L-ORNITHINE L-ASPARTATE [LOLA] IMPROVES BOTH SEVERE ENCEPHALOPATHY AND SURVIVAL IN PATIENTS WITH LIVER CIRRHOSIS: RESULTS OF RCTS, SYSTEMATIC REVIEWS AND META-ANALYSES

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ISHEN 20.23
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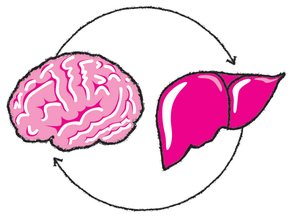
27-29 September 2023



INTRODUCTION

- Liver Cirrhosis remains a leading cause of death in 2023.
- Variations in age-standardized death rates according to geographic location and etiology of cirrhosis [1]
- LOLA: improves encephalopathy grade and survival in many studies [2]

AIMS

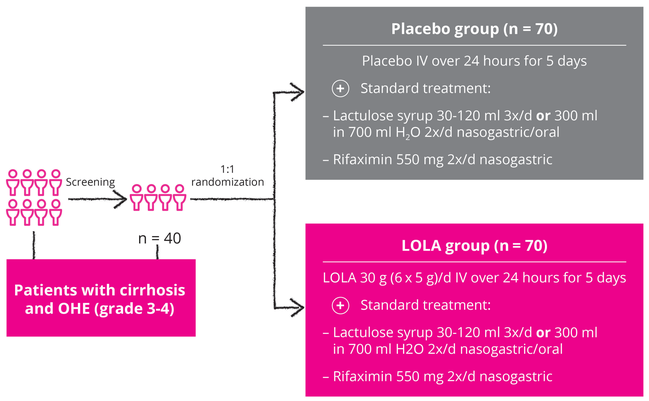
- Systematic review of evidence from RCTs of improved HE and survival by LOLA

METHODS

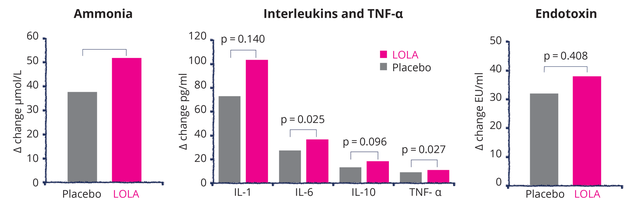
- Electronic/manual searches of data from published RCTs
- Use of Random Effects Model [Pooled Risk Ratio, RR] with 95 % CI

RESULTS

- **LOLA reduced mortality by > 50 % in majority of published RCTs**
- **Intravenous and oral formulations of LOLA equally effective** [3]
  - Kircheis et al., 1997: No significant effects of iv LOLA on mortality
  - Stauch et al., 1998: No significant effects of oral LOLA on mortality
  - Chen et al., 2005: Decreased mortality from 7/40 in control by iv LOLA [p<0.005]
  - Ahmad et al., 2008: Decreased mortality from 4/40 in control by iv LOLA [p<0.022]
  - Abid et al., 2011: Decreased mortality from 7/60 in control to 4/60 by iv LOLA
  - Mittal et al., 2011: No significand effects of oral LOLA on mortality
  - Sharma et al., 2016: Decreased mortality from 2/30 in control to 0/31 by oral LOLA
  - Varakanahalli et al., 2017: Decreased mortality from 10/72 to 5/73 by oral LOLA
  - Sidhu et al., 2018: Decreased mortality from 6/95 to 1/98 by oral LOLA
- **Follow-up meta-analysis by Cochrane Database Procedure** [4]
  - significant reduction of all-cause mortality with RR:0.42, 95 % CI:0.24 to 0.72
- **LOLA/lactulose/rifaximin combined more effective than lactulose/rifaximin alone for improvement of OHE and 28-day mortality rates** [5]
  - Jain et al., 2021: Hepatology, DOI:10.1002/hep.3225.
  - 140 patients randomized to receive LOLA or placebo in combination with rifaximin + lactulose
  - Outcome measures: improvement in OHE by day 5, mortality at 28 days
- **Consort Diagram [design, randomization, outcomes]**



Protective effects of LOLA: Possible mechanisms involving LOLA-induced reductions of ammonia and proinflammatory markers

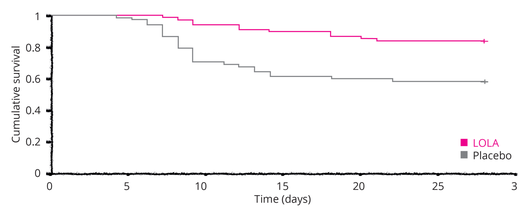


The decreases in ammonia, IL-6, and TNF-α levels were significantly greater in the LOLA group.

1]. Significantly greater reductions of blood ammonia in LOLA-treatment group compared to placebo.

2]. Selective reductions of proinflammatory markers [TNF-alpha, IL-6] in LOLA Treatment group compared to placebo.

3]. Improved 28-day survival in patients treated with LOLA compared to placebo [Kaplan Meier analysis]



LOLA	67	67	63	60	57	56
Placebo	67	65	47	41	40	39

Combination therapy with LOLA resulted in significantly higher survival rates.*

At 28 days of follow-up, 11 of 67 patients (16.4%) in the LOLA arm died, compared to 28 of 67 patients (41.8%) in the placebo arm (p = 0.001).

CONCLUSIONS

[1] Pooled data from 9 RCTs confirmed significant beneficial effects of LOLA on OHE grades with improvements in survival rates in 6 trials compared to placebo

[2] Intravenous and oral formulations of LOLA equally effective

[3] Findings confirmed by meta-analyses

[4] Combination therapy [LOLA, lactulose, rifaximin] superior to lactulose/rifaximin alone for treatment of OHE grades and 28-day mortality [4]

[5] Beneficial effects of LOLA in combination therapy trial accompanied by greater reductions of hyperammonemia and selective reduced levels of pro-inflammatory markers

[6] Beneficial effects on HE and survival in cirrhosis likely result from bimodal actions of LOLA on systemic inflammation and hyperammonemia

REFERENCES & CONTACT

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(2) Butterworth RF, 2019, Metabolic Brain Dis., doi:10.1007/s/11011-019-00463-8.

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[5] Jain A, et al., Hepatology, 2021, 00(1-10), doi.org/10.1002/hep.32255.

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