%CI (4.10, 8.38), p<0.0001] as shown in Figure 3.2; In the studies using continuous variables, their heterogeneity is larger (2=61.18, P<0.001, I2=92%), even after we applied

Table 2. GRADE quality classification of outcome indicator

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Lactulose	Control	Relative (95% CI)	Absolute		
Bowel cleanliness												
4	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	332/368 (90.2%)	226/368 (61.4%)	OR =5.82 (3.88 , 8.71)	288 more per 1000 (from 247 more to 319 more)	MODERATE	CRITICAL
adverse reaction												
10	randomized trials	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	154/794 (19.4%)	420/783 (53.6%)	See comment	21 more per 1000 (from 113 fewer to 161 more)	LOW	IMPORTANT
tolerability												
2	randomized trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	reporting bias[3]	255/260 (98.1%)	200/260 (76.9%)	OR 15.36 (6.18 to 38.19)	212 more per 1000 (from 184 more to 223 more)	LOW	IMPORTANT

[1] 3 articles did not specify the random allocation method; [2] Less overlap of confidence intervals, small P value in heterogeneity test, combined result showing a larger I^2 value; [3] Few included studies, may contain a large publication bias

the random effects model and sensitivity analysis, the heterogeneity is still large (I2>50%). Hence, we performed subgroup analysis for different evaluation scales, namely the Ottawa Bowel Preparation Scale and Boston Bowel Preparation Scale. It showed that lactulose had no clear-cut advantage over the other oral solutions in terms of cleaner colon; the difference was not statistically significant [MD =0.26, 95%CI (-0.31, 0.82), p=0.38] as shown in Figure 3

The influence of lactulose on the incidence of adverse reaction in adult colonoscopy

A total of 10 literatures7-13, 15-17 analyzed the rate of adverse reaction of lactulose, and after testing for heterogeneity among the studies (I2=86%), we adopted the random effects model and performed sensitivity analysis due to the large heterogeneity (I2>50%). From the above results, after excluding the study by Nian13, the heterogeneity decreased considerably (I2=72%), and the difference was statistically significant. The adverse reaction rate between the lactulose group and other control groups is statistically significant [RD=-0.09, 95%CI (-0.17, -0.01), p=0.02], as seen in Figure 4 below.

The effect of lactulose on the tolerability of adult colonoscopy

A total of 3 articles11, 15, 17 analyzed the tolerability of patients to lactulose. Our findings showed that the tolerance of patients in the lactulose group was better than that of the control group, and the difference was statistically significant [OR=13.58, 95CI% (6.10, 30.24), p<0.0001], as seen in Figure 5.

DISCUSSION

Colonoscopy is currently one of the most important tools used in clinical screening, diagnosis and treatment of colon-related lesions, and ideal intestinal condition is the basis for improving the diagnostic accuracy of colonoscopy. Studies have shown that cleaner colon walls can increase the effectiveness and safety of colonoscopy, and affect the detection rate of adenoma through colonoscopy18. A total of 11 RCT studies were included in this study, and our

evaluation of the study quality was moderately low, which was mainly related to the fault in their study design: a total of 9 studies used the random allocation method, and 2 of them used single-blind intervention. Taking into account that the difference in fluid intake in the lactulose experimental group (30mL 100mL) and the polyethylene glycol control group (1000mL 4000mL) is quite considerable, it is almost impossible to use the double-blind method for the subjects and intervention implementers, which may contribute to bias in the final results.

For the evaluation of bowel cleanliness, there are currently two main recognized assessment scales for bowel preparation quality in the world: the Boston Bowel Preparation Scale and the Ottawa Bowel Preparation Scale. 6 points in the Boston scale, and 7 points in the Ottawa scale both indicate adequate bowel preparation19. The results of our study show that no matter which evaluation scale was used, the effect of lactulose on colon cleanliness is not significantly better than that of the control group (for example: polyethylene glycol, magnesium sulfate, etc.), with no statistically significant differences between groups [WMD=0.26, 95%CI (-0.31, 1.07), p=0.38]. It shows that lactulose has no obvious advantages in intestinal preparation when compared with other commonly used cleansing agents, which is also consistent with the research results of Ouyang et al[20].

As a bowel cleanser, lactulose has the advantages of better taste during consumption and less gastrointestinal-related side effects16. The results of this study also showed that compared with the control group, patients in the experimental group tolerated better than the control, and there was a statistically significant difference between them [OR=15.36, 95%CI (6.18, 38.19), p<0.00001]. This is also consistent with the results of Lin et al. The subjects' tolerance to lactulose is better than that of the polyethylene glycol group[16]. However, the study by Menacho et al6 suggested that the subject tolerance of lactulose and polyethylene glycol was the same with no significant discrepancy. In terms of the incidence of adverse reactions, we found that the lactulose group had lower incidence than that of the control group, and the difference was statistically significant [RD=-0.09, 95%CI (-0.17, -0.01), p=0.02], consistent with the results from Zhang et al[14].

Lactulose is a commonly used pre-colonoscopy cleanser. It effectively softens stools, stimulates intestinal peristalsis, induces mild catharsis, has a good taste and is well tolerated by patients. Therefore, it is widely used in clinical practice[21]. The results of this study show that although lactulose has no obvious advantages over other classical laxative agents in terms of colon cleanliness, it is significantly better than the control group in terms of tolerability and incidence of adverse reactions, which means that lactulose is generally better than the others in clinical settings. However, there still exist discrepancies in the dosage of lactulose, pre-examination fasting type and time, and the concentration of lactulose. For example, Li et al16. diluted 200 mL of lactulose by adding 2000 mL of drinking water in their experimental group, resulting in an incidence of vomiting as high as 38.1%. Studies have shown that when bowel preparation requires the subject to consume a large amount of water, about 5% to 15% of patients will be unable to complete the procedure[22]. Moreover, none of the literature included in this study mentioned any restriction in diet or fasting prior to colonoscopy. Studies have shown that the use of a standardized low-residue diet the day prior will significantly improve the quality of bowel preparation, patient compliance and satisfaction, however diet restriction of more than 24h does not improve the quality of bowel

preparation[23-25]. With that said, the above factors may be contributing to heterogeneity found between these studies.

CONCLUSION

This study has its limitations: (1) The included literature is limited to the Chinese and English language, with studies in other languages not included. (2) The 11 included articles have varying degrees of methodological limitations, with a moderate overall research quality, and some indicators cannot be included in the analysis due to the difference in evaluation tools. Therefore, the inclusible sample for this meta-analysis is limited. We should hold a degree of scientific skepticism towards the stated conclusion of this study. (3) In addition, this meta-analysis did not further analyze the lactulose concentration, timing of consumption and other issues. In future studies, this aspect can be further analyzed to provide evidence-based results for clinical decision-makers.

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