Efficacy and safety of PEG-asparaginase versus E. coli L-asparaginase in Chinese children with acute lymphoblastic leukemia: A meta-analysis

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Abstract

Background: Multi-agent chemotherapy is the primary treatment for acute lymphoblastic leukemia (ALL), of which the asparaginase including Escherichia coli L-asparaginase (E. coli L-Asp) and Pegylated-asparaginase (PEG-Asp) is a cornerstone component. The study aimed to conduct a meta-analysis to compare the efficacy and safety of PEG-Asp with E. coli L-Asp in Chinese children with ALL. Methods: A systematic literature search was conducted to collect randomized controlled trials (RCTs) on PEG-Asp versus E. coli L-Asp in Chinese children with ALL. Two reviewers independently selected articles and extracted data. Risk-of-bias assessment used the Cochrane recommendation tool. Pooled estimates and risk ratios with 95% confidence intervals (CIs) for all outcomes in Review Manager 5.3. Results: 15 studies of a total of 470 publications were included, involving 1 194 patients. Pooled estimates showed that there were no significant differences in CR, ORR, gastrointestinal symptoms, and coagulation abnormalities rate between the PEG-Asp and E. coli L-Asp group (all P>0.05). Hypersensitivity (RR=0.63; 95%CI 0.40-1.01; P=0.05) and hepatic injury rate (RR=0.45; 95%CI 0.27-0.75; P=0.002) were lower in the PEG-Asp group. The frequency of administration and length of hospital stay of patients in the PEG-Asp group was less than that in the E. coli L-Asp group (both P<0.0001). Conclusions: Current evidence pointed out a similarity efficacy in the two groups. While the PEG-Asp group had a lower hypersensitivity and hepatic injury rate. Besides, using PEG-Asp decreased the frequency of administration and the length of hospital stay, which, to some extent, might reduce patients' burden caused by medical resources consumption.

ABSTRACT

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Methods: A systematic literature search was conducted to collect randomized controlled trials (RCTs) on PEG-Asp versus E. coli L-Asp in Chinese children with ALL. Two reviewers independently selected articles and extracted data. Risk-of-bias assessment used the Cochrane recommendation tool. Pooled estimates and risk ratios with 95% confidence intervals (CIs) for all outcomes in Review Manager 5.3.

Result s: 15 studies of a total of 470 publications were included, involving 1 194 patients. Pooled estimates showed that there were no significant differences in CR, ORR, gastrointestinal symptoms, and coagulation abnormalities rate between the PEG-Asp and *E. coli* L-Asp group (all P>0.05). Hypersensitivity (RR=0.63; 95%CI 0.40-1.01; P=0.05) and hepatic injury rate (RR=0.45; 95%CI 0.27-0.75; P=0.002) were lower in the

PEG-Asp group. The frequency of administration and length of hospital stay of patients in the PEG-Asp group was less than that in the E. coli L-Asp group (both P<0.0001).

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Key words: PEG-asparaginase; *E. coli*L-asparaginase; childhood acute lymphoblastic leukemia; Meta-analysis

1 INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most common subtype of leukemia in children and adolescents, characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs.[1] In China, the prevalence rate of leukemia was about 4/100000 under 15 years of age which was reported in 2019 in published literature.[2] The number of ALL cases account for 81.75% in 2018 of total childhood malignant tumor in the same period, up from 34.78% in 2008.[2]

The multi-agent chemotherapy used in the treatment of children with ALL already achieved good efficacy, 5-year overall survival (OS) in children with ALL is 86–89%.[1] [3]Escherichia coli L-asparaginase (*E.coli*L-Asp) is an enzyme as the cornerstone component in multi-agent chemotherapy, has been an important part of regimens in ALL. However, the delivery of asparaginase can be highly immunogenic, as it is derived from bacteria.[4] [5] Which may cause adverse events including hypersensitivity, thromboembolic events, and hepatotoxicity.[6]Pegylated-asparaginase (PEG-Asp) is an inert compound, an enzyme-conjugated to polyethylene glycol (PEG) molecules. PEG-Asp greatly diminishes the immunogenicity while maintaining the biological activity of asparaginase.[7] And the half-life period of PEG-Asp (7±2d) is significantly longer than *E.coli* L-Asp (20h), which indicated PEG-Asp can reduce the frequency of administration.[8]

PEG-Asp is recommended as the first line of treatment by the*Chinese Guideline for the Diagnosis and Management of Children with ALL (2018)* and was admitted into the national reimbursement drug list (NRDL) through national drug price negotiation in 2018. The agreement is valid until the end of 2020. Whether it will belong to NRDL drugs in the future still needs to be negotiated, While *E. coli* L-Asp has always been in the NRDL. In fact, there was no clear evidence to prove that PEG-Asp and *E.coli* L-Asp have a significant difference in efficacy and safety among the published research.[8-13]And there is no meta-analysis targeted at china's pediatric ALL patients. Therefore, the objective of this study was to conduct a meta-analysis to compare the efficacy and safety of PEG-Asp and *E. coli* L-Asp in Chinese children with acute lymphoblastic leukemia, with the aim of providing evidence support for clinical medication and future negotiation of the NRDL adjustment.

2 MATERIALS AND METHODS

2.1 Data Sources and Search Strategy.

The meta-analysis was conducted according to the Cochrane Collaboration recommendations. We searched PubMed, Cochrane Library, China National Knowledge Infrastructure (CNKI), WanFang Data, and VIP Chinese periodical service platform, from inception to December 2019. Medical Subject Heading (MesH) and text words included polyethylene glycol conjugated asparaginase, pegaspargase, PEG-Asp,*Escherichia coli* L-Asparaginase, *E. coli* L-Asp, childhood acute lymphoblastic leukemia, and ALL. References of included studies were traced to dig out more relevant studies.

2.2 Inclusion and Exclusion Criteria.

The PICO strategy recommended by Cochrane[14] was used to define the eligibility criteria. RCTs, containing a control group and an intervention group, which fulfill the following criteria were eligible for inclusion: (1) study population consisted of Chinese patients aged 0-18 years with ALL; (2) PEG-Asp as a component of multi-agent chemotherapy was the experimental group (PEG-Asp group), and *E.coli* L-Asp included in multi-agent chemotherapy was used for the control group (*E.coli* L-Asp group). Other drugs involved in multi-agent chemotherapy for two groups are consistent basically, including Vincristine or Vindesine, Daunorubicin or Pirarubicin, and Prednisone or Prednisolone or Dexamethasone; (3) Efficacy outcomes included complete responses (CR) and overall response rate (ORR). Safety outcomes included hypersensitivity rate, hepatic injury rate, gastrointestinal symptoms, and coagulation abnormalities. Each Study should report at least one outcome of those; (4) published in full manuscript form; (5) published in Chinese or English.

Studies were excluded if they were (1) study population with severe complications (such as pulmonary infection) or other diseases (such as diabetes); and (2) duplicate publications.

2.3 Data Extraction and Risk-of-Bias Assessment.

Two authors (ZD and YH) extracted data independently and disagreements were resolved by consensus. For each eligible study, the following information was extracted: (1) basic information (e.g. first author, year of publication, sample size); (2) intervention and study population's baseline characteristics; (3) efficacy and safety outcomes as mentioned in inclusion criteria. The quality of included studies was assessed using the Cochrane risk-of-bias tool.[14] Assessment items include selection bias, performance bias, detection bias, attrition bias, reporting bias, and other biases. Publication bias assessment was performed in Stata/MP version 13.0 (StataCorp LLC, Texas, USA), using the Egger's test.[15] If publication bias existed, the trim and fill approach was implemented to generate an estimated pooled RR that accounts for unpublished negative findings.[16]

2.4 Statistical Analysis.

The meta-analysis was undertaken in Review Manager version 5.3 (Cochrane Collaboration, Copenhagen, Denmark). The risk ratio (RR) with 95% CI was generated to evaluate dichotomous outcomes. The mean difference (MD) with 95%CI was generated to evaluate continuous outcomes. Heterogeneity was assessed using the I^2 estimate and the P-value of $?^2$-test. If the P-value > 0.10 and $I^2 < 50\%$, homogeneity was assumed and the fixed-effects model (FE) was used to analyze. Otherwise, heterogeneity was assumed and the source of heterogeneity should be further determined by subgroup analysis or meta-regression. In the absence of clear clinical and methodological heterogeneity, the random-effects model (RE) was used to analyze the outcomes.

3 RESULTS

3.1 Included studies.

Our search identified 470 publications through database searching. After screening titles and abstracts, 32 studies were considered potentially eligible and were retrieved for full-text review.15 studies[17-31] of these were finally included in this meta-analysis. All included studies were in Chinese. The search procedure and exclusion reasons can be found in the flowchart (Figure 1).

3.2 Study Characteristics.

The characteristics of the included studies were summarized in Table 1. A total of 1 194 patients were involved, of which 594 were treated with PEG-Asp, and 600 were treated with *E. coli* L-Asp.

3.3 Risk-of-Bias Assessment.

The category "Random sequence generation" exhibited a high risk of bias in three of fifteen studies. The methods taken to generate random sequence and arrange groups in these three studies did not accord with the randomization standard. Six[17-19, 21, 24, 31]studies described the methods of randomization in detail. Only one study[18] illustrated the allocation concealment. Blinding was not mentioned in any of the included studies. One study[23] did not completely report the pre-specified outcomes and was assessed as high risk. No subjects withdrew from the studies. The category "other bias" exhibited an unclear risk of bias associated with a lack of information. Details were shown in Figure 2.

3.4 Meta-Analysis Results

After summarizing the characteristics of the included studies, we found that the dosage of the PEG-Asp group was similar while there was some difference in the *E. coli* L-Asp group. Therefore, we conducted a subgroup analysis based on the dosage of the *E. coli* L-Asp group reported in the included studies. Subgroups were divided into (1) *E. coli* L-Asp: [?] 6000 U/m^2 once, 6-10 times, (2) *E. coli*L-Asp: 6000-10000 U/m^2 once, 6-10 times, (3) *E. coli* L-Asp: 700U/m^2 once, 7 times, and (4) *E. coli* L-Asp: 200U/kg once, 8 times.

3.4.1 CR. All fifteen studies reported CR, 1 194 patients were involved. The pooled analysis demonstrated that there was no significant difference in CR under the fixed-effects model between the PEG-Asp group and the *E. coli* L-Asp group (RR=1.01; 95%CI 0.96-1.08; P=0.64; Figure 3). No heterogeneity between studies was noted in each subgroup (I^2=0%, P=0.86 in the subgroup with *E. coli*L-Asp: [?] 6000 U/m^2 once, 6-10 times; and I^2=26%, P=0.25 in the subgroup with *E. coli*L-Asp: 6000-10000 U/m^2 once, 6-10 times).

3.4.2 ORR. Thirteen studies reported ORR, 1 099 patients were involved. Homogeneity was assumed as P-value > 0.10 and I^2 < 50% in each subgroup and the pooled estimates. The fixed-effects model was applied and pooled estimates showed there was no significant difference in ORR between the PEG-Asp group and the *E. coli* L-Asp group (RR=1.03; 95%CI 1.00-1.06; P=0.06; Figure 4).

3.4.3Adverse events. Eight studies (715 patients) reported hypersensitivity rate and four studies (239 patients) reported hepatic injury rate. Homogeneity was assumed as the I^2 was 0%. The fixed-effects model was applied and the results showed that there was a lower hypersensitivity rate (RR=0.63; 95%CI 0.40-1.01; P=0.05) and a lower hepatic injury rate (RR=0.45; 95%CI 0.27-0.75; P=0.002) in the PEG-Asp group compared with the *E.coli* L-Asp group. In terms of gastrointestinal symptoms and coagulation abnormalities reported by ten and nine studies respectively, the differences between the PEG-Asp group and the *E.coli* L-Asp group were not significant(P>0.05). Details were shown in Figure 5.

3.4.4 Frequency of administration and length of hospital stay. Besides the efficacy and adverse events, we considered some relevant resources used during the treatment, such as the administration and hospital stay. Five studies (407 patients) of the included studies reported the frequency of administration and the length of hospital stay. The analysis was conducted under the fixed-effects model as I^2 was 0%. The frequency of administration and length of hospital stay of patients in the PEG-Asp groups both significantly less than that of patients in the*E.coli* L-Asp groups(MD=-5.58, 95%CI -5.92 to -5.24; MD=-7.04, 95%CI -8.06 to -6.02; both P<0.00001; Figure 6).

3.5 Publication bias

The P-value of 0.031 (95% CI 0.82–1.44) was calculated by Egger's test, indicating the presence of publication bias. The trim and fill approach was applied to generate an estimated pooled fixed effects RR of -0.010 (95% CI -0.053-0.033), four study were filled. The initial estimated pooled fixed effects RR was -0.002 (95% CI -0.046-0.041), which changed clearly.

4

4 DISSCUSSION

This meta-analysis focused on the efficacy and safety of PEG-asparaginase versus *E. coli* L-asparaginase in Chinese children with acute lymphoblastic leukemia. Fifteen studies,1 194 patients, were involved. The dosage of the PEG-Asp group was similar, often be $2500U/m^2$ once and a total of twice. While there was some apparent difference in the dosage of the *E. coli*L-Asp group, a subgroup analysis was conducted according to the dosage difference. The result showed that there was no significant difference between the two groups in each subgroup in terms of CR and ORR. Which seemed that the difference of *E. coli* L-Asp dosage would not impact on the pooled result. Further, we removed the two extreme dosage subgroups (*E. coli* L-Asp: $700U/m^2$ once, 7 times, and *E. coli* L-Asp: $200U/kg$ once, 8 times), the pooled estimates results did not change.

Our study didn't conduct quantitative analysis on long-term efficacy, because only one included study[22] provided the predicted progression-free survival (PFS) and overall survival (OS) by using Kaplan-Meier analysis. They predicted that a 5-year PFS of 63.5%±12.5% for the PEG-Asp group and 77.8%±9.8% for the *E.coli* L-Asp group; a 5-year OS of 68.9%±11.8% for the PEG-Asp group and 82.1%±9.5% for the *E.coli* L-Asp group. The difference was not significant between groups. This is consistent with the systematic evaluation result of scholar Medawar[32], which was performed based on the population of the USA, Puerto Rico and Canada. And researches from the United States and India with evaluation on the local patients also proved that there were no significant differences between the two groups in terms of event-free survival and overall survival.[10, 11, 14]

As for safety, our meta-analysis showed that PEG-Asp group had lower hypersensitivity rate and hepatic injury rate, but with no significant differences in gastrointestinal symptoms rate and coagulation abnormalities rate. One thing worth noting in this meta-analysis is that all included studies administered PEG-Asp intramuscularly, which is the recommended administration in *the Chinese Guideline for the Diagnosis and Management of Children with ALL (2018)* . However, due to patients' anxiety and pain, intravenous delivery is also available in practice. And as for the hypersensitivity rate between intramuscular and intravenous administration, one meta-analysis reported it was not statistically significant.[33] In addition, our results showed that the frequency of administration and length of hospital stay of patients in PEG-Asp group both were significantly less than that of patients in *E.coli*L-Asp group, which indicated that using PEG-Asp in the treatment could reduce the economic burden caused by less used medical resources including administration and hospital stay.

In total, this study examined 1 194 patients, which allows for substantially more statistical power and precision. However, there were several limitations to this meta-analysis. Firstly, all the included studies were published in Chinese, study populations were all small-scale. And the results of Egger's test and trim and fill approach indicated the presence of publication bias. Secondly, the result of the risk-of-bias assessment presented a large proportion of uncertain risks associated with insufficient information in the trial methods. Thirdly, our study lacked an analysis of long-term outcomes. Only one included study[22] provided long-term outcomes, which cannot carry out a quantitative synthesis. Thus, more studies relevant to long-term outcomes of PEG-Asp in treatment with Chinese children with ALL are needed in the future to confirm the long-term efficacy and safety of PEG-Asp.

5 CONCLUSIONS

In summary, current evidence shows that the use of PEG-Asp as a core component in multi-agent chemotherapy was not superior to *E. coli* L-Asp in terms of efficacy in the treatment of Chinese children with ALL. More trials with adequate methods and longer follow-up are necessary to classify their efficacy. However, the assessment of the data collected showed that patients in the PEG-Asp groups had a lower hypersensitivity rate and hepatic injury rate. The use of PEG-Asp reduced the frequency of administration and shorten the length of hospital stay, which indicates that using PEG-Asp in the pharmacotherapy could reduce the economic burden caused by used medical resources.

Although there were some limitations to this study we discussed earlier, this study complements special evidence based on the Chinese population by conducting a meta-analysis to analyze the efficacy and safety of PEG-Asp in the treatment of Chinese children with ALL. The results are more macroscopic, representative. Which could help reduce the possibility of experts misled by differences between individual RCTs, and can provide data support for clinical medication and future negotiation of the NRDL adjustment.

Data availability statement All data relevant to the study are included in the article or can be found from references. No additional data are available.

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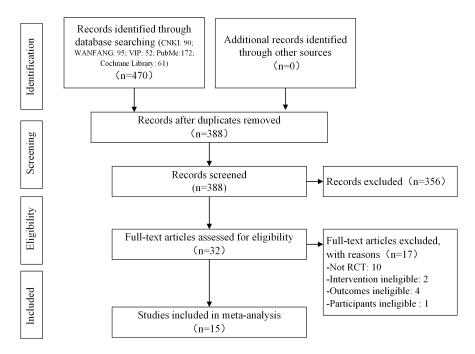16. Dreyer NA, Velentgas P, Westrich K, Dubois R. The GRACE checklist for rating the quality of obser-

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TABLE 1 Characteristics of included studies.docx   available   at   https://authorea.com/

Identification

Records identified through database searching (CNKI: 90; WANFANG: 95; VIP: 52; PubMe:172; Cochrane Library: 61)
（n=470）

Additional records identified through other sources
（n=0）

Screening

Records after duplicates removed
（n=388）

Records screened
（n=388）

Records excluded （n=356）

Eligibility

Full-text articles assessed for eligibility
（n=32）

Full-text articles excluded, with reasons （n=17）
-Not RCT: 10
-Intervention ineligible: 2
-Outcomes ineligible: 4
-Participants ineligible : 1

Included

Studies included in meta-analysis
（n=15）

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	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Cheng XD 2015	+	?	?	?	+	+	?
Cooperation group 2008	+	+	?	?	+	+	?
Feng JQ 2015	+	?	?	?	+	+	?
Jin HY 2014	?	?	?	?	+	+	?
Li F 2019	+	?	?	?	+	+	?
Liu F 2010	?	?	?	?	+	+	?
Liu ZR 2019	?	?	?	?	−	−	?
Shi HL 2019	+	?	?	?	+	+	?
Tang Y 2016	−	?	?	?	+	+	?
Wu H 2016	?	?	?	?	+	+	?
Xia LP 2016	−	?	?	?	+	+	?
Xie SP 2013	?	?	?	?	+	+	?
Zhang HM 2017	−	?	?	?	+	+	?
Zhang SH 2015	?	?	?	?	+	+	?
Zhang SH et al. 2015	+	?	?	?	+	+	?

9

Study or Subgroup	PEG-Asp group Events	Total	E.coli L-Asp group Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 E. coli L-Asp: ≤ 6000 U/m² once, 6-10 times						
Cheng XD 2015	42	74	46	74	10.3%	0.91 [0.70, 1.19]
Cooperation group 2008	55	65	59	66	13.1%	0.95 [0.83, 1.08]
Feng JQ 2015	20	37	23	37	5.2%	0.87 [0.59, 1.28]
Liu F 2010	26	27	18	19	4.7%	1.02 [0.89, 1.16]
Shi HL 2019	33	37	32	37	7.2%	1.03 [0.87, 1.22]
Wu H 2016	21	35	18	35	4.0%	1.17 [0.77, 1.78]
Xia LP 2016	8	10	17	25	2.2%	1.18 [0.78, 1.77]
Zhang SH 2015	28	30	27	30	6.1%	1.04 [0.89, 1.21]
Subtotal (95% CI)		315		323	52.8%	0.99 [0.91, 1.08]
Total events	233		240			
Heterogeneity: Chi² = 3.29, df = 7 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.30 (P = 0.77)						
1.1.2 E. coli L-Asp: 6000-10000 U/m² once, 6-10 times						
Liu ZR 2019	33	38	33	38	7.4%	1.00 [0.84, 1.19]
Tang Y 2016	16	31	10	31	2.2%	1.60 [0.87, 2.96]
Xie SP 2013	47	50	48	50	10.8%	0.98 [0.89, 1.07]
Zhang HM 2017	20	27	18	27	4.0%	1.11 [0.78, 1.57]
Zhang SH et al. 2015	45	48	45	47	10.2%	0.98 [0.89, 1.08]
Subtotal (95% CI)		194		193	34.6%	1.04 [0.96, 1.13]
Total events	161		154			
Heterogeneity: Chi² = 5.42, df = 4 (P = 0.25); I² = 26%						
Test for overall effect: Z = 0.90 (P = 0.37)						
1.1.3 E. coli L-Asp: 700U/m² once, 7 times						
Jin HY 2014	31	40	28	40	6.3%	1.11 [0.85, 1.44]
Subtotal (95% CI)		40		40	6.3%	1.11 [0.85, 1.44]
Total events	31		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.76 (P = 0.45)						
1.1.4 E. coli L-Asp: 200U/kg once, 8 times						
Li F 2019	29	45	28	44	6.3%	1.01 [0.74, 1.38]
Subtotal (95% CI)		45		44	6.3%	1.01 [0.74, 1.38]
Total events	29		28			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.94)						
Total (95% CI)		594		600	100.0%	1.01 [0.96, 1.08]
Total events	454		450			
Heterogeneity: Chi² = 7.24, df = 14 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.46 (P = 0.64)						
Test for subgroup differences: Chi² = 1.12, df = 3 (P = 0.77), I² = 0%						

Favours [PEG-Asp group]   Favours [E.coli L-Asp group]

Study or Subgroup	PEG-Asp group Events	Total	E.coli L-Asp group Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 E.coli L-Asp: ≤ 6000 U/m² once, 6-10 times						
Cheng XD 2015	72	74	70	74	13.8%	1.03 [0.96, 1.10]
Cooperation group 2008	60	65	62	66	12.1%	0.98 [0.90, 1.08]
Feng JQ 2015	35	37	34	37	6.7%	1.03 [0.91, 1.16]
Liu F 2010	26	27	19	19	4.5%	0.97 [0.87, 1.09]
Shi HL 2019	35	37	34	37	6.7%	1.03 [0.91, 1.16]
Wu H 2016	31	35	29	35	5.7%	1.07 [0.88, 1.30]
Subtotal (95% CI)		275		268	49.5%	1.02 [0.97, 1.06]
Total events	259		248			
Heterogeneity: Chi² = 1.63, df = 5 (P = 0.90); I² = 0%						
Test for overall effect: Z = 0.73 (P = 0.46)						
1.2.2 E.coli L-Asp: 6000-10000 U/m² once, 6-10 times						
Liu ZR 2019	36	38	37	38	7.3%	0.97 [0.89, 1.07]
Tang Y 2016	25	31	20	31	3.9%	1.25 [0.91, 1.71]
Xie SP 2013	50	50	49	50	9.8%	1.02 [0.97, 1.08]
Zhang HM 2017	26	27	25	27	4.9%	1.04 [0.91, 1.18]
Zhang SH et al. 2015	47	48	46	47	9.2%	1.00 [0.94, 1.06]
Subtotal (95% CI)		194		193	35.1%	1.03 [0.98, 1.09]
Total events	184		177			
Heterogeneity: Chi² = 4.53, df = 4 (P = 0.34); I² = 12%						
Test for overall effect: Z = 1.27 (P = 0.20)						
1.2.3 E.coli L-Asp: 700U/m² once, 7 times						
Jin HY 2014	40	40	36	40	7.2%	1.11 [0.99, 1.24]
Subtotal (95% CI)		40		40	7.2%	1.11 [0.99, 1.24]
Total events	40		36			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.81 (P = 0.07)						
1.2.4 E.coli L-Asp: 200U/kg once, 8 times						
Li F 2019	43	45	41	44	8.2%	1.03 [0.93, 1.14]
Subtotal (95% CI)		45		44	8.2%	1.03 [0.93, 1.14]
Total events	43		41			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.48 (P = 0.63)						
Total (95% CI)		554		545	100.0%	1.03 [1.00, 1.06]
Total events	526		502			
Heterogeneity: Chi² = 7.95, df = 12 (P = 0.79); I² = 0%						
Test for overall effect: Z = 1.89 (P = 0.06)						
Test for subgroup differences: Chi² = 2.01, df = 3 (P = 0.57), I² = 0%						

Favours [PEG-Asp group]   Favours [E.coli L-Asp group]

10

	PEG-Asp group		E.coli L-Asp group			Risk Ratio	Risk Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Fixed, 95% CI	M-H, Fixed, 95% CI
1.3.1 Hypersensitivity rate							
Liu ZR 2019	7	38	19	38	51.6%	0.37 [0.18, 0.77]	
Shi HL 2019	6	37	9	37	24.4%	0.67 [0.26, 1.68]	
Xia LP 2016	1	10	5	25	7.8%	0.50 [0.07, 3.76]	
Zhang HM 2017	2	27	6	27	16.3%	0.33 [0.07, 1.51]	
Subtotal (95% CI)		112		127	100.0%	0.45 [0.27, 0.75]	
Total events	16		39				
Heterogeneity: Chi² = 1.13, df = 3 (P = 0.77); I² = 0%							
Test for overall effect: Z = 3.05 (P = 0.002)							
1.3.2 Hepatic injury rate							
Cheng XD 2015	4	74	2	74	5.0%	2.00 [0.38, 10.59]	
Cooperation group 2008	3	65	4	66	9.9%	0.76 [0.18, 3.27]	
Jin HY 2014	2	40	4	40	10.0%	0.50 [0.10, 2.58]	
Li F 2019	2	45	4	44	10.1%	0.49 [0.09, 2.53]	
Tang Y 2016	1	31	2	31	5.0%	0.50 [0.05, 5.23]	
Wu H 2016	11	35	13	35	32.4%	0.85 [0.44, 1.62]	
Xia LP 2016	1	10	16	25	22.8%	0.16 [0.02, 1.03]	
Xie SP 2013	1	50	2	50	5.0%	0.50 [0.05, 5.34]	
Subtotal (95% CI)		350		365	100.0%	0.63 [0.40, 1.01]	
Total events	25		47				
Heterogeneity: Chi² = 5.02, df = 7 (P = 0.66); I² = 0%							
Test for overall effect: Z = 1.93 (P = 0.05)							
1.3.3 Gastrointestinal symptoms rate							
Cheng XD 2015	14	74	12	74	12.3%	1.17 [0.58, 2.35]	
Jin HY 2014	5	40	7	40	7.2%	0.71 [0.25, 2.06]	
Li F 2019	4	45	6	44	6.2%	0.65 [0.20, 2.15]	
Liu ZR 2019	12	38	10	38	10.3%	1.20 [0.59, 2.44]	
Shi HL 2019	5	31	6	31	6.2%	0.83 [0.28, 2.45]	
Tang Y 2016	23	35	24	35	24.7%	0.96 [0.69, 1.33]	
Wu H 2016	3	10	9	25	5.3%	0.83 [0.28, 2.46]	
Xia LP 2016	9	50	10	50	10.3%	0.90 [0.40, 2.02]	
Xie SP 2013	6	27	8	27	8.2%	0.75 [0.30, 1.87]	
Zhang SH et al. 2015	10	48	9	47	9.3%	1.09 [0.49, 2.44]	
Subtotal (95% CI)		398		411	100.0%	0.95 [0.75, 1.20]	
Total events	91		101				
Heterogeneity: Chi² = 1.91, df = 9 (P = 0.99); I² = 0%							
Test for overall effect: Z = 0.46 (P = 0.65)							
1.3.4 Coagulation abnormalities rate							
Cheng XD 2015	32	74	34	74	21.0%	0.94 [0.66, 1.35]	
Jin HY 2014	21	40	24	40	14.8%	0.88 [0.59, 1.29]	
Li F 2019	0	45	1	44	0.9%	0.33 [0.01, 7.80]	
Shi HL 2019	12	37	19	37	11.7%	0.63 [0.36, 1.11]	
Tang Y 2016	10	31	13	31	8.0%	0.77 [0.40, 1.48]	
Wu H 2016	16	35	17	35	10.5%	0.94 [0.57, 1.55]	
Xia LP 2016	4	10	16	25	5.6%	0.63 [0.28, 1.41]	
Xie SP 2013	24	50	23	50	14.2%	1.04 [0.69, 1.58]	
Zhang SH et al. 2015	20	48	21	47	13.1%	0.93 [0.59, 1.48]	
Subtotal (95% CI)		370		383	100.0%	0.87 [0.74, 1.03]	
Total events	139		168				
Heterogeneity: Chi² = 3.48, df = 8 (P = 0.90); I² = 0%							
Test for overall effect: Z = 1.62 (P = 0.11)							

0.01 0.1 1 10 100
Favours [PEG-Asp group]   Favours [E.coli L-Asp group]

	PEG-Asp group			E.coli L-Asp group				Mean Difference	Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Fixed, 95% CI	IV, Fixed, 95% CI
1.4.1 Frequency of administration									
Jin HY 2014	1.8	0.2	40	7.8	2.3	40	22.3%	-6.00 [-6.72, -5.28]	
Tang Y 2016	2.1	0.7	31	7.7	2.2	31	17.3%	-5.60 [-6.41, -4.79]	
Wu H 2016	2.1	1	35	7.2	1.8	35	24.5%	-5.10 [-5.78, -4.42]	
Xie SP 2013	1.9	0.9	50	7.5	2.3	50	24.4%	-5.60 [-6.28, -4.92]	
Zhang SH et al. 2015	1.9	0.8	48	7.6	3.4	47	11.5%	-5.70 [-6.70, -4.70]	
Subtotal (95% CI)			204			203	100.0%	-5.58 [-5.92, -5.24]	
Heterogeneity: Chi² = 3.29, df = 4 (P = 0.51); I² = 0%									
Test for overall effect: Z = 32.35 (P < 0.00001)									
1.4.2 Length of hospital stay									
Jin HY 2014	11.5	3.9	40	19.5	4.5	40	30.5%	-8.00 [-9.85, -6.15]	
Tang Y 2016	12.2	4.5	31	18.9	5.9	31	15.2%	-6.70 [-9.31, -4.09]	
Wu H 2016	11.4	4.6	35	17.8	5.9	35	16.9%	-6.40 [-8.88, -3.92]	
Xie SP 2013	12.1	5.3	50	18.7	6.3	50	19.9%	-6.60 [-8.88, -4.32]	
Zhang SH et al. 2015	12.1	4.8	48	18.9	7.1	47	17.4%	-6.80 [-9.24, -4.36]	
Subtotal (95% CI)			204			203	100.0%	-7.04 [-8.06, -6.02]	
Heterogeneity: Chi² = 1.54, df = 4 (P = 0.82); I² = 0%									
Test for overall effect: Z = 13.54 (P < 0.00001)									

-10 -5 0 5 10
Favours [PEG-Asp group]   Favours [E.coli L-Asp group]