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Bowel Movement Frequency is not Linked with Cognitive Function in Cirrhosis

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Introduction:

The spectrum of hepatic encephalopathy (HE) ranges from overt (OHE) to cognitive impairment i.e. covert HE (CHE)[1]. The first-line therapy is lactulose, which is titrated to achieve ~2-3 soft/loose daily bowel movements (BM). This metric is considered dogma for practitioners despite erratic results, GI adverse events and poor tolerance in Western countries[1].There are logistic barriers for the widespread uptake of rifaximin, the second-line therapy. Moreover, while BM frequency-directed dose titration of lactulose is the usual practice, its impact on objective cognitive performance is unclear. Our aim is to determine the impact of BM frequency on cognition in patients with/without prior OHE.

Methods:

We enrolled cirrhosis outpatients from the Richmond VAMC. We included those without substance abuse for >3 months, without uncontrolled neurocognitive diagnoses, mini-mental status exam≥25 and medication adherence for ≥6 months. Demographics, cirrhosis etiology, MELD score, prior OHE, weekly BM frequency and medications (lactulose, rifaximin, opioids, stool softeners) were recorded. Patients underwent block design, digit symbol, number connection-A/B test compared to norms for CHE (≥2 abnormal=CHE)[2]. Since lactulose can impact BMs and we do not initiate it before OHE, we analyzed patients with prior OHE/not separately and compared 2-3 BMs/day versus rest.

Within each group we correlated the number of tests impaired (0-4) with BM frequency. Finally, regression models with number of abnormal tests as the outcome was performed

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Author contributions: JSB conceptualized and was involved in all aspects, AF performed cognitive testing, ND, BR, HS, ON, CA and RH performed data collection and analysis. All authors approved the final manuscript.

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for the entire group and within prior OHE/not using clinical (MELD, opioids, alcohol-related etiology, within OHE [lactulose, rifaximin]), demographics (age, sex) and BMs as independent variables.

Results:

269 patients, mostly men (93%), with hepatitis C (n=131) followed by alcohol (n=68) NAFLD (n=42) and others (n=28) were included. Opioid and stool softener use was similar across groups (Figure S1).

Prior OHE(n=120):

Twenty-nine were on lactulose-only, 17 on rifaximin-only and 74 on both. Weekly BM frequency was similar in those on lactulose only (19.2±10.6), lactulose+rifaximin (19.2±7.9) and rifaximin alone (18.0±7.9, p=0.91). Most patients had CHE (Table). Number of cognitive tests impaired was not correlated with BMs (r=0.13, p=0.2, Figure S2) or MELD (r=−0.04, p=0.73) but to age (r=0.3, p=0.007). On regression number of impaired tests were associated only with age [0.05(CI:0.07-0.03),p=0.007] but not with sex, MELD, BM frequency or use of lactulose/rifaximin/both.

Without OHE(n=149):

The majority had CHE (Table). Number of cognitive tests impaired was not correlated with BMs (r=−0.04, p=0.62 Figure S2) or MELD (r=−0.19, p=0.09), age (r=0.2, p=0.06). On regression number of impaired tests were associated only with age [0.01(CI:0.002-0.018),p=0.001] but not with sex, MELD or BM frequency.

In the entire group CHE vs no-CHE:

CHE was found in 220 patients who were older and more likely to be on lactulose+rifaximin (Table). BMs were again similar regarding number of abnormal tests (none:14.2±2.3, one:14.0±7.4, two:15.5±8.3, three:15.1±10.3 and four:16.5±10.4, p=0.62) and not correlated with number of tests impaired (r=0.09, p=0.13 Figure S2). On regression only prior-OHE[[0.011(CI:0.005-0.017),p<0.001] and higher age [0.01(CI:0.004-0.016),p<0.0001] were significantly associated with number of abnormal CHE tests.

2-3 daily BMs/not:

No difference in CHE/cognitive tests and demographics was seen (Table S1).

Discussion:

We found that BM frequency did not associate with cognitive function regardless of lactulose or rifaximin use in an outpatient cirrhosis cohort. Since lactulose can be a confounder or even mediator regarding BM frequency, we performed these analyses separately between groups with/without OHE and found similar patterns. Moreover, BM frequency, regardless of 2-3/day or not did not affect cognitive performance.

Cognitive testing objectively reflects the burden of HE and could be used to gauge success of HE-directed therapies[3]. Since cognition is linked with OHE recurrence and daily function, metrics used to guide therapy should be related to it [4,5,6]. However, we did not find a consistent relationship between BMs and cognition through regression, within subgroups (prior-HE/not, CHE/not, 2-3BMs/day or not), and on individual tests. It is possible that HE-treatment benefits could be obtained without reaching the 2-3 daily BM frequency[7]. These results may have important implications since BM frequency is used by clinicians, patients, and caregivers to titrate lactulose therapy[3] despite unpredictable and distressing adverse events[8], often leading to poor adherence. Therefore, metrics other than the number of BMs, such as cognitive function and stool characteristics may need to be used. Our study is limited by male predominance, lack of quality-of-life or longitudinal analyses. However, even when subdivided into groups on lactulose versus not, we found a similar pattern.

We conclude that cognitive performance in an outpatient cirrhosis cohort is not associated with bowel movement frequency regardless of lactulose use. De-emphasizing bowel movement frequency as a metric for adequate lactulose dosing could potentially improve adherence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table: Comparison of Patients with and without overt or covert hepatic encephalopathy

Variables	Prior OHE vs No-OHE (entire group)			Variables	CHE vs no-CHE (entire group)		
	No-OHE (n=149)	Prior OHE (n=120)	P value		No-CHE (n=49)	CHE (n=220)	P value
Age	58.1±7.7	60.4±6.3	0.01	Age	56.2±7.9	59.7±6.9	0.008
Men (%)	142 (95%)	105 (88%)	0.9	Men (%)	42 (86%)	209 (95%)	0.95
Alcohol etiology (%)	31 (21%)	36 (30%)	0.007	Alcohol etiology (%)	9 (18%)	56 (25%)	0.41
MELD score	10.6±4.5	16.4±5.2	<0.0001	MELD score	12.1±5.5	13.1±5.6	0.28
Opioid Use	44 (30%)	33 (28%)	0.71	Opioid Use	10 (20%)	67 (30%)	0.14
Stool softeners	24 (16%)	27 (12%)	0.18	Stool softeners	6 (12%)	45 (20%)	0.18
CHE (%)	121 (81%)	99 (83%)	0.78	Prior OHE (%)	29 (59%)	91(41%)	0.02
NCT-A (sec)	43.8±19.0	59.3±32.7	<0.0001	NCT-A (sec)	29.8±8.1	54.4±27.1	<0.0001
NCT-B (sec)	119.6±70.1	184±119	<0.0001	NCT-B (sec)	70.7±16.6	162±101	<0.0001
DST (number)	48.4±13.0	37.9±13.8	<0.0001	DST (number)	58.5±13.0	40.8±12.6	<0.0001
BDT (number)	27.2±12.6	20.7±13.1	<0.0001	BDT (number)	38.7±10.1	20.7±11.3	<0.0001
Number of tests impaired 0/1/2/3/4	6/30/31/48/34	3/10/19/24/64	<0.0001	Number of tests impaired 0/1/2/3/4	9/40/0/0/0	0/0/50/72/98	<0.0001
Lactulose (%)	-	29 (24%)	Only in prior OHE	Lactulose (%)	4 (8%)	24 (11%)	0.79
L+R (%)	-	74 (62%)		L+R (%)	10 (20%)	64 (29%)	0.03
Rif alone (%)	-	17 (14%)		Rif alone (%)	3 (6%)	14 (6%)	1.0
Weekly BM number	13.8±8.5	18.4±10.4	<0.0001	Weekly BM number	14.2±6.6	15.9±10.0	0.14
Weekly BM 14-21	62	62	0.02	Weekly BM 14-21	22	102	0.12
Weekly BM <14	68	33	<0.001	Weekly BM <14	21	80	0.61
Weekly BM >21	19	25	0.13	Weekly BM >21	6	38	0.11

OHE: overt hepatic encephalopathy, CHE: covert hepatic encephalopathy, BM: bowel movements, Rif: rifaximin, L+R: lactulose and rifaximin, Four tests used to diagnose CHE: NCT-A/B: Number connection tests A/B; higher score indicates worse cognition on these two tests, DST: digit symbol and BDT: block design tests: lower score indicates worse cognition on these two tests. Impairment on 2 or more tests indicates CHE. Variables are presented as mean ± SD unless otherwise written