Journal of Clinical Gastroenterology

Comparative Effectiveness and Safety of Polyethylene Glycol Electrolyte Solution Versus Lactulose for Treatment of Hepatic Encephalopathy: A Systematic Review and Meta-Analysis

(Supplementary File)
Supplementary file 1. Search term

1. Pubmed

1# ((("Hepatic Encephalopathy"[Mesh]) OR (((((((((((((((((((((((((Encephalopathies, Hepatic) OR (Hepatic Encephalopathies)) OR (Encephalopathy, Hepatic) OR (Portal-Systemic Encephalopathy)) OR (Portal Systemic Encephalopathy) OR (Encephalopathy, Portal-Systemic) OR (Encephalopathies, Portal-Systemic) OR (Encephalopathy, Portal Systemic) OR (Portal-Systemic Encephalopathies)) OR (Encephalopathy, Portosystemic) OR (Portal Systemic Encephalopathy) OR (Encephalopathy, Portal Systemic) OR (Portosystemic Encephalopathies)) OR (Encephalopathy, Hepatocerebral) OR (Encephalopathies, Hepatocerebral) OR (Hepatocerebral Encephalopathies)) OR (Hepatic Coma) OR (Coma, Hepatic) OR (Comas, Hepatic) OR (Hepatic Stupors) OR (Hepatic Comas)) OR (Hepatic Stupors)) OR (Stupor, Hepatic) OR (Stupors, Hepatic) OR (Fulminant Hepatic Failure with Cerebral Edema))))

2# ("Polyethylene Glycols"[Mesh]) OR (((((((((polyethylene glycol electrolyte powder) OR (Macrogol)) OR (Macrogols)) OR (Polyethylene Oxide)) OR (Oxide, Polyethylene)) OR (Oxides, Polyethylene)) OR (Polyethylene Oxides)) OR (Polyethyleneoxide)) OR (Polyethyleneoxides) OR (Polyoxyethylenes)) OR (Polyoxyethylene) OR (Polyglycol) OR (Polyglycols)) OR (Polyethylene Glycol) OR (Glycol, Polyethylene)) OR (Glucols, Polyethylene) OR (Carbowax)))

3# (randomized controlled trial[Publication Type] OR randomized[Title/Abstract] OR placebo[Title/Abstract])

2. Embase

1# 'Encephalopathies, Hepatic':ab,ti or 'Hepatic Encephalopathies':ab,ti or 'Encephalopathy, Hepatic':ab,ti or 'Portal-Systemic Encephalopathy':ab,ti or 'Portal Systemic Encephalopathy':ab,ti or 'Encephalopathies, Portal-Systemic':ab,ti or 'Encephalopathy, Portal-Systemic':ab,ti or 'Portal-Systemic Encephalopathies':ab,ti or 'Encephalopathy, Portosystemic':ab,ti or 'Portosystemic Encephalopathies':ab,ti or 'Hepatocerebral Encephalopathy':ab,ti or 'Hepatocerebral':ab,ti or 'Encephalopathies, Hepatocerebral':ab,ti or 'Hepatocerebral Encephalopathies':ab,ti or 'Hepatic Coma':ab,ti or 'Hepatic Stupor':ab,ti or 'Hepatic Stupors':ab,ti or 'Fulminant Hepatic Failure with Cerebral Edema':ab,ti

2# 'Polyethylene glycol electrolyte powder':ab,ti or 'Macrogol':ab,ti or 'Macrogols':ab,ti or 'Polyethylene Oxide':ab,ti or 'Oxide, Polyethylene':ab,ti or 'Oxides, Polyethylene':ab,ti or 'Polyethylene Oxides':ab,ti or 'Polyethyleneoxide':ab,ti or 'Polyethyleneoxides':ab,ti or 'Polyoxyethylenes':ab,ti or 'Polyoxyethylene':ab,ti or 'Polyglycol':ab,ti or 'Polyglycols':ab,ti or 'Polyethylene Glycol':ab,ti or 'Glycol, Polyethylene':ab,ti or 'Glycols, Polyethylene':ab,ti or 'Carbowax':ab,ti

3# 'randomized controlled trial':ab,ti or 'randomized':ab,ti or 'placebo':ab,ti or 'RCT':ab,ti
3. Web of science
1# hepatic encephalopathy OR Encephalopathies, Hepatic OR Hepatic Encephalopathies OR Encephalopathy, Hepatic OR Portal-Systemic Encephalopathy OR Portal Systemic Encephalopathy OR Encephalopathy, Portal-Systemic OR Encephalopathies, Portal-Systemic OR Encephalopathy, Portal Systemic OR Portal-Systemic Encephalopathies OR Encephalopathy, Portosystemic OR Hepatocerebral Encephalopathy OR Portosystemic Encephalopathy OR Hepatic Encephalopathies, Portosystemic OR Portosystemic Encephalopathies OR Encephalopathy, Hepatocerebral OR Encephalopathies, Hepatocerebral OR Hepatic Coma OR Coma, Hepatic OR Hepatic Comas OR Hepatic Stupor OR Hepatic Stupors OR Stupor, Hepatic OR Stupors, Hepatic OR Fulminant Hepatic Failure with Cerebral Edema

2# Polyethylene Glycol OR polyethylene glycol electrolyte powder OR Macrogol OR Macrogols OR Polyethylene Oxide OR Oxide, Polyethylene OR Oxides, Polyethylene OR Polyethylene Oxides OR Polyethyleneoxide OR Polyethyleneoxides OR Polyoxymethylene OR Polyoxyethylene OR Polyglycol OR Polyglycols OR Polyethylene Glycol OR Glycol, Polyethylene OR Glycols, Polyethylene OR Carbowax

3# randomized controlled trial OR randomized OR placebo OR RCT

4. COCHRANE
1# (hepatic encephalopathy):ti,ab,kw OR (Encephalopathies, Hepatic):ti,ab,kw OR (Hepatic Encephalopathies):ti,ab,kw OR (Encephalopathy, Hepatic):ti,ab,kw OR (Portal-Systemic Encephalopathy):ti,ab,kw OR (Portal Systemic Encephalopathy):ti,ab,kw OR (Encephalopathy, Portal-Systemic):ti,ab,kw OR (Encephalopathies, Portal-Systemic):ti,ab,kw OR (Portal Systemic):ti,ab,kw OR (Portal-Systemic Encephalopathies):ti,ab,kw OR (Encephalopathy, Portosystemic):ti,ab,kw OR (Encephalopathies, Portosystemic):ti,ab,kw OR (Portal-Systemic Encephalopathy):ti,ab,kw OR (Portal Systemic Encephalopathy):ti,ab,kw OR (Encephalopathy, Hepatocerebral):ti,ab,kw OR (Hepatocerebral):ti,ab,kw OR (Hepatocerebral Encephalopathy):ti,ab,kw OR (Hepatic Coma):ti,ab,kw OR (Coma, Hepatic):ti,ab,kw OR (Comas, Hepatic):ti,ab,kw OR (Hepatic Comas):ti,ab,kw OR (Hepatic Stupor):ti,ab,kw OR (Hepatic Stupors):ti,ab,kw OR (Stupor, Hepatic):ti,ab,kw OR (Stupors, Hepatic):ti,ab,kw OR (Fulminant Hepatic Failure with Cerebral Edema):ti,ab,kw

2# (Polyethylene Glycol):ti,ab,kw OR (polyethylene glycol electrolyte powder ):ti,ab,kw OR (Macrogol):ti,ab,kw OR (Macrogols):ti,ab,kw OR (Polyethylene Oxide):ti,ab,kw OR (Oxide, Polyethylene):ti,ab,kw OR (Oxides, Polyethylene):ti,ab,kw OR (Polyethylene Oxides):ti,ab,kw OR (Polyethyleneoxide):ti,ab,kw OR (Polyethyleneoxides):ti,ab,kw OR (Polyoxymethylene):ti,ab,kw OR (Polyoxyethylene):ti,ab,kw OR (Polyglycol):ti,ab,kw OR (Polyglycols):ti,ab,kw OR (Polyethylene Glycol):ti,ab,kw OR (Glycol, Polyethylene):ti,ab,kw OR (Glycols, Polyethylene):ti,ab,kw OR (Carbowax):ti,ab,kw

3# (randomized controlled trial):ti,ab,kw OR (OR randomized):ti,ab,kw OR (Placebo):ti,ab,kw OR (RCT):ti,ab,kw
Supplementary file 2. Outcomes on improvement of polyethylene glycol vs lactulose on hepatic encephalopathy

| Study                          | RR    | 95% Conf. Interval | % Weight |
|-------------------------------|-------|--------------------|----------|
| Ahmed, S. (2020)              | 1.924 | 1.073              | 3.451    | 11.40    |
| Ismail, K. B. (2020)          | 1.417 | 0.947              | 2.119    | 14.15    |
| Naderian, M. (2017)           | 1.293 | 0.972              | 1.719    | 17.33    |
| Rahimi, R. S. (2014)          | 1.756 | 1.180              | 2.612    | 14.69    |
| Shehata, H. H. (2018)         | 1.306 | 1.083              | 1.573    | 42.44    |

M-H pooled RR | 1.456 | 1.260 | 1.682 | 100.00 |

Heterogeneity chi-squared = 3.73 (d.f. = 4) p = 0.444
I-squared (variation in RR attributable to heterogeneity) = 8.8%

Test of RR=1 : z = 5.09 p = 0.000

Figure S2A Meta-analysis of the comparison of the clinical efficacy of PEG with lactulose at 24 hours.

Figure S2B Funnel plot illustrating the comparison of the clinical efficacy of PEG with lactulose at 24 hours.
Figure S2C Publication bias of included studies on the comparison of the clinical efficacy of PEG with lactulose at 24 hours.

Supplementary file 3. Outcomes on adverse effects of polyethylene glycol vs lactulose on hepatic encephalopathy.

| Study                | RR     | [95% Conf. Interval] | % Weight |
|----------------------|--------|----------------------|----------|
| Ahmed, S. (2020)     | 2.138  | 0.588                | 7.767    | 8.61       |
| Bajwa, K. N. (2019)  | 0.714  | 0.244                | 2.091    | 20.78      |
| Rahimi, R. S. (2014) | 0.652  | 0.175                | 2.428    | 14.22      |
| Shehata, H. M. (2018)| 0.579  | 0.308                | 1.088    | 56.39      |
| Ismail, K. B. (2020) | (Excluded) |                   |          |            |
| Naderian, M. (2017)  | (Excluded) |                   |          |            |
| Raja W, (2019)       | (Excluded) |                   |          |            |

M-H pooled RR | 0.752 0.475 1.189 100.00

Heterogeneity chi-squared = 3.23 (d.f. = 3) p = 0.357
I-squared (variation in RR attributable to heterogeneity) = 7.2%

Test of RR=1 : z = 1.22 p = 0.222

Figure S3A Meta-analysis of adverse events experienced by patients treated with PEG vs lactulose.
Figure S3B Funnel plot illustrating adverse events experienced by patients treated with PEG vs lactulose.

Begg's Test

adj. Kendall's Score (P-Q) = 2
Std. Dev. of Score = 2.94
Number of Studies = 4
z = 0.68
Pr > |z| = 0.497
z = 0.34 (continuity corrected)
Pr > |z| = 0.734 (continuity corrected)

Egger's test

| Slope | Coef. | Std. Err. | t   | P>|t|  | 95% Conf. Interval |
|-------|-------|-----------|-----|------|-------------------|
| Bias  | 1.956589 | 1.956589 | 1.23 | 0.235 | -4.566803 to 8.384926 |

Figure S3C Publication bias of included studies on the comparison of adverse events of PEG with lactulose.
Supplementary file 4. Outcomes on hospitalization of polyethylene glycol vs lactulose on hepatic encephalopathy

| Study                          | WMD  | 95% Conf. Interval | % Weight |
|-------------------------------|------|--------------------|----------|
| Ahmed, S. (2020)              | -3.874 | -4.681 -3.068          | 18.62    |
| Bajwa, K. N. (2019)           | -0.810 | -1.568 -0.052         | 18.93    |
| Naderian, M. (2017)           | -2.100 | -2.481 -1.719         | 20.86    |
| Rahimi, R. S. (2014)          | -4.000 | -8.861 0.861          | 3.16     |
| Raja W, (2019)                | 0.040  | -0.872 0.952          | 17.93    |
| Shehata, H. H. (2018)         | -1.700 | -2.167 -1.233         | 20.51    |
| D+L pooled WMD                | -1.781 | -2.716 -0.845         | 100.00   |

Heterogeneity chi-squared = 50.74 (d.f. = 5) p = 0.000
I-squared (variation in WMD attributable to heterogeneity) = 90.1%
Estimate of between-study variance Tau-squared = 1.0535

Test of WMD=0 : z = 3.73 p = 0.000

Figure S4A Meta-analysis of serum ammonia concentration before treating with PEG vs lactulose.
(fixed effects analysis).

Figure S4B Funnel plot illustrating the comparison of hospital stays of PEG with lactulose.
Begg's Test

adj. Kendall's Score (P-Q) = 3
Std. Dev. of Score = 5.32
Number of Studies = 6
z = 0.56
Pr > |z| = 0.573
z = 0.38 (continuity corrected)
Pr > |z| = 0.707 (continuity corrected)

Egger's test

| Std_Eff | Coef.    | Std. Err. | t      | P>|t| | [95% Conf. Interval] |
|---------|----------|-----------|--------|------|----------------------|
| slope   | -1.956431| .9560221  | -2.05  | 0.110| -4.610774, 0.6979113 |
| bias    | .3514514 | 3.062102  | 0.11   | 0.914| -0.150306, 8.853208  |

Figure S4C Publication bias of included studies on the comparison of hospital stays of PEG with lactulose

Figure S4D Sensitivity analysis of length of hospital stay comparing PEG with lactulose
Supplementary file 5. Outcomes on serum ammonia of polyethylene glycol vs lactulose on hepatic encephalopathy

| Study                  | WMD   | [95% Conf. Interval] | % Weight |
|------------------------|-------|----------------------|----------|
| Ahmed, S. (2020)       | 8.652 | -1.351 19.055        | 88.02    |
| Naderian, M. (2017)    | 9.600 | -27.764 46.964       | 6.66     |
| Rahimi, R. S. (2014)   | -29.00| -70.139 12.139       | 5.41     |
| I-V pooled WMD         | 6.851 | -2.721 16.424        | 100.00   |

Heterogeneity chi-squared = 3.09 (d.f. = 2) p = 0.214
I-squared (variation in WMD attributable to heterogeneity) = 35.2%

Test of WMD=0 : z = 1.40 p = 0.161

Figure S5A Meta-analysis of serum ammonia concentration before treating with PEG vs lactulose. (fixed effects analysis).

Figure S5B Forest plot illustrating serum ammonia concentration before treating with PEG vs lactulose. (fixed effects analysis).
| Study                  | WMD  | [95% Conf. Interval] | % Weight |
|------------------------|------|----------------------|----------|
| Ahmed, S. (2020)      | -9.996 | -18.819 | -1.173 | 38.73 |
| Naderian, M. (2017)   | 8.100  | -7.360  | 23.560 | 34.77 |
| Rahimi, R. S. (2014)  | 38.000 | 10.972  | 65.028 | 26.50 |
| D+L pooled WMD        | 9.017  | -14.394 | 32.427 | 100.00 |

Heterogeneity chi-squared = 13.20 (d.f. = 2) p = 0.001
I-squared (variation in WMD attributable to heterogeneity) = 84.9%
Estimate of between-study variance Tau-squared = 348.1093

Test of WMD=0 : z = 0.75 p = 0.450

Figure S5C Meta-analysis of serum ammonia concentration after treating with PEG vs lactulose. (random effects analysis).