

The advantage of polyethylene glycol electrolyte solution combined with lactulose in patients with long interval preparation-to-colonoscopy

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ABSTRACT

Background/Aims: The main aim of the present study was to assess the efficacy of polyethylene glycol electrolyte (PEG) solution combined with lactulose in bowel preparation to find a new method for colonoscopy preparation to improve the quality of colonoscopy in patients with long interval preparation-to-colonoscopy (P-C).

Materials and Methods: A prospective, randomized, endoscopist-blinded and placebo-controlled study was conducted. Three hundred sixty patients who were scheduled for colonoscopy were enrolled in the study. They were randomly divided into the PEG-lactulose group and the PEG-placebo group with 180 patients per arm. Two of the most common methods for estimating the quality of bowel preparation were the use of the Boston Bowel Preparation Scale and the measurement of the Bubble Scale and adenoma detection rate (ADR) as a secondary outcome of observation.

Results: The PEG-lactulose group had a significant improvement in the quality of bowel preparation compared with the PEG-placebo group including colon cleanliness in interval P-C at 8 and 9 h ($p < 0.05$) and bubble elimination in interval P-C at 5, 6, 7, 8, and 9 h ($p < 0.05$). Compared with the PEG-placebo group, the ADR (23.3% vs. 15.0%, $p < 0.05$) and the size (≤ 5 mm) of the adenoma (45.2% vs. 18.5%, $p < 0.05$) increased in the PEG-lactulose group, and there were significant differences between the two groups.

Conclusion: PEG solution combined with lactulose can improve the quality of colonoscopy in patients with long interval P-C to allow the patients to select more flexible colonoscopy time. It is worth further popularizing in clinical practice.

Keywords: Polyethylene glycol electrolyte, lactulose, bowel preparation, colonoscopy, preparation-to-colonoscopy

INTRODUCTION

In a recent article in the European Society of Gastrointestinal Endoscopy and United European Gastroenterology providing a brief set of key performance measures for lower gastrointestinal endoscopy (1), adequate bowel preparation has received considerable critical attention. Polyethylene glycol electrolyte (PEG) is essential for a wide range of bowel preparation, with advantages such as high security, reliable effect, no dehydration, and electrolyte disturbance (2). Despite its safety and efficacy, PEG suffers from a major drawback; it is obvious that the quality of colon cleaning is decreasing with the prolongation of interval preparation-to-colonoscopy (P-C), especially in patients with colonoscopy in the afternoon (3). Lactulose is a treatment of functional constipation osmotic laxatives. There is evidence that lactulose plays a unique role of bacterial inhibition in the colon (4), which can increase colon cleanliness and prolong the effect time of PEG. Therefore, lactulose can play an important role

in addressing the issue of the low quality of colonoscopy in patients with long interval P-C. Several studies of the addition of lactulose before using the PEG solution (traditional regimen) have confirmed the effectiveness of improving the quality of colonoscopy (5-7). However, the research to date has not been able to provide robust evidence for the role of traditional regimen on improving the low quality of colonoscopy in patients with long interval P-C. After continuous clinical practice and observation, it is found that the addition of lactulose after using the PEG solution (modified regimen) can effectively improve the low quality of colonoscopy in patients with long interval P-C.

MATERIALS AND METHODS

Study design

This study was a prospective, randomized, endoscopist-blinded and placebo-controlled trial that compared

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two bowel preparation methods at the Center of Endoscopy. The study protocol was reviewed and approved by the ethics committee of the institutional review board of the university.

Participants

A total of 360 patients who were scheduled for colonoscopy were enrolled in the study. Inclusion criteria were age between 20 and 80 years, all included patients and their families must provide a written informed consent, and they could tolerate PEG and lactulose. Exclusion criteria included patients who were pregnant and lactating, had prior bowel resection, coronary heart disease, congestive heart failure, diabetes, significant constipation, active inflammatory bowel disease, bowel obstruction, structural intestinal disorders, and liver failure (8).

Randomization and blinding

In each day of the study, all eligible patients were randomly numbered. Patients with odd numbers were assigned to the PEG-lactulose group, whereas patients with even numbers were assigned to the PEG-placebo group. This information was kept blinded from the endoscopists and endoscopy researchers. The colonoscopy procedure for patients of both groups, whom were randomly single blinded, was operated by two senior chief physicians (NIU 51.4% and LIN 48.6%, Table 1). The time for colonoscopy in two groups of patients was 14:00-18:00 pm, and the specific time of colonoscopy (interval P-C at 5, 6, 7, 8, and 9 h) for each patient was randomly selected by the patient.

Procedure

Prior to colonoscopy, to begin this process, the patients should be informed of the possible risk during colonoscopy and needed to comply with colonoscopy for dietary requirement (a low-fiber diet started on the day before colonoscopy) (9). Written informed consent was obtained from the patients. They received two boxes of PEG powder (Jiangxi Heng Kang Pharmaceutical Industry Co., Ltd., China) and asked to dissolve one box of PEG powder (69.56 g) in each 1000 mL of drinking water, sufficiently mixed to form the PEG solution. In the follow-up phase of the study, the participants were instructed to consume 2000 mL of PEG solution, drinking every 20 min with an oral dose of 200 mL, at 6:00-9:00 am on the day of colonoscopy. On completion of the oral last dose of PEG solution after a 1-hour interval, the participants in the PEG-lactulose group were instructed to take 100 mL lactulose (Beijing Han Mei Pharmaceutical Co., Ltd., China) orally, whereas the participants in the PEG-placebo group

were asked to take 100 mL placebo (100 mL normal saline, normal saline is a solution of 0.9% w/v of NaCl) until two groups of participants excreted pale yellow or almost transparent watery feces. Individuals who participated in the Boston Bowel Preparation Scale (BBPS) and Bubble Scale were well trained for two scales, and two researchers independently evaluated and recorded the scores as part of the blinded study. To increase the reliability of measures, each score was tested twice by two researchers. When the scores of the evaluation were widely divergent, two researchers could consult with experts (NIU) (2).

Table 1. Characteristics of 360 patients (%).

	PEG-lactulose n=180	PEG-placebo n=180	p
Patients (male/female) ^a	180 (97/83)	180 (102/78)	0.60
Age (mean±SD) (years) ^b	50.03±12.37	52.16±11.94	0.10
Indications, n (%) ^a			
Screening ^a	71 (39.4%)	67 (37.2%)	0.67
Abdominal pain ^a	24 (13.3%)	22 (12.2%)	0.75
Abdominal distension ^a	21 (11.7%)	26 (14.4%)	0.43
Hematochezia ^a	13 (7.2%)	9 (5.0%)	0.38
Diarrhea ^a	15 (8.3%)	23 (12.8%)	0.17
Abdominal mass ^a	1 (0.6%)	3 (1.7%)	0.62
Weight loss ^a	2 (1.1%)	5 (2.8%)	0.45
Other ^a	33 (18.3%)	25 (13.9%)	0.25
Family tumor history, n (%) ^a	16 (8.9%)	19 (10.6%)	0.59
Interval P-C (mean±SD) (h) ^b	5.31±1.39	5.44±1.40	0.41
5 h ^a , n (%)	43 (23.9%)	38 (21.1%)	0.53
6 h ^a , n (%)	35 (19.4%)	43 (23.9%)	0.31
7 h ^a , n (%)	41 (22.8%)	36 (20.0%)	0.52
8 h ^a , n (%)	31 (17.2%)	34 (18.9%)	0.68
9 h ^a , n (%)	30 (16.7%)	29 (16.1%)	0.89
NIU ^a , n (%)	99 (55.0%)	86 (47.8%)	0.17
LIN ^a , n (%)	81 (45.0%)	94 (52.2%)	

PEG-lactulose: the addition of lactulose after using polyethylene glycol electrolyte solution. PEG-placebo: the addition of placebo after using polyethylene glycol electrolyte solution. Interval P-C (5-9 h): time interval between the bowel preparation completed and the beginning of the colonoscopy. NIU: Chief Physician NIU Jianping to do colonoscopy examination of the number of patients. LIN: Deputy Chief Physician LIN Tao to do colonoscopy examination of the number of patients. Data are given as number and proportion and as mean±SD.

^aStatistics by chi-square test.

^bStatistics by one-way analysis of variance.

Quality of bowel preparation

The first step in this process was to evaluate colon cleansing by using the BBPS, which was widely available and had been used in many bowel preparation studies (10). The BBPS was used to divide the whole colon into three segments (Table 2). A total BBPS score ≥ 6 was considered as satisfactory bowel preparation, whereas a total BBPS score < 6 was considered as unsatisfactory bowel preparation. If the total score was 0, the bowel preparation was considered to be invalid, and it was recommended that the colonoscopy should be examined again after 2 weeks (11).

According to McNally et al. (12), the Bubble Scale had been utilized for the estimation of the amount of bubbles. A four-point scoring system (0, no bubbles; 1, minimal or occasional bubbles; 2, moderate or obviously present; and 3, severe or many bubbles that vision is obscured) was used to examine the severity of a bubble according to the effect of bubbles on the visual field of the bowel mucosa. The entire colon might be classified according to the distribution of foam in the gut into five segments (Table 2) (13).

All patients who detected the lesions were examined by pathology during colonoscopy, with the diameter of adenomas as the main object of observation (14).

Sample size calculation

The sample size was calculated to consider adequate bowel preparation (BBPS ≥ 6) with the 1.5 L PEG deemed as 71.1% in a recent article (15). By assuming an adequate preparation rate of 70.0%, an error of 5% was considered in the present study, and at least 323 patients were required to participate in the study. Eventually, the sample size was determined for 360 patients (180 cases per arm).

Statistical description and analysis

Data management and analysis were performed using IBM SPSS version 19.0 for Windows (SPSS Inc., Chicago, IL, USA). The software used for drawing was GraphPad Prism 7 (GraphPad Software Inc., San Diego, CA, USA). Data were presented as number and percentage for categorical variables and were analyzed using chi-square test, as appropriate, and as mean $\pm$ SD for continuous data. Comparison of different groups was performed by one-way analysis of variance. A p value < 0.05 was considered significant.

RESULTS

The researchers carefully screened patients who were scheduled for colonoscopy through inclusion and ex-

clusion criteria in the Center of Endoscopy from January 2018 to June 2018. Of the 360 patients who completed the colonoscopy, there were 83 female and 97 male patients in the PEG-lactulose group and 78 female and 102 male patients in the PEG-placebo group ($p > 0.05$). The mean ages of the patients were 50.03 ± 12.37 years in the PEG-lactulose group and 52.16 ± 11.94 years in the PEG-placebo group ($p > 0.05$). The mean interval P-C of the patients was 5.31 ± 1.39 min in the PEG-lactulose group and 5.44 ± 1.41 min in the PEG-placebo group ($p > 0.05$). According to the length of interval P-C divided into 5, 6, 7, 8, and 9 h, the number of patients undergoing colonoscopy for each interval P-C period between the two groups was 43, 35, 41, 31, and 30 in the PEG-lactulose group and 38, 43, 36, 34, and 29 in the PEG-placebo group ($p > 0.05$). There was no statistically significant difference in basic information between the two groups ($p > 0.05$, Table 1).

From the data in Table 2, it is apparent that the BBPS scores of satisfactory (BBPS ≥ 6) were present in 164/180 in the PEG-lactulose group and 143/180 in the PEG-placebo group (satisfactory 91.1% vs. 79.4%, $p < 0.05$). The mean scores of the BBPS for patients who underwent colonoscopy in interval P-C at 8 and 9 h were 7.06 ± 1.63

Table 2. Comparison of BBPS and Bubble Scale scores between the two groups.

	PEG-lactulose (mean $\pm$ SD) ^a n=180	PEG-placebo (mean $\pm$ SD) ^a n=180	pb
BBPS			
Right	2.16 $\pm$ 0.59	1.89 $\pm$ 0.68	<0.001
Transverse	2.64 $\pm$ 0.52	2.46 $\pm$ 0.64	0.004*
Left	2.38 $\pm$ 0.60	2.09 $\pm$ 0.63	<0.001
Total BBPS	7.18 $\pm$ 1.43	6.46 $\pm$ 1.69	<0.001
Satisfactory, n (%)	164 (91.1%)	143 (79.4%)	0.02*
Bubble Scale score			
Rectosigmoid	0.19 $\pm$ 0.49	0.53 $\pm$ 0.63	<0.001
Descending	0.20 $\pm$ 0.47	0.49 $\pm$ 0.65	<0.001
Transverse	0.16 $\pm$ 0.44	0.42 $\pm$ 0.63	<0.001
Ascending	0.33 $\pm$ 0.59	0.64 $\pm$ 0.71	<0.001
Cecum	0.21 $\pm$ 0.46	0.46 $\pm$ 0.63	<0.001
Total bubble score	1.09 $\pm$ 1.16	2.54 $\pm$ 1.47	<0.001

PEG-lactulose: the addition of lactulose after using polyethylene glycol electrolyte solution. PEG-placebo: the addition of placebo after using polyethylene glycol electrolyte solution. Satisfactory: BBPS ≥ 6 .

^aData are given as mean $\pm$ SD.

^bStatistics by one-way analysis of variance.

Table 3. Comparison of two groups of BBPS and Bubble Scale scores in interval P-C at 5-9 h.

Interval P-C	n	PEG-lactulose (mean±SD) ^a	n	PEG-placebo (mean±SD) ^a	p ^b
BBPS					
5 h	43	7.42±1.20	38	6.92±1.32	0.08
6 h	35	7.34±1.06	43	6.77±1.54	0.06
7 h	41	7.07±1.33	36	6.58±1.76	0.17
8 h	31	7.06±1.63	34	6.18±1.82	0.04*
9 h	30	6.90±1.94	29	5.59±1.80	0.01*
Bubble Scale score					
5 h	43	0.88±1.01	38	2.11±1.11	<0.001
6 h	35	0.74±0.82	43	2.16±0.95	<0.001
7 h	41	0.85±1.20	36	2.19±1.56	<0.001
8 h	31	1.39±1.09	34	2.91±1.33	<0.001
9 h	30	1.83±1.39	29	3.69±1.85	<0.001

PEG-lactulose: the addition of lactulose after using polyethylene glycol electrolyte solution. PEG-placebo: the addition of placebo after using polyethylene glycol electrolyte solution. Interval P-C (5-9 h): time interval between the bowel preparation completed and the beginning of the colonoscopy.

^aData are given as mean±SD.

^bStatistics by one-way analysis of variance.

Table 4. Comparison of adenoma detection between the two groups.

	PEG-lactulose n=180	PEG-placebo n=180	p
Pathological diagnosis, n (%)			
Tumor ^a	2 (1.1%)	1 (0.6%)	1.00
Adenoma ^a	42 (23.3%)	27 (15.0%)	0.045*
Polyp ^a	51 (28.3%)	48 (26.1%)	0.64
IBD ^a	4 (2.2%)	3 (1.7%)	1.00
Other ^a	6 (3.3%)	4 (2.2%)	0.52
Adenoma size, n (%)			
≤5 mm ^a	19 (45.2%)	5 (18.5%)	0.02*
6-9 mm ^a	12 (28.6%)	10 (37.0%)	0.46
≥10 mm ^a	11 (26.2%)	12 (44.4%)	0.12
Withdrawal time (min mean±SD) ^b	6.23±1.56	6.60±1.73	0.04*
Cecal intubation time (min mean±SD) ^b	7.23±2.34	7.61±2.42	0.13

PEG-lactulose: the addition of lactulose after using polyethylene glycol electrolyte solution. PEG-placebo: the addition of placebo after using polyethylene glycol electrolyte solution.

IBD, inflammatory bowel disease.

Data are given as number and proportion and as mean±SD.

^aStatistics by chi-square test.

^bStatistics by one-way analysis of variance.

versus 6.18±1.82 and 6.90±1.94 versus 5.59±1.80 (Table 3), and the difference between the PEG-lactulose and PEG-placebo groups was significant (p<0.05).

Table 5. Two groups of adverse events.

	PEG-lactulose ^a n=180	PEG-placebo ^a n=180	p ^b
Nausea, n (%)	11 (6.1%)	14 (7.8%)	0.53
Vomiting, n (%)	10 (5.9%)	12 (6.7%)	0.66
Abdominal pain, n (%)	7 (3.9%)	9 (5.0%)	0.61
Bloating, n (%)	18 (10.0%)	24 (13.3%)	0.33
Headache, n (%)	1 (0.6%)	3 (1.7%)	0.62

PEG-lactulose: the addition of lactulose after using polyethylene glycol electrolyte solution. PEG-placebo: the addition of placebo after using polyethylene glycol electrolyte solution.

^aData are given as number and proportion.

^bStatistics by chi-square test.

The results, as shown in Table 2, indicate that the total bubble scores for the whole colon are 1.09±1.16 in the PEG-lactulose group and 2.54±1.47 in the PEG-placebo group (p<0.05). The mean scores of the bubble score in interval P-C at 5, 6, 7, 8, and 9 h were 0.88±1.01 versus 2.11±1.11, 0.74±0.82 versus 2.16±0.95, 0.85±1.20 versus 2.19±1.56, 1.39±1.09 versus 2.91±1.33, and 1.83±1.39 versus 3.69±1.85, respectively (Table 3), and there was a significant difference between the two groups (p<0.05).

Data from Table 4 show that the adenoma detection rate (ADR) (23.3% vs. 15.0%, p<0.05) and the size (≤5 mm) of the adenoma (45.2% vs. 18.5%, p<0.05) in PEG-lactulose group were higher than those in the PEG-placebo

group, and the differences between the two groups were statistically significant ($p < 0.05$). However, the observed difference between cecal intubation time and adverse events (Table 5) in the present study was not significant ($p > 0.05$).

DISCUSSION

Colonoscopy is crucial to the diagnosis and treatment of gastrointestinal disorders. Adequate bowel preparation is a common condition that has considerable impact on the quality of colonoscopy. The discovery of PEG in 1985 triggered a huge amount of innovative scientific studies especially in bowel preparation (16). PEG is an important component in adequate bowel preparation and plays a key role in the quality of colonoscopy.

Surveys, such as those conducted by Seo et al. (17), have shown that colon cleanliness was the highest at time intervals of 3-5 h after a one-time oral administration of 4 L of PEG solution, whereas colon cleanliness was significantly decreased at time intervals of <3 or >7 h. It is not hard to find that the optimal time for colonoscopy is difficult to determine because patients have a variety of interval P-C. Data from previous study (Siddiqui, 2009) suggested that the time interval of the duration of oral laxative completion and the time the colonoscopy started (interval P-C) increased by 1 h each time, and the right colon and/or the entire bowel would be reduced by 10% in chance for cleaning (3). The findings from these studies suggested that interval P-C has an effect on the quality of colon cleansing. Currently, no large-scale studies have been performed to investigate the prevalence of improving the quality of colonoscopy in patients with long interval P-C in China.

Bacteria in intestinal feces account for 20%-30% of the solid weight of feces (18). This also accords with our earlier observations that the PEG solution can only effectively remove solid residues in feces and has no significant effect on colonic bacteria and flora. Previous studies of lactulose (Liang et al. (4)) have demonstrated that it could reduce the amounts of solids in the feces by reducing the number of bacteria and the formation of intestinal flora in the colon (19), which could make the quality of bowel preparation to reach a very ideal state.

Thus far, the safety and efficacy of PEG solution in bowel preparation have been widely recognized (20). However, the single use of PEG solution for bowel preparation is difficult to achieve the desired level of bowel cleanliness. In this regard, there were a large number of published stud-

ies (e.g., Soh et al. (5)) that described the effect of PEG combined with lactulose in bowel preparation (6,7,21), and research on the subject had been mostly restricted to the use of lactulose before PEG solution, which caused the suitable pH and bacteriostatic effect of lactulose to be diluted by PEG solution, so that the role of lactulose had not been sufficiently played.

In the present study, the oral administration of lactulose after PEG solution to patients and the effect on the quality of bowel preparation in patients with long interval P-C were assessed. The results of the present study indicated that the mean scores of the BBPS for patients who underwent colonoscopy in interval P-C at 8 and 9 h were 7.06 ± 1.63 versus 6.18 ± 1.82 and 6.90 ± 1.94 versus 5.59 ± 1.80 ($p < 0.05$, Table 3), and the Bubble Scale scores in interval P-C at 5, 6, 7, 8, and 9 h were 0.88 ± 1.01 versus 2.11 ± 1.11 , 0.74 ± 0.82 versus 2.16 ± 0.95 , 0.85 ± 1.20 versus 2.19 ± 1.56 , 1.39 ± 1.09 versus 2.91 ± 1.33 , and 1.83 ± 1.39 versus 3.69 ± 1.85 , respectively ($p < 0.05$, Table 3), and the differences between total BBPS and Bubble Scale scores were highlighted ($p < 0.05$) in Fig. 1. In Fig. 2, there was a clear trend of the quality of bowel preparation decreasing with the prolongation of interval P-C, and following the addition of lactulose, a significant increase ($p < 0.05$) in the quality of bowel preparation was recorded. As can be seen from Table 5, the ADR (28.3% vs. 17.8%, $p < 0.05$), as well as the size (≤ 5 mm) of the adenoma (45.2% vs. 18.5%, $p < 0.05$), increased with colon cleansing, and the

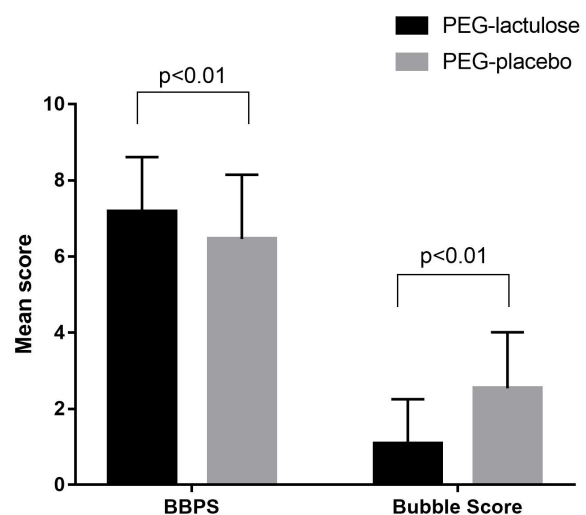


Figure 1. Comparison of BBPS and Bubble score between the two groups; PEG-lactulose, the addition of lactulose after using polyethylene glycol electrolyte solution; PEG-placebo the addition of placebo after using polyethylene glycol electrolyte solution.

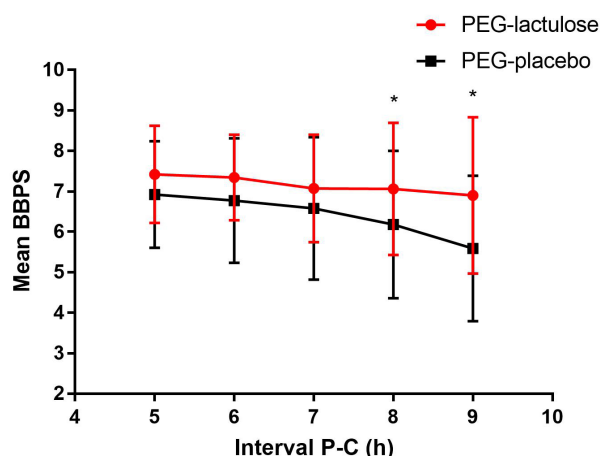


Figure 2. Comparison two groups of BBPS in interval P-C 5-9 h; PEG-lactulose, the addition of lactulose after using polyethylene glycol electrolyte solution; PEG-placebo the addition of placebo after using polyethylene glycol electrolyte solution; Interval P-C(5-9h), interval time between the bowel preparation completed and the beginning of the colonoscopy; * $p < 0.05$.

ADR was similar to that of comparable studies (e.g., Matro et al. (22)).

The findings in the present study are subject to at least three limitations. First, this research had only examined patients who underwent colonoscopy in the afternoon, so these results might not be applicable to the wider population. Second, an additional uncontrolled factor was the possibility of the number of colonoscopies in each time period of P-C; with insufficient sample size in interval P-C at 7-8 h (Table 1), caution must be applied as the results might be susceptible to group bias. Third, the study lacked more supporting evidence because it was only a single-center study. Thus, more research on this topic is needed to examine the effects of modified regimen on bowel preparation.

In conclusion, PEG solution combined with lactulose improves the quality of bowel preparation in patients with long interval P-C, which makes patients to have no restriction on the time of colonoscopy, and benefits more patients who need colonoscopy.

Ethics Committee Approval: Ethics committee approval for this study was received from the institutional ethics committee of Xi'an Medical University.

Informed Consent: Written informed consent was not obtained due to the retrospective nature of the study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - L.T.; Design - Y.H.; Supervision - M.M., L.X.; Resources - L.T., N.J.; Materials - L.T., N.J.; Data Collection and/or Processing - Y.H.; Analysis and/or Interpretation - Y.H., N.J.; Literature Search - Y.H., N.J.; Writing Manuscript - Y.H., N.J.; Critical Review - N.J., M.M.

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