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SAFETY AND TOLERABILITY OF LEVOSULPIRIDE IN THE PREVENTION OF GASTRIC FEED INTOLERANCE IN ICU PATIENTS

Rahul Sharma[1], Rupesh Choudhary[2], Divya Drishti[3]* and Ankita Jamwal[4]

[1,2]Junior Resident, Deptt. of Anaesthesia, Indira Gandhi Medical College & Hospital, Shimla.
[3]Medical Office, PHC Pharer, Kangra.
[4]Senior Resident, Deptt. of Obstetrics & Gynaecology, Shri Lal Bahadur Shastri Government Medical College & Hospital, Mandi.

***Corresponding Author: Dr. Divya Drishti**

[3]Medical Office, PHC Pharer, Kangra.

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ABSTRACT

Background: The objective of this study was to assess the effectiveness and safety of levosulpiride in patients with dysmotility-like functional dyspepsia including nonerosive reflux esophagitis in conditions of daily practice. Dysmotility-like functional dyspepsia is a condition characterized by delayed gastric emptying and a sense of fullness. Non-erosive reflux disease is a condition where patients experience symptoms of gastroesophageal reflux disease without evidence of esophageal mucosal injury. **Method:** The study aimed to evaluate the safety and tolerability of levosulpiride in preventing gastric feed intolerance in ICU patients. The trial was a prospective, open-label, single-arm study involving 50 ICU patients receiving levosulpiride at a dose of 25 mg three times a day for five days. The results showed that levosulpiride was well tolerated, with no serious adverse events reported, and was effective in preventing gastric feed intolerance in ICU patients. **Results:** Levosulpiride was found to significantly decrease dyspeptic symptoms and was well-tolerated in patients with dysmotility-like functional dyspepsia and non-erosive reflux disease. **Conclusion:** Levosulpiride is an effective and safe treatment for dysmotility-like functional dyspepsia and non-erosive reflux disease, demonstrating a significant decrease in symptoms and no study abandonment due to adverse events.

KEYWORDS: Levosulpiride, Dysmotility-like functional dyspepsia, Non-erosive reflux disease, Treatment efficacy.

INTRODUCTION

It is a challenge that how to assess and treat patients with dyspepsia most effectively is a frequent challenge in basic care. A relevant workload for general[1] is accounted for by dyspepsia. Results of several research have revealed that among the eight doctors who took part in a prevalence study of dyspepsia,[2] the percentage of dyspepsia patients who visited their general practitioner ranged widely from 3% to 45%. An overall six-month prevalence of dyspepsia of 38% has been recorded in population-based studies conducted in England (CitationJones and Lydeard 1992). In a Danish study, the yearly incidence rate of dyspepsia was 3.4%[3] whereas in a sample of people from the Mediterranean, the prevalence was 24% .[4] Recently, it has been proposed that dysregulation of the brain-gut axis is the primary cause of dyspepsia and that it is a biopsychosocial disorder.[5]

Functional dyspepsia's pathogenesis is unclear, but a few potential theories have been put up. There is a lot of evidence to imply that functional dyspepsia symptoms and disturbed motility are related. Antral hypomotility and delayed gastric emptying, myoelectrical anomalies of the gastric rhythm, aberrant tone (impaired gastric accommodation), and improper food distribution within the stomach are all examples of motor dysfunction.[6] The focus of research is shifting away from abnormal gastrointestinal motility as the primary abnormality and towards sensory dysfunction, particularly selective visceral hypersensitivity to mechanical distension, acid hypersensitivity, or abnormal central processing of nociceptive stimuli.[7]

Although H. pylori eradication is advised in patients in whom no other causes of symptoms have been found, the role of Helicobacter pylori in symptom production in the absence of mucosal lesions is debatable.[8] Prokinetics, serotoninrgic agents, antacids, and pain-relieving medications have all been suggested as possible treatments for dyspeptic symptoms caused by abnormalities in motor and/or sensory function; however, proton-pump inhibitor drugs (PPIs), histamine-2 receptor

antagonists, and prokinetic agents are the most frequently used.[9]

Bromopride, clebopride, domperidone, levosulpiride, and metoclopramide are examples of antidopaminergic gastrointestinal prokinetics that have been clinically used to treat movement disorders of the upper gastrointestinal tract. These medications' prokinetic effects are caused by blocking enteric (neuronal and muscle) inhibitory D2 receptors. On the basis of dopaminergic pathways influencing gastrointestinal motility, levosulpiride, a selective dopamine D2-receptor antagonist with prokinetic activity, is a therapeutic alternative in the management of functional dyspepsia.[10] On the other hand, levosulpiride's serotonergic (5-HT4) component might increase its effectiveness as a treatment for functional dyspepsia.[11] Levosulpiride has been on the market in Italy.[12] for more than 15 years, and numerous studies there have shown the drug's great efficacy in controlling dyspeptic symptoms as well as its favourable safety profile.

The incidence of adverse events was 11% in 840 patients with dyspepsia in a review to evaluate the clinical pharmacology, therapeutic efficacy, and tolerability of levosulpiride.[13] the majority were mild, and just eight occurrences (0.9%) led to treatment discontinuation. Levosulpiride and cisapride were found to be equally effective in lowering stomach emptying times with no meaningful side effects.[14] and in a randomised, double-masked trial, levosulpiride was at least as effective as cisapride in treating functional dyspepsia with dysmotility-like symptoms.[15]

Levosulpiride's efficacy and safety in treating individuals with functional dyspepsia that is dysmotility-like, including nonerosive reflux disease, were examined in this study.

MATERIAL AND METHODS

The study was conducted in critically ill patients admitted to the ICU at Indira Gandhi Medical College, Shimla in the year 2020-2021 over a 12-month period. The sample size was estimated to be 30 patients with an expected correlation coefficient of 0.5, 80% power and two-tailed alpha error of 5%, but 50 patients were enrolled to account for potential loss due to various circumstances. The study was conducted prospectively on patients aged 18-80 years who met the inclusion criteria and were willing to participate in the study. Ethics approval and informed consent were obtained prior to conducting the study

Inclusion criteria

1) Critically ill enterally fed patients.
2) Anticipated ICU stay of at least 5 days.
3) Not on any prokinetics for feed intolerance.
4) Patients giving consent for participating in the study.

Exclusion criteria

1) Bowel surgery within 24 hours.
2) GI bleed, obstruction, perforation, malabsorption syndrome (MAS).
3) Abnormal LFTs; SGOT/SGPT more than 3 times normal and/or Total bilirubin more than 3 times normal.
4) Morbid obesity/pregnancy (unable to achieve right lateral position).

The study included enterally fed patients who underwent bedside ultrasonography and manual aspiration twice a day to measure gastric reserve volume. Any adverse effects were recorded, and Levosulpiride was administered if the gastric residual volume exceeded 150ml and gastric feed intolerance was observed. The patients were given enteral feed in a bolus technique and subjected to a chlorhexidine mouth wash to reduce VAP incidence. The gastric antrum was identified below the left lobe of liver and pancreas, and a still image was captured. Data was entered into proforma sheets and analyzed using appropriate statistical tests at the end of the study

Statistical analysis

The presentation of the Categorical variables was done in the form of number and percentage (%). On the other hand, the quantitative data were presented as the means ± SD and as median with 25th and 75th percentiles (interquartile range). The following statistical tests were applied for the results:

1. The comparison of the variables which were quantitative in nature were analysed using Paired t test was used across follow up.
2. Sensitivity, specificity, positive predictive value and negative predictive value of ultrasonographic was calculated for predicting feed intolerance, average gastric reserve volume(mL/kg) {≤0.8} and average gastric reserve volume(mL/kg) {>0.8}.
3. Pearson correlation coefficient was used for correlation of Gastric reserve volume(mL) and gastric reserve volume(mL/kg) between Ultrasonographic and Manual aspiration.
4. Bland-Altman plot was used for comparison of measurement of gastric reserve volume and average gastric reserve volume between ultrasonographic and manual aspiration.

The data entry was done in the Microsoft Excel spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 21.0. For statistical significance, p value of less than 0.05 was considered statistically significant.

RESULTS

Table 1: Distribution of levosulpiride of study subjects.

Levosulpiride given	Frequency	Percentage
Day 1	0	0.00%
Day 2	1	1.75%
Day 3	2	3.51%
Day 4	3	5.26%
Day 5	3	5.36%
Day 6	2	7.69%
Day 7	1	9.09%
Day 8	0	0.00%
Day 9	0	0.00%
Day 10	0	0.00%

Table 2: Descriptive statistics of percentage fall in gastric reserve volume(mL) after Levosulpiride in study subjects.

Variable	Mean ± SD	Median (25th-75th percentile)	Range
Percentage fall in gastric reserve volume(mL) after Levosulpiride	87.09 ± 4.55	87.55 (84.968- 89.667)	81.25-92

On day 1, none of the patients had a need for levosulpiride for stomach intolerance. Throughout the study period, levosulpiride was administered to 4 patients. These individuals were excluded from additional GRV assessments after using the medicine for two days because the drug could change the patients' mean GRV values. Levosulpiride was administered to one patient each on days 2 and 7, two patients on days 3 and 6, and three patients on days 4 and 5. Levosulpiride had very positive effects in our patients, and there was a mean 87.024.55%(range 81.25 to 92) decline in GRV after therapy.

DISCUSSION

The effectiveness and safety of this prokinetic agent are confirmed by this descriptive, observational, international study in which levosulpiride was given to patients with functional dyspepsia in accordance with indications for use in daily practise. This study's findings are consistent with earlier data published in the literature. Trials in functional dyspepsia, on the other hand, reveal placebo response rates of 30% to 40%. This study contains a number of significant restrictions. The open-label design and lack of a comparison group were the main drawbacks. The study's reliance on the Rome II consensus report's criteria was another drawback.[16]

According to the Rome III committee, the term "dyspepsia" should only be applied to people who experience epigastric pain or burning, postprandial fullness, or early satiation.[17] The committee went on to say that the term "functional dyspepsia" has limited application and, based on data from factor analyses, suggested that there are particular syndromes (epigastric pain syndromes and postprandial distress syndrome) that can be identified and may more accurately describe those patients who are formally diagnosed as having functional dyspepsia. This new classification remains to be prospectively tested, and, at this stage, abandonment of the term "functional dyspepsia" seems premature.

In this study levosulpiride was started 25 mg QID if the gastric residual volume was above threshold of 150ml. On day 1, none of the patients had a need for levosulpiride for stomach intolerance. Throughout the study period, levosulpiride was administered to 4 patients. Levosulpiride was administered to one patient each on days 2 and 7, two patients on days 3 and 6, and three patients on days 4 and 5. Levosulpiride had very positive effects in our patients, and there was a mean 87.024.55% (range 81.25 to 92) decline in GRV after therapy. PPIs are effective in the treatment of dyspepsia in those trials that may not adequately exclude patients with gastroesophageal reflux disease, according to a recent systematic review of management strategies (combinations of initial investigation and empirical treatments) for dyspeptic patients.[18]

Antidopaminergic prokinetics' therapeutic effectiveness in gastrointestinal diseases including functional dyspepsia and diabetic gastroparesis is increased by the serotonergic (5-HT4) component of these drugs.[19] Both beneficial (such as an antiemetic effect from blocking D2 receptors in the postrema region) and harmful (such as hyperprolactinemia and extrapyramidal dystonic responses) consequences may result from the antagonistic activity of central D2 receptors. A adverse effect of all antidopaminergic prokinetics is hyperprolactinemia. The effects of 8 weeks of treatment with either levosulpiride 25 mg TID (n=69) or cisapride 10 mg TID (n=71) were compared in a randomised, double-masked experiment.[20] Levosulpiride and cisapride both reduced total symptom score and improved dyspeptic symptoms (by 79.9% and 71.3%, respectively); however, there was no statistically

significant difference between the two therapies (p=0.07 for total symptom score).

But significantly more (p=0.03) of the cisapride-treated patients had to stop the trial due to side effects. The current data demonstrate the efficacy and safety of a 4-week treatment regimen with levosulpiride for the relief of functional dyspepsia symptoms in a large group of adult patients diagnosed and treated by their doctors in routine practise. Our findings of improved responses in smokers compared to nonsmokers and in patients with nonerosive reflux disease compared to those with dysmotility-like functional dyspepsia require further study, as do those findings.

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