Management Patterns of Hepatic Encephalopathy: A Nationwide Survey in India

Praveen Sharma^{*}, Barjesh Chander Sharma[†]

^{*}Department of Gastroenterology, Sir Ganga Ram Hospital, New Delhi, India and [†]Department of Gastroenterology, G.B. Pant Hospital, New Delhi, India

Introduction and aim: Hepatic encephalopathy (HE) is a common complication of cirrhosis. There is no standard practice for its management. This survey was done to determine the diagnostic and therapeutic practices of physicians treating patients with HE in patients with cirrhosis. **Material and method:** We designed a 21-item questionnaire, which was given to physicians working in academic and non-academic institutes and regularly treating patients with HE. **Results:** Of 500 printed questionnaires, we received 451 questionnaires [323 (72%) general physicians and 128 (28%) gastroenterologists] from academic and non-academic institutes. Commonest precipitating event of HE was upper gastrointestinal bleed (47%), constipation (18%) and spontaneous bacterial peritonitis (12%). Arterial ammonia was always measured at admission by 156 (35%) physicians, never measured by 128 (28%) and sometimes by 167 (37%). Prophylactic antibiotics were used by 54% of physicians on the day of admission irrespective of any precipitating event, and 13% used antibiotics only if cultures were positive while others used antibiotics only if patient needs intubation or had variceal bleed as the cause of precipitation of HE. Disaccharides remained the mainstay of treatment in the management of HE and were always used by 87% ($n = 391$) followed by LOLA ($n = 297$, 66%) and rifaximin ($n = 276$, 61%). Combination of therapy was used by 84% of respondents. Lactulose enema was used in patients with HE by 280 (62%) physicians and was thought to be as good as giving lactulose by mouth or nasogastric tube in the treatment of HE. Regarding the recovery of HE with the present mode of therapy, of 451 responses, only 11% ($n = 49$) got 90–100% response to present therapy for the recovery of HE, while 70–90% response was seen by $n = 152$ (34%) and 50–70% response was seen by $n = 183$ (41%). Lactulose was prescribed as secondary prophylaxis agent more by gastroenterologists than non-gastroenterologists (76% vs 41%, $P = 0.001$). Similarly, rifaximin was more prescribed by gastroenterologists at discharge compared to non-gastroenterologists (32% vs 17%, $P = 0.001$). **Conclusion:** Non-absorbable disaccharides are the most commonly prescribed treatment for HE and for secondary prophylaxis of HE. Combination of therapy (lactulose and LOLA or lactulose and rifaximin) was commonly used by treating physicians. (J CLIN EXP HEPATOL 2015;5:199–203)

Hepatic encephalopathy (HE) is a challenging clinical complication of liver dysfunction with a wide spectrum of neuropsychiatric abnormalities that range from mild disturbances in cognitive function and consciousness to coma and death.¹ The prevalence of overt HE at the time of diagnosis of cirrhosis is 10–14% in general, 16–21% in those with decompensated cirrhosis and 10–50% in patients with transjugular intrahepatic portosystemic shunt (TIPS).^{2–4} The cumulated numbers indicate that overt HE will occur in 30–40% of those with cirrhosis at some time during their clinical course and in the survivors in most cases repeatedly. The pathogenesis of HE in cirrhosis is complex and multifactorial, but a key role is thought to

be played by circulating gut-derived toxins of the nitrogenous compounds, most notably ammonia. Therapeutic treatment options for HE are currently limited and have appreciable risks and benefits associated with their use. Management of HE primarily involves avoidance of precipitating factors, limitation of dietary protein intake and administration of various ammonia-lowering therapies such as non-absorbable disaccharides and select antimicrobial agents.⁵ Non-absorbable disaccharides, such as lactulose, have traditionally been regarded as first-line pharmacotherapy for patients with HE. Rifaximin is a novel antimicrobial agent with a wide spectrum of activity that has shown promise as an alternative antimicrobial treatment option for HE.^{6–9} Several clinical trials have compared rifaximin to the disaccharides, lactulose and lactitol and the antimicrobial neomycin. Rifaximin appears to be at least as effective as conventional drug therapy and has been associated with fewer adverse effects due to its limited systemic absorption. Patients with recurrent HE episodes despite lactulose use benefit from the addition of rifaximin, which decreases the frequency of recurrent HE episodes and related hospitalizations.^{10–12}

Keywords: hepatic encephalopathy, survey

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Address for correspondence: Praveen Sharma, Associate Professor, GRIPMER and Sir Ganga Ram Hospital, New Delhi, India. Tel.: +91 9810365151.

E-mail: Drpraveen_sharma@yahoo.com

Abbreviations: HE: hepatic encephalopathy; TIPS: transjugular intrahepatic portosystemic shunt

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In most countries, Internists and Gastroenterologists are the primary doctors who take care of patients with HE. However, there is no standard treatment protocol in most countries for the management of HE. We conducted a nationwide survey in India amongst Internists and Gastroenterologists to know their management practices in patients with HE and cirrhosis.

MATERIAL AND METHODS

This survey was designed and initiated by the author (P.S.). A printed questionnaire was sent to participants identified from the membership lists of various physician societies. The questionnaire was divided into several sections: (1) participant information (place of practice and speciality, number of patients with cirrhosis and HE which were seen in a month); (2) precipitants of HE and treatment regimen used; (3) prophylaxis of HE if any used at the time of discharge; and (4) ways of increasing awareness among physicians.

STATISTICAL ANALYSIS

Data were expressed as mean $\pm$ S.D. For a comparison of categorical variables, chi-square and Fisher's exact tests were used, and for continuous variables, a Mann-Whitney test for unpaired data and a Wilcoxon rank sum test for paired data were used as appropriate.

RESULTS

Study Participants

Five hundred questionnaires were printed and distributed at random to various physicians who had completed 3 years of internal medicine training after graduation and had at least 3 years of experience in clinical practice. Similarly, questionnaire was given to specialists in gastroenterology who had 3 years of training in the field of gastroenterology after completing their internal medicine training. Of 500 printed questionnaires, 451 completed responses were collected manually by volunteers for this study from their working place, and hence, we had a good response rate of 90%. The characteristics of the surveyed physicians are listed in Table 1. Most physicians had a hospital-based practice and 60% were from non-teaching hospital.

Management of HE

The commonest precipitating event of HE was upper gastrointestinal bleed (47%), constipation (18%) and spontaneous bacterial peritonitis (12%). However, according to this survey, no cause could be elicited in 21% and infections other than spontaneous bacterial peritonitis was the cause of HE in only 2% (Figure 1).

Table 1 Baseline Characteristics of Physicians.

Parameters	n (%)
General physicians (M.D.)	323 (72%)
Gastroenterologists (M.D, D.M.)	128 (28%)
Place of work	
Teaching hospital	167 (37%)
Non-teaching hospital	284 (63%)
Number of cirrhosis patients with HE seen in a month	
1–5	270 (60%)
6–10	110 (24%)
>10	71 (16%)

M.D., Master in Internal Medicine; D.M., Master in Gastroenterology.

Prophylactic endotracheal intubation is not a routine practice even in patients with higher grade of HE (HE 3, 4) in patients with cirrhosis. Only 39% ($n = 174$) routinely intubate patients with grade 3 and 4 HE, while 61% ($n = 277$) did not intubate these patients and manage patients with constant strict supervision care. We did not find any difference between Gastroenterologists and Internists regarding prophylactic intubation of patients with grade 3 and 4 HE (38% vs 41%, $P = 0.08$). Similarly, there was no difference between physicians working in teaching vs non-teaching hospital regarding prophylactic endotracheal intubation in these patients (41% vs 37%, $P = 0.48$).

Arterial ammonia was always measured at admission by 156 (35%) physicians, never measured by 128 (28%) and sometimes by 167 (37%). We find significant difference between Gastroenterologists and Internists (40% vs 20%, $P = 0.01$) regarding the role of ammonia measurement during management of HE.

Management of Acute Episode of HE with Disaccharides, Rifaximin, LOLA and Combination Therapy

Prophylactic antibiotics were used by 54% of physicians on the day of admission irrespective of any precipitating event, and 13% used antibiotics only if cultures were positive, while others used antibiotics only if patient need intubation or had variceal bleed as the cause of precipitation of HE. Disaccharides remain the mainstay of treatment in the management of HE and were always used by 87% ($n = 391$) followed by LOLA ($n = 297$, 66%) and rifaximin ($n = 276$, 61%). Combination of therapy was used by 84% of respondents (Table 2). However, 378 respondents (84%) still believe that there should be more studies on combination therapy for the treatment of HE, while 38 (8%) were convinced with the present data available and further 8% were not sure of this combination therapy.

Figure 1 Precipitating factors of hepatic encephalopathy in patients with cirrhosis.

Table 2 Preferred Modes of Treatment in Patients with Overt Hepatic Encephalopathy ($n = 451$) at the Time of Admission.

Treatment	Always	<10% of time	Never used
Disaccharides	391 (87%)	46 (10%)	14 (3%)
Rifaximin	276 (61%)	119 (27%)	56 (12%)
LOLA	297 (66%)	97 (22%)	57 (12%)
Combination therapy	377 (84%)	74 (16%)	–

Hence, disaccharides remain the main stay of treatment. Lactulose enema was used in patients with HE by 280 (62%) physicians and was thought to be as good as giving lactulose by mouth or nasogastric tube in the treatment of HE. Regarding the recovery of HE with present mode of therapy, of 451 responses only 11% ($n = 49$) got 90–100% response to present therapy for the recovery of HE, while 70–90% response was seen by $n = 152$ (34%) and 50–70% response was seen by $n = 183$ (41%). Only 14% respondents had <50% response with present therapy.

Side Effects of Therapy During Hospitalization

Lactulose was the commonest first line treatment used for the treatment of HE. Side effects due to lactulose or rifaximin needing change of therapy were seen only in 2% of the patients. Of 451 responses, 285 (63%) physicians using lactulose were comfortable and observed that patients could tolerate the therapy till discharge, while 391 (67%) physicians found no problems with use of rifaximin till discharge of the patient.

Advise at the Time of Discharge for Secondary Prophylaxis of HE

On asking the question about secondary prophylaxis of HE and the agent used for it, there was significant difference in prescribing lactulose as secondary prophylaxis by gastroenterologists vs non-gastroenterologists (76% vs 41%, $P = 0.001$). Similarly, rifaximin was more prescribed by gastroenterologists at discharge compared to non-gastroenterologists (32% vs 17%, $P = 0.001$).

Eighty-six ($n = 387$) physicians felt the need of some Indian guidelines for the management of overt HE and 89% ($n = 401$) felt that continuing medical education was the best way to learn more about HE and its current management trends.

DISCUSSION

This survey, which included a large number of Internists and Gastroenterologists, showed that for the management of overt HE, lactulose was the initial treatment along with

correcting the underlying precipitating factor. Combination of therapy (lactulose with rifaximin and/or LOLA) was used by 84% of respondents. Prophylactic endotracheal intubation is not a routine practice even in patients with higher grade of HE (HE 3, 4) in patients with cirrhosis. More than half of the physicians used prophylactic antibiotics at the time of admission in patients with HE.

HE is a brain dysfunction caused by liver insufficiency and/or portosystemic shunt; it manifests as a wide spectrum of neurological or psychiatric abnormalities ranging from subclinical alterations to coma.¹³ The risk for the first bout of overt HE is 5–25% within 5 years after cirrhosis diagnosis. Subjects with a previous bout of overt HE were found to have a 40% cumulative risk of recurring HE at 1 year, and subjects with recurrent overt HE have a 40% cumulative risk of another recurrence within 6 months, despite lactulose treatment.^{1,13}

Lactulose is generally used as initial treatment for OHE. A large meta-analysis of trial data did not completely support lactulose as a therapeutic agent for treatment of overt HE.⁶ However, in this survey, we found that lactulose was used as the primary mode of treatment by 87% of physicians and combination therapy by 84% of the respondents. Reversal of HE was seen in majority of the patients and only 14% of the respondents found that with present mode of therapy success rate was less than 50%. Lactulose was used as secondary prophylaxis of HE by 76% of gastroenterologists and 41% by non-gastroenterologists. Hence, this survey showed that despite lack of good quality trials for lactulose in the management of HE, still lactulose remained the first line of treatment for HE and secondary prophylaxis of HE. Side effects leading to change of therapy were seen only in 2% of the patients.

Rifaximin has been used for the therapy of HE in a number of trials comparing it with placebo, other antibiotics, non-absorbable disaccharides and in dose-ranging studies.¹⁴ These trials showed effect of rifaximin that was equivalent or superior to the compared agents with good tolerability. However, this survey showed that rifaximin as the initial mode of therapy was used by only 61% of the physicians and it was used mainly in combination with lactulose. For secondary prophylaxis of HE, it was used only by 32% of all Gastroenterologists and only 17% by Internists. So despite evidence in favour of rifaximin for the treatment of overt HE, it was not the preferred mode of treatment for acute episode of HE and for secondary prophylaxis of HE.

Antibiotics were commonly (54%) used by physicians at the time of admission irrespective of precipitating factor in the treatment of HE along with correcting the precipitating factors. Hence, widespread use of prophylactic intravenous antibiotics in all cases of HE should be avoided in view of rising trends of bacterial resistance in India. Prophylactic intubation was not a common practice by most of the physicians and it was done only in 39% of patients

with higher grades of HE. It was also surprising to find no difference in prophylactic intubation rate between Gastroenterologists and Internists. Whether it was due to lack of intensive care beds or early recovery of these patients had not been asked in this survey and needs to be evaluated in future survey.

Ammonia is often considered as one of the key agent in causation of HE.¹ All the agents used in the management of HE were targeted against lowering the ammonia level. However, routine ammonia measurement was not done by majority of the physicians. Only 35% measured it at the time of admission. We found that more gastroenterologists measure ammonia level than non-gastroenterologists. All felt the need of continued medical education for the treatment trends and newer development in management of HE and some standard guidelines for the management of overt HE. As many cases of HE were treated by Internists, some standard guidelines in this complicated field of HE need further evaluation in developing countries.

The main strength of this study was large number of Internists and Gastroenterologists and inclusion of physicians working in both academic and non-academic institutes. This gives us the clear picture of perception and practices in real life world. In conclusion, this survey provides a snapshot of the current perception of HE and its management amongst physicians practising in a large Eastern country. To conclude, lactulose was the initial mode of treatment along with correcting the underlying precipitating factor for HE. Combination of therapy (lactulose with rifaximin and/or LOLA) was used by 84% and prophylactic intravenous antibiotics were used by majority of the physicians. Need of continued medical education and standard guidelines was felt to know the latest development in the field of HE and practices that should be followed by all the physicians in the management of HE.

CONFLICTS OF INTEREST

The authors have none to declare.

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