Lactulose vs PEG for treatment of hepatic encephalopathy. HELP RCT- Hepatic Encephalopathy: Lactulose vs PEG

Reference: Authors: Rahimi R, Singal A, Cuthbert J, Rockey D. JAMA Internal Medicine September 2014

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Groundwork:

HE is delirium induced by a mechanism presumed to be accumulation of nitrogen containing products such as ammonia that are normally cleared by the liver in the setting of liver dysfunction. The products are taken up by the cerebral astrocytes, cerebral edema occurs and delirium develops. The nitrogen products are produced by bacteria in the colon and the treatment is to suppress their production and increase their clearance with laxatives- lactulose being the primary product studied for this purpose. You can also use non absorbable antibiotics such as Rifaximin or Neomycin and there is even some data to support the use of probiotics.

Lactulose is a disaccharide that is not digested in the small intestine and osmotically draws fluid into the bowel. In the large intestine it is fermented by gut flora producing further compounds that have osmotic properties and stimulate gut motility. One of these products is methane gas that this causes bloating and flatulence. It is believed that it converts ammonia to ammonium and excretes it.

PEG works similarly as a laxative in that it draws fluid into the lumen osmotically, but it is not broken down by the gut flora. Moreover, it contains electrolytes that result in a more neutral balance and thus does not result in serum electrolyte imbalances and does not cause gas/bloating.

Abstract:

IMPORTANCE Hepatic encephalopathy (HE) is a common cause of hospitalization in patients with cirrhosis. Pharmacologic treatment for acute (overt) HE has remained stable for some decades

OBJECTIVE To compare polyethylene glycol 3350–electrolyte solution (PEG) and lactulose treatments in patients with cirrhosis admitted to the hospital for HE. We hypothesized that rapid catharsis of the gut using PEG may resolve HE more effectively than lactulose.

DESIGN, SETTING, AND PARTICIPANTS The HELP (Hepatic Encephalopathy: Lactulose vs Polyethylene Glycol 3350-Electrolyte Solution) study is a randomized clinical trial in an academic tertiary hospital of 50 patients with cirrhosis (of 186 screened) admitted for HE.

INTERVENTIONS Participants were block randomized to receive treatment with PEG, 4-L dose (n = 25), or standard-of-care lactulose (n = 25) during hospitalization.

MAIN OUTCOMES AND MEASURES The primary end point was an improvement of 1 or more in HE grade at 24 hours, determined using the hepatic encephalopathy scoring algorithm (HESA), ranging from 0 (normal clinical and neuropsychological assessments) to 4 (coma). Secondary outcomes included time to HE resolution and overall length of stay.

RESULTS A total of 25 patients were randomized to each treatment arm. Baseline clinical features at admission were similar in the groups. Thirteen of 25 patients in the standard therapy arm (52%) had an improvement of 1 or more in HESA score, thus meeting the primary outcome measure, compared with 21 of 23 evaluated patients receiving PEG (91%) ($P < .01$); 1 patient was discharged before final analysis and 1 refused participation. The mean (SD) HESA score at 24 hours for patients receiving standard therapy changed from 2.3 (0.9) to 1.6 (0.9) compared with a change from 2.3 (0.9) to 0.9 (1.0) for the PEG-treated groups ($P = .002$).

The median time for HE resolution was 2 days for standard therapy and 1 day for PEG ($P = .01$). Adverse events were uncommon, and none was definitely study related.

CONCLUSIONS AND RELEVANCE PEG led to more rapid HE resolution than standard therapy, suggesting that PEG may be superior to standard lactulose therapy in patients with cirrhosis hospitalized for acute HE.

Strengths: Simple design RCT direct head to head comparison with a somewhat objective measurement. Similar population of patients, different blinded reviewers using different versions of the test at each time point. HE a common complication of liver failure and the study presents a cheap and potentially more effective alternative to standard therapy.

Weaknesses: Small study- only 25 per group selected based on the fewest possible participants to achieve statistical significance. Single center unblinded in that the patients and administers knew what they were receiving. 1 dose of lactulose could be given in the PEG group. Route of lactulose could be PO vs PR. Very high volume PEG 4L resulting in total bowel prep and very high number of BMs- impractical for common use and may not be a fair comparison due to dosage difference, ie 4L of prep has 14 standard PEG doses vs 3 standard doses of lactulose. Is there a role for PEG for prophylaxis or for an effective, lower dose? The study could have standard dose lactulose compared to various doses of PEG.

Relevance to palliative care: The liver is one of the most common sites for metastases and liver failure/ hepatic encephalopathy is no uncommon in our population. Moreover, given the high incidence of pain- opioids are commonly used and PEG is the first line therapy to treat/ prevent opioid-induced constipation and thus this medication is already widely used. PEG was preferred for taste and SEs and some pts switched to this therapy from lactulose at the time of discharge.