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An Open-Label Observational Study Assessing the Efficacy and Safety of Levopraid Injection 25mg (levosulpiride) in Three Tertiary Care Hospitals in Pakistan

BY

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Abstract

Dyspepsia is referred to as discomfort arising from proximal GIT, leads to other conditions such as Gastroesophageal Reflux Disease (GERD), Nausea and Vomiting (NV), and Irritable Bowel Syndrome (IBS), which pose significant challenges in primary care and affects patient quality of life. In spite of many treatment options, gastroprokinetic drugs are still considered as profound treatment options, this study aimed to assess the efficacy and safety of levosulpiride injection, an antidopaminergic gastrointestinal prokinetic. Study conducted between January and March 2023 across three tertiary care hospitals in Pakistan, this open-label observational study evaluated the use of levosulpiride in the treatment of epigastric functional dyspepsia (EGFD), GERD, NV, and IBS in 137 patients aged 13-83. Patients' symptoms were monitored over several visits after receiving levosulpiride 25mg IM/IV injections, with symptom resolution times ranging from 1 to 5 days. Results demonstrated a significant difference in mean symptom duration across the hospitals, with a decrease in symptom resolution time associated with a dosage increase. The regression analysis yielded a mathematical model for the relationship between dosage and symptom resolution time. Meanwhile, the findings suggest the potential therapeutic benefits of levosulpiride. Further research is needed to investigate the recurrence of symptoms and the long-term safety and efficacy of this treatment option.

Key Words: *Functional dyspepsia, Levosulpiride injectable, Gastroesophageal Reflux Disease (GERD), Nausea and Vomiting (NV), Irritable Bowel Syndrome (IBS)*

INTRODUCTION

Dyspepsia is characterized by pain and discomfort arising from the proximal gastrointestinal tract (GIT) at the upper abdomen. This affects the patient's quality of life and is more of a significant clinical challenge, with the primary care burden accentuated by related conditions such as Gastroesophageal Reflux Disease (GERD), Nausea and Vomiting (NV), and Irritable Bowel Syndrome (IBS). These related conditions often coexist with dyspepsia and compound the complexity of its management, contributing to the considerable impact on patient's quality of life and healthcare resources. The management and evaluation of dyspepsia lead to challenges in primary care, contributing to a significant workload of general practitioners (Huggett et al., 2020; Kearney et al., 2010). The development and progression of these conditions have multiple contributing factors that affect their underlying mechanisms, involving complex interactions of motor, sensory, and central nervous system factors, as suggested by the brain-gut axis theory (Aziz & Tack, 2013).

The primary focuses of previous research highlighted the sensory dysfunction as a primary abnormality, especially visceral hypersensitivity, acid hypersensitivity, or abnormal central processing of pain stimuli, which can cause selective mechanical distension (Bisschops et al., 2008). Secondly, H-Pylori infection also plays an important role in symptom production in the absence of mucosal lesions, which may sometimes be controversial for its management. In such cases, eradicating bacteria (H-Pylori) is recommended in patients with no other causes of symptoms have been identified (Ford et al., 2021). Dyspepsia is common and varies in prevalence and incidence rates across different regions. For instance, the

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six-month prevalence in England was 38% (Jones & Lydeard, 1992), while in Denmark, the annual incidence rate was 3.4% (Meineche-Schmidt & Krag, 1998). In a Mediterranean region study, dyspepsia prevalence was reported as 24% (Caballero Plasencia et al., 2000). Variations in these rates could be due to patient characteristics, geography, and cultural factors like dietary habits and stress levels (Moayyedi et al., 2017). Regardless of the variation in prevalence and incidence rates, dyspepsia remains a common condition that poses a significant challenge to primary care physicians regarding evaluation and management. As such, there is a need for ongoing research to understand better the pathophysiology and etiology of dyspepsia, as well as to develop more effective treatment strategies for this condition. Antidopaminergic gastrointestinal prokinetics have been clinically utilized, such as bromopride, clebopride, domperidone, levosulpiride, and metoclopramide, to treat motor disorders of the upper gastrointestinal tract and additionally, levosulpiride serotonergic (5-HT4) component may enhance its therapeutic efficacy in functional dyspepsia (Andresen & Camilleri, 2006). Despite a myriad of treatment options, including proton-pump inhibitors (PPIs), histamine-2 receptor antagonists, serotoninergic agents, antacids, and pain-modulating medications and prokinetics, the management of these gastrointestinal disorders remains a challenge (Moayyedi et al., 2019). Among prokinetic drugs, levosulpiride, a selective dopamine D2-receptor antagonist with prokinetic activity, has demonstrated potential therapeutic benefits in managing these conditions (Lacy et al., 2017). Due to its dopamine D2 receptor antagonism and possible action on serotonergic (5-HT4) pathways, early research indicates that levosulpiride may improve gastric motility (Andresen & Camilleri, 2006). While previous studies have demonstrated the efficacy and safety of levosulpiride for dyspepsia (Franceschi et al., 2003; Saggioro, 2006), few have examined its role across a broad spectrum of symptoms, including GERD, NV, and IBS, particularly using an injectable preparation. Numerous studies, many of which were conducted in Italy, where levosulpiride has been available for more than 15 years, have demonstrated its high efficacy in controlling dyspeptic symptoms and favorable safety profile (Franceschi et al., 2003; Saggioro, 2006). In a review assessing the clinical pharmacology, therapeutic efficacy, and tolerability of levosulpiride, the incidence of adverse events was 11% in 840 patients with dyspepsia, most of which were mild, and only eight cases (0.9%) resulted in treatment discontinuation. Therefore, levosulpiride is a potentially effective and safe option for managing dyspeptic symptoms (Abenavoli et al., 2008).

Consequently, this study aims to evaluate the safety and efficacy of injectable levosulpiride for the treatment of patients with epigastric pain functional dyspepsia (EGFD), gastrointestinal reflux disease (GERD), nausea and vomiting (NV), and irritable bowel syndrome (IBS), thus providing a comprehensive assessment of its potential role in the management of these prevalent and challenging conditions.

Methodology

Between January 2023 and March 2023, an open-label, observational, multicenter study was conducted at three sites in Pakistan: Service Institute of Medical Sciences, Lahore (SIMS-H), Khawaja Muhammad Safdar Medical College Sialkot (KSMC-H), and District Head Quarter Gujranwala (DHQ-GH). It aimed to evaluate the safety and tolerability of levosulpiride injectable preparation in the treatment of patients with epigastric pain functional dyspepsia (EGFD), gastrointestinal reflux disease (GERD), nausea and vomiting (NV), irritable bowel syndrome (IBS). Levosulpiride injection was administered per the specified conditions of use as outlined in the product's technical form for injectable presentations. The study lasted 12 weeks and focused on assessing the immediate relief of symptoms and observing the safety of this medicine. However, follow-up and investigation of the potential for symptom recurrence are future directions for this study. Before participation, all patients were provided with comprehensive information about the study's objectives and characteristics, and they provided oral consent. The study protocol received approval from the local ethical committees of SIMS, KSMC, and DHQ-G. The study medication used was a commercially available product prescribed for approved indications.

The study conducted at SIMS included patients ranging from 13 to 83 years of age, while at DHQ KSMC, patients aged 16 to 62 were included, and at DHQ Gujranwala, patients aged 21 to 82 were included. These patients were required to have at least three of the following symptoms: postprandial upper abdominal fullness, postprandial pain/discomfort centered in the upper abdomen with early satiety, nausea, pyrosis, and regurgitation. These symptoms needed to occur at least once or twice weekly in the preceding weeks. To be eligible for the study, patients needed to have the results of routine laboratory tests (blood cell count, biochemical profile, and urinalysis), and if necessary, they underwent an upper gastrointestinal endoscopy. Patients with a known or suspected history of organic lesions, those who had undergone abdominal surgery, individuals with lactose intolerance, pregnant or nursing women, and patients taking medications known to affect gastrointestinal motility were excluded from the study. The study lasted for 90 days. During the baseline visit, the physician evaluated the eligibility criteria and initiated treatment with levosulpiride (Injection Levopraid 25mg by Pacific Pharmaceuticals Ltd, Pakistan) once daily or twice daily based on the following requirements of each patient.

During the study, individual symptoms such as postprandial pain/discomfort, postprandial fullness, postprandial bloating or abdominal distention, early satiety, nausea, vomiting, pyrosis, and regurgitation were assessed at baseline visits 1, 2, and 3 after initiating treatment. A computer-based questionnaire was employed to evaluate the presence of these symptoms. The frequency of symptoms was rated on a 3-point scale (0 = no symptom, 1 = symptom present for 1-3 days). The severity of symptoms was scored on a scale of 0 to 3 (0 = no symptom, 1 = mild and easily tolerable, 2 = moderate or affecting normal daily activities, and 3 = severe or preventing

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normal daily activities). A global symptom score was also calculated, encompassing upper abdominal pain, postprandial upper pain or discomfort, postprandial heaviness, early satiety, nausea, pyrosis, and regurgitation. Adverse events reported by patients or observed by investigators were recorded and names (such as headache, redness, swelling, etc.) to assess their relationship to the study drug (not related, possibly related, probably related) and their severity (mild, moderate, or severe presented in Figure 2). Compliance with the prescribed dosing regimen and concomitant medication usage were evaluated during follow-up visits. At the final visit, both patients and physicians provided ratings on the overall safety of the treatment, using qualitative scales such as excellent, good, regular, or bad.

The safety population included all patients assessed at baseline and receiving at least one dose of the study medication. The data were presented as mean and standard deviation (SD) for quantitative variables, while categorical variables were expressed as numbers. A one-way ANOVA and posthoc testing using Tukey's HSD test were conducted to compare the mean duration of symptoms. The linear regression analysis was executed to model the relationship between the dosage of Levosulpiride Injection (Either OD or BD) and the number of days it took for symptoms to resolve. A chi-square test was performed to determine whether there is a significant association between the dosage and the occurrence of side effects. Statistical calculations were performed using Medcalc 22, considering $p<0.05$ as the threshold for statistical significance, and Microsoft 365 Excel was used to plot graphs and tables.

Results

During the study period, treatment with levosulpiride was indicated in 137 patients from three hospitals: SIMS-H, DHQ-GH, and KSMC-H. All patients who met the inclusion criteria were included in the study. The study population consisted of diverse patients with different complaints and symptoms. Patients were treated with levosulpiride 25mg IM/IV injection, and their responses were monitored over several visits. The duration of symptom resolution is measured in 1-5 days. Among all 137 patients with a mean (SD) Standard Deviation of Age 41.03 (13.93), 56.20% were male, while 35 (25.11%) were female, 14 (10.22%) were lesser the age of 25 years, and patients between the age of 25-45 years were 79 (57.66%) and above 45 years were 44 (32.12%). The mean duration of symptoms was 36.56 days 55.41% (with SD 20.25 days), Symptoms duration < 30 days were 46 (33.58%), and symptoms duration of 30–45 days was 49 (35.77%), while the symptoms duration > 45 days were 42 (30.66%) underlined for all of three institutions.

Table 1: Patient Characteristics and Treatment Modalities	**Patients (n) %age**
Total number of patients	137
Male Patients	77 (56.20%)
Female Patients	60 (43.80%)
Age, years, mean (SD) Standard Deviation of Age	41.03 (13.93)
Age < 25	14 (10.22%)
Age 25-45	79 (57.66%)
Age > 45	44 (32.12%)
The mean duration of symptoms	36.56 days
Duration of symptoms, months, mean (SD)	20.25 days (55.41%)
Symptoms duration < 30 days	46 (33.58%)
Symptoms duration 30–45 days	49 (35.77%)
Symptoms duration > 45 days	42 (30.66%)
Current smokers, n (%)	38 (27.59%)
Laxatives	24 (88.03%)
PPIs	17 (65.89%)
Dopamine receptor antagonists	9 (33.46%)
Histamine-2 Blocker	28 (31.34%)
Antacids	1 (52.05%)
Anti-spasmodic medicine	19 (20.60%)
Others: used in digestive remedies	11 (43.97%)

In the SIMS-H, 42 patients participated, with a near-equal distribution of males (45.2%) and females (54.8%) with 44.76 years average age, and the mean duration of symptoms reported was 35.52 days. 35.7% of patients experienced symptoms for > 30 days, between 30-45 days, 33.3%, and 31.0% for more than 45 days. The most common complaint was Nausea, Vomiting, and Epigastric Pain, comprising 33.33% of all complaints lodged in SIMS-H.

In DHQ-GH, patients are evenly split between males (50%) and females (50%), with a mean age of 41.24 years. The average symptom duration was 30.94 days; 42% reported symptoms lasting less than 30 days, 40% for 30-45 days, and 18% for more than 45 days, and the most frequent complaint was Nausea and Vomiting, making up 14.00% of all complaints.

In KSMC-H 45 patients, males (73.3%) were represented more than females (26.7%). The average age was 37.31 years, and the mean duration of symptoms was 43.76 days, with 22.2% >30 days, 33.3% for 30-45 days, and 44.4% for more than 45 days. The most common complaint was 'NV/EP,' just like at SIMS-H. Still, it represented a slightly lower proportion of total complaints, specifically 11.11%; however, the most common complaint across all three hospitals is 'NV/EP,' accounting for approximately 14.60% of all complaints.

Table 2: Comparison of Patient Characteristics and Symptoms among Different Health Centers

Statistic	**SIMS-**	**DHQ-**	**KSMC-H**

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	H	GH	
Total Patients	42	50	45
Male Patients	19	25	33
Female Patients	23	25	12
Mean Age	44.76	41.24	37.31
Standard Deviation of Age	16.02	12.39	12.73
Patients under 25 years	2	3	9
Patients between 25 and 45 years	23	32	24
Patients over 45 years	17	15	12
Mean Duration of Symptoms	35.52	30.94	43.76
Standard Deviation of Duration of Symptoms	21.48	18.36	19.31
Patients with symptoms for less than 30 days	15	21	10
Patients with symptoms for 30-45 days	14	20	15
Patients with symptoms for more than 45 days	13	9	20

To compare the mean duration of symptoms across all three institutions, a one-way ANOVA test resulted in a significant difference in mean symptom duration between at least one pair of hospitals ($F=5.11$, $p=0.0073$). Post-hoc testing using Tukey's HSD test revealed a significant difference in mean symptom duration between DHQ-GH and KSMC-H (mean difference=-12.45, $p<0.05$). Since the ANOVA test only tells us a difference between the groups but not where that difference lies, a post hoc test was performed to compare all possible pairs of means to determine which are significantly different. In this case, the test revealed a significant difference in mean symptom duration between DHQ-GH and KSMC-H.

Association between Dosage and Symptom Resolution Time:

The linear regression analysis was executed to model the relationship between the dosage of Levosulpiride Injection (Either OD or BD) and the number of days it took for symptoms to resolve by keeping the 'Dosage' as the independent variable and 'Symptoms Resolved in Days (SRD)' as the dependent variable. The result of this regression analysis was a mathematical model that describes the relationship between these two variables as a straight line. The equation for this line is $SRD = -1.44 \times Dosage + 3.31$. The coefficient of dosage (-1.44) suggests that going from 'OD' to 'BD' is associated with a decrease of approximately 1.44 days in the time it takes for symptoms to resolve, holding all else constant. The intercept (3.31) is the average number of days for symptoms to resolve.

Dosage	Encoded Dosage	Intercept + Coefficient * Encoded Dosage	Final Results
OD	0	3.31	Symptoms resolve in approx. 3.31 days on average
BD	1	1.88	Symptoms resolve in approx. 1.88 days on average

Comparison of Side Effects between Dosages:

A chi-square test was performed to determine whether there is a significant association between the dosage and the occurrence of side effects. The Chi-square test resulted in a Chi-square statistic of approximately 5.15 and a p-value of approximately 0.995. Based on this dataset, there is insufficient evidence to conclude that there is a significant association between the dosage and the occurrence of side effects. Additionally, it is worth mentioning that this simplistic analysis needs to account for potential confounding factors. The relationship between dosage and side effects might be influenced by other variables (like age, gender, or the type of complaint), and a more comprehensive analysis might be needed to understand this relationship fully.

Figure 1

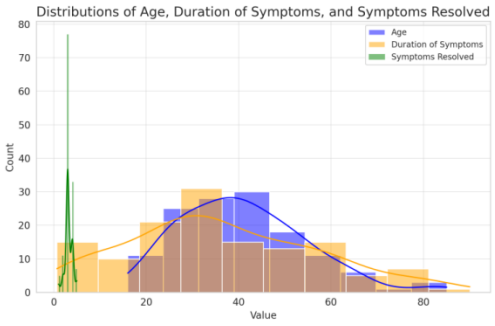

Figure 1: The histogram above represents the distributions of three variables: Age, duration of symptoms, and resolved symptoms. A different color represents each variable, and the distributions are overlaid on the same axes for comparison.

Age (Blue Line): The age distribution appears to be normal, indicating that patients of a wide range of ages were treated with levosulpiride. This would suggest that the treatment applies to a broad age range, which is a positive outcome regarding the potential reach of this treatment. Duration of Symptoms (Orange Line): The distribution is skewed to the right, peaking at 0-5 days. This suggests that most patients had a short duration of symptoms before receiving treatment,

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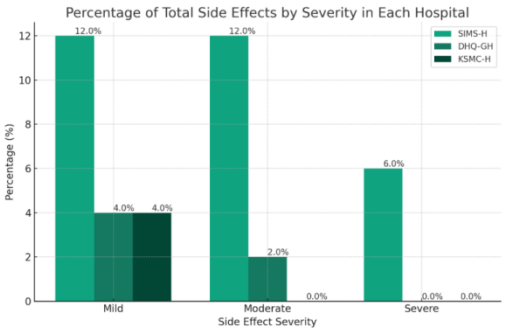
a positive outcome regarding early detection and intervention. Symptoms Resolved (Green Line): The Symptoms Resolved distribution also peaks at around 0-5 days, indicating that most patients had their symptoms resolved within a few days after the treatment. This is a highly positive outcome, suggesting that the treatment quickly resolved symptoms for most patients.

Tolerance / Safety

Treatment with levosulpiride 25mg injection was well tolerated, and only 36 very common side effects were encountered among all hospitals. 61.90% of patients reported no side effects, 61.90% Headache, 9.52%Drowsiness, 7.14%Depression, 4.76%Fatigue: 4.76%Redness, 2.38%Drowsiness, Depression 2.38%, Fatigue/Drowsiness 2.38%, Fatigue/Headache 2.38%, and Palpitation 2.38%. As per standard adverse event (ADRs) classification, these side effects were classified (Nebeker et al., 2004). Mild (Headache, Redness, Fatigue), Moderate **(**Drowsiness, palpitations, Fatigue/Drowsiness, Fatigue/Headache), Severe (Depression, Drowsiness, Depression).

Figure 2: Represents the percentage of total side effects by severity in SIMS-H, DHQ-GH, KSMC-H



Discussion

The current study is a prospective, open-label, observational, multicenter study conducted in three sites across Pakistan, aiming to assess the effectiveness and safety of levosulpiride for the treatment of functional dyspepsia, gastroesophageal reflux disease (GERD), nausea, and vomiting. This study expands upon the body of knowledge regarding the safety and efficacy of levosulpiride, a prokinetic agent that has demonstrated effectiveness and good tolerance in previous research (Franceschi et al., 2003; Saggioro, 2006; Abenavoli et al., 2008).

The study was conducted with a diverse patient population, with an age range between 13 to 83 years old, experiencing symptoms of postprandial fullness, postprandial pain or discomfort, early satiety, nausea, pyrosis, and regurgitation. This broad patient profile allows for a comprehensive examination of the response to levosulpiride across different age groups and symptom presentations, adding robustness to the results. Our results suggest that levosulpiride offers a significant therapeutic benefit for patients with these conditions. The average duration of symptom resolution was between 1-5 days, indicating the rapid action of the drug. Moreover, the study found a significant difference in the mean duration of symptoms between the three hospitals, suggesting possible regional differences in treatment response, which warrants further investigation (Huggett et al., 2020). There was a significant disparity in the mean duration of symptoms across the three studied institutions, indicating possible regional differences or variations in patient profiles or care quality.

A robust association was found between the levosulpiride dosage and symptom resolution time. A linear regression model revealed that switching from once to twice daily dosage is associated with a decrease of approximately 1.44 days in symptom resolution time.

Regarding safety, a Chi-square test indicated no significant association between the dosage and the occurrence of side effects, affirming levosulpiride's safety at both once-daily and twice-daily dosages. Overall, treatment with levosulpiride was well-tolerated, with only 36 common side effects reported, most of which were mild.

Interestingly, the dosage of levosulpiride (once daily or twice daily) was associated with the time it takes for symptoms to resolve. This result aligns with previous findings regarding the benefits of higher doses of prokinetic agents in dyspepsia treatment (Tack et al., 2019).

Regarding safety, levosulpiride was well tolerated by the patients, with only 36 reported side effects, most of which were mild, such as headache, redness, and fatigue. Severe side effects like depression were reported but occurred in a smaller proportion of the patient population. No significant association was found between the dosage and the occurrence of side effects, implying the drug's safety at both once-daily and twice-daily dosages. This finding is consistent with previous studies showing a favorable safety profile for levosulpiride (Abenavoli et al., 2008).

However, the study has several limitations to consider. The absence of a control group and the open-label design may introduce bias in the results. The symptom assessment was based on patient reports and severity resolution scale (present or absence of symptom), which subjective interpretations could influence. The study population was also limited to patients from three hospitals in Pakistan, which may limit the generalizability of the results to other populations.

Despite these limitations, this study adds to the growing body of evidence supporting the efficacy and safety of levosulpiride in treating functional dyspepsia and related conditions. The findings suggest that levosulpiride can provide rapid relief from symptoms and is well-tolerated by patients, making it a potentially valuable treatment option. Despite the study's limitations, including the open-label design and absence of a control group, the findings contribute to the body of evidence supporting levosulpiride's efficacy and safety in treating functional dyspepsia and related conditions.

Future research should consider randomized controlled trials to confirm these findings and further explore the potential regional differences in treatment response. Also, it would be

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beneficial to investigate the long-term effects of levosulpiride treatment and assess the potential for symptom recurrence.

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