



Comparison of efficacy and safety of Levosulpiride and Domperidone in functional dyspepsia.

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Article info

Abstract

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Objective: To compare the efficacy and safety of levosulpiride with domperidone in patients with functional dyspepsia Material & Method: It was a prospective, double blind, randomized study conducted on 182 patients in two groups of 91 each. Group A: levosulpiride 25mg TID daily orally for 4 weeks, Group B: Domperidone 10mg TID daily orally for 4 weeks. Individual symptoms (Abdominal pain, discomfort, nausea, vomiting, anorexia, post prandial bloating, belching, regurgitation, heart burn & abdominal fullness) and severity of symptoms were assessed by predetermined grading system at baseline (0), 2, 4 & 8 weeks i.e. 1st, 2nd, 3rd, & 4th visit respectively. Results: Among 182 patients 171 completed the study most of the cases were in 20 to 40 years (69%) with male preponderance (71.35%). Highly significant ($p > 0.001$) improvement in symptoms like post prandial bloating (82%) and abdominal pain (81.63%) were noticed with levosulpiride as compared to domperidone [post prandial bloating (57%), abdominal pain (45%)]. Both the treatment groups were comparable for other symptoms. Conclusion: levosulpiride is more effective but less safe than domperidone in FD.

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INTRODUCTION

Functional Dyspepsia (FD) is among the most common gastrointestinal disorder that is burden to both patients and society. Nearly 25% of population has dyspepsia at least 6 times yearly, but only 10-20% of these individuals present to physician [1]. Patients with FD have no evident biochemical or organic cause of the symptoms [2] therefore FD is a diagnosis of exclusion. A variety of terms have been used synonymously including non ulcer dyspepsia and non organic dyspepsia. Various studies suggest that these chronic symptoms have a significant impact upon quality of life, interfering with daily activities and contributing to emotional stress [3-6].

FD patients presents with upper abdominal pain, belching, nausea (with or without vomiting), abdominal bloating (the sensation of abdominal fullness without objective distention), early satiety (the sensation of fullness after a very small amount of food) and possibly abdominal distention (swelling as opposed to bloating).

Pathophysiology includes gastric hypersecretion, gastro intestinal motility disorder, visceral hypersensitivity, psychological disturbance, genetic predisposition and H. pylori infection. The physical examination with FD usually is normal. FD may report epigastric tenderness of distension [1].

Various drugs used for FD includes prokinetics, spasmolytics, acid suppressing drugs (H₂ blockers), H. Pylori eradication, anti psychotic medications, phytotherapeutic treatment alternatives.

Levosulpiride (substituted benzamide : a levo- isomer of Sulpiride) acts selectively at Dopamine type 2 receptors, which exerts antidopaminergic activity at both D1 and D2 receptor subtypes and has action on both central and peripheral levels [8]. It is an Atypical Neuroleptic (Anti-Psychotic) and also has proven prokinetic effect making it useful in treatment of various GI disorders. Also it interact with serotonergic receptors. It has moderate partial 5-HT₄ receptor agonist property and extremely weak 5-HT₃ antagonism [9], making it a useful antiemetic. Unlike metoclopramide, it does not cause much of extrapyramidal side effects. Extrapyramidal or sleep disturbances may be seen at very high doses. It is a useful drug in gastro esophageal reflux disease diabetic gastroparesis, nausea and vomiting, chemotherapy induced emesis and irritable bowel syndrome. It can be administered parenterally as well as orally and the most common adverse effects include drowsiness/ sedation and endocrine effects like amenorrhea, gynecomastia, galactorrea and decrease libido [10].

Table 1. Rome III criteria for Functional Dyspepsia [7]

Patients must have had one or more of the following symptoms for the past 3 months with symptoms onset at least 6 months prior to diagnosis:
Post prandial fullness
Early satiety
Epigastric burning
As well as no evidence of structural disease that is likely to explain symptoms (including any condition detected by upper endoscopy)
A. Postprandial distress syndrome
Diagnostic criteria must include the following:
Bothersome post prandial fullness, occurring after ordinary-sized meals, at least several times per week
Early satiation that prevents finishing a regular meal, at least several times per week
Other symptoms may include:
Upper abdominal bloating or postprandial nausea or excessive belching
Epigastric pain syndrome may coexist
B. Epigastric pain syndrome
Diagnostic criteria must include all of the following:
Pain or burning localized to the epigastrium, of at least moderate severity at least once per week
Pain is intermittent
Pain is not generalized or localized to other abdominal or chest regions
Pain is not relieved by defecation or passage of flatus
Pain does not fulfill criteria for biliary pain
Other symptoms may include:
Epigastric pain of a burning quality, but without a retrosternal component
Pain induced or relieved by ingestion of a meal, but which also may occur while fasting
Postprandial distress syndrome may coexist

Domperidone (Butyrophenone Derivative) - is D2 receptor antagonist which exerts antidopaminergic properties at peripheral D2 receptors [11]. It increases lower oesophageal sphincter pressure and accelerates gastric emptying. It does not cross blood-brain barrier, and therefore extra pyramidal side effects are rare [12]. It acts at CTZ which is not protected by blood brain barrier and this makes it useful as antiemetic agents. But antiemetic efficacy is lower than metoclopramide. Unlike metoclopramide, it does not cause any adverse neurological symptoms as it has minimal penetration through the blood-brain-barrier. It is used orally and the most common side effects are due to hyperprolactinemia caused by it [8] (Leading to gynecomastia, galactorrhea, amenorrhea and impotence etc.) Other side effects are dry mouth, loose stool, headache and rashes.

In view of above background our study was done to compare the efficacy and safety of levosulpiride and domperidone in the patients of FD.

MATERIAL AND METHODS

This study was conducted in the gastroenterology OPD of SMS Medical College Jaipur after approval from Institutional Ethical Committee in the patients of FD. Guidelines for good clinical practice were followed during the study and the informed written consent was taken from all the patients.

Patients

182 patients having symptoms of FD [7] for 2-3 months were included in the study and divided into two groups (Group A received levosulpiride 25 mg tid daily for 4 weeks and Group B received Domperidone 10 mg tid daily for 4 weeks [13]. Treatment was given only for 4 weeks and at the end of 8 weeks i.e. on 4th visit reappearance of symptoms were observed.

Inclusion criteria

Following patients were included -

Patients aged 18-50 years with at least 3 symptoms of FD like post prandial bloating, abdominal pain, discomfort, belching, regurgitation, nausea, vomiting, heart burn, early satiety & abdominal fullness [7].

Exclusion criteria: Following patients were excluded from the study

- Organic lesion (when ever necessary by performing upper GI endoscopy)
- Gall stone, pancreatic disease, intestinal dysfunction.
- Pregnant woman, nursing mother
- Patients treated with the drugs and medications that were known to affect GI motility
- Patient with high prolactin level [8]

Study Design

This was a prospective, double blind, randomized study conducted for one year duration. After screening enrolled patients were treated with levosulpiride or domperidone started by randomizations. Patients were assessed at 0, 2, 4 & 8 week i.e. 1st, 2nd, 3rd and 4th visit and following parameters were recorded on case report form.

Efficacy parameters

- Individual symptoms were assessed at each visit.
- Severity of symptoms was assessed by following grading system [8].

Using a 3-point scale 1 =mild, 2= moderate, 3= severe on enrollment and on completion of 2 week & 4 week treatment period outcome categorized as *excellent*

[complete relief of symptoms], *good* [improvement with only occasional symptoms] and *nil* [no improvement]. While in the study done by C.W. Song *et al* 1998 [8] therapeutic efficacy was assessed by 4 point scale by both physician patient.

- Reappearance of symptoms were noted at the end of 8th Week.

Safety parameters

- **Based on adverse effects :**

To assess tolerability of the study drugs patients were asked for adverse effects related to systems like GIT, CVS, CNS endocrine and others and noted at each visit in case report form, besides that instruction were given if they experience/feel any kind of side effect they have to report the investigator.

- **Based on investigation**

Serum prolactin level were done at the baseline (0 week) and end of the 4 week.

Statistical Parameter

Data is expressed as numbers and percentage for categorical variables. The Chi square (χ^2) test and Mann Whitney U test were used for analysis of data. $p < 0.05$ were considered as statistical significance and $p < 0.001$ as highly significant.

RESULTS

In our study 182 patients were enrolled, out of them 171 patients completed the study, 11 patients (6 from group A & 5 from group B) did not come for the follow up visits. Most of the patients were in the age group of 20-40 years (69%), mean age was 30 ± 10 years. 122 patients were male and 49 were female i.e. male preponderance (71.35%) was found.

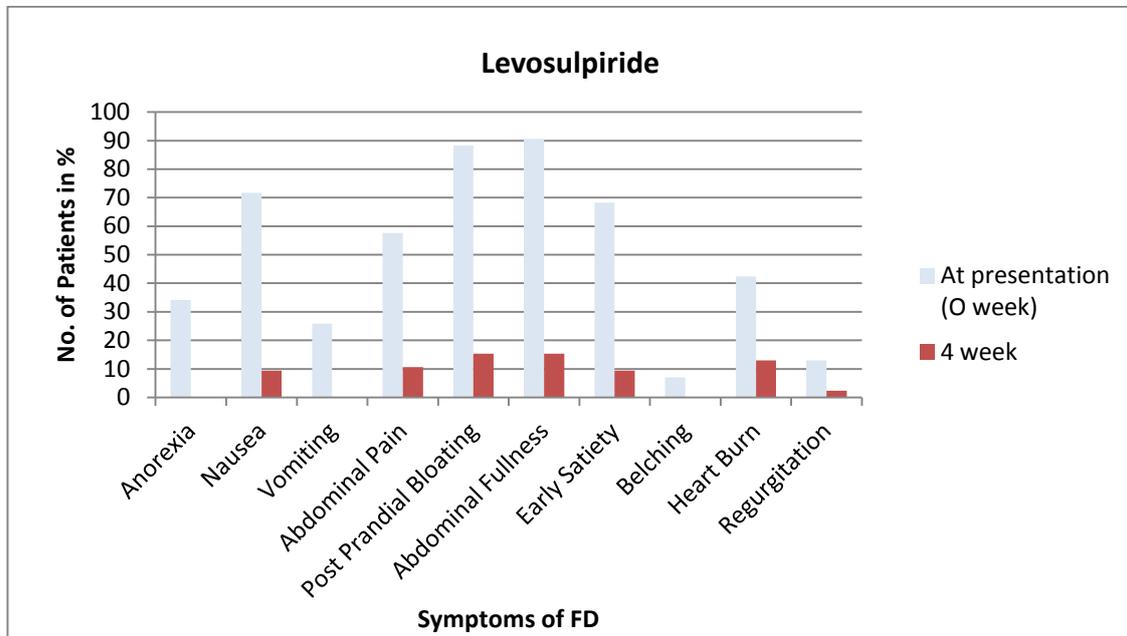
Most common symptom seen in the study were abdominal fullness (88.88%), post prandial bloating (86.54%), early satiety (74.85%), nausea (74.85%), heartburn (42.35%) & other symptoms like regurgitation (12.94%), belching (7.06%) were among less common symptoms.

At the end of four weeks of therapy the efficacy of two treatment groups was compared. A significant improvement in symptoms like nausea, vomiting, anorexia, abdominal pain, belching, early satiety and regurgitation were noticed in both treatment groups. But symptoms like post- prandial bloating and abdominal pain were significantly improved with levosulpiride in comparison to domperidone as shown in Graph 1.

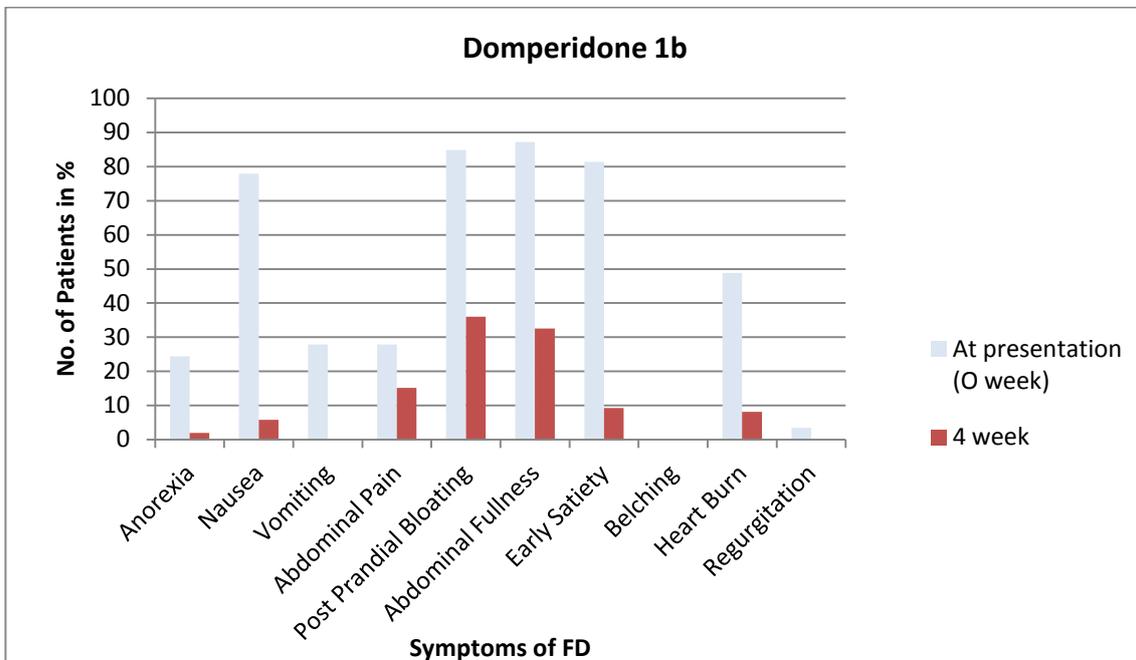
Graph 1 (1a/1b)

Comparison of effect of Levosulpiride (1a) and Domperidone (1b) in patients of FD after 4 weeks (Based on individual symptoms)

1a



1b



At the first OPD visit 77.64% in group A & 63.95% in group B presented with severe disease, 22.35% in Group A & 32.55% in Group B presented with moderate disease, no patients in

group A & 3.48% in Group B presented mild disease. At the end of four weeks symptoms in 81.17% in group A & 60.46% in group B were fully controlled whereas in 8.23% in group A & 32.55% in group B were incompletely controlled and Symptoms in 10.58% group A & 6.97% in group B remained uncontrolled as shown in Table - 2.

Table 2

Comparison of effect of Levosulpiride and Domperidone in patients of FD (Based of severity of symptoms).

Severity at presentation/1st visit/0 week

	GROUP A	GROUP B
Mild	0 (0%)	3 (3.48%)
Moderate	19 (22.35%)	28 (32.55%)
Severe	66 (77.64%)	55 (63.95%)

Severity of symptoms/control of symptoms after 2 week of therapy

	GROUP A	GROUP B
Excellent	42 (49.41%)	41 (47.67%)
Good	28 (32.94%)	39 (45.34%)
Nil	15 (17.64%)	6 (6.97%)

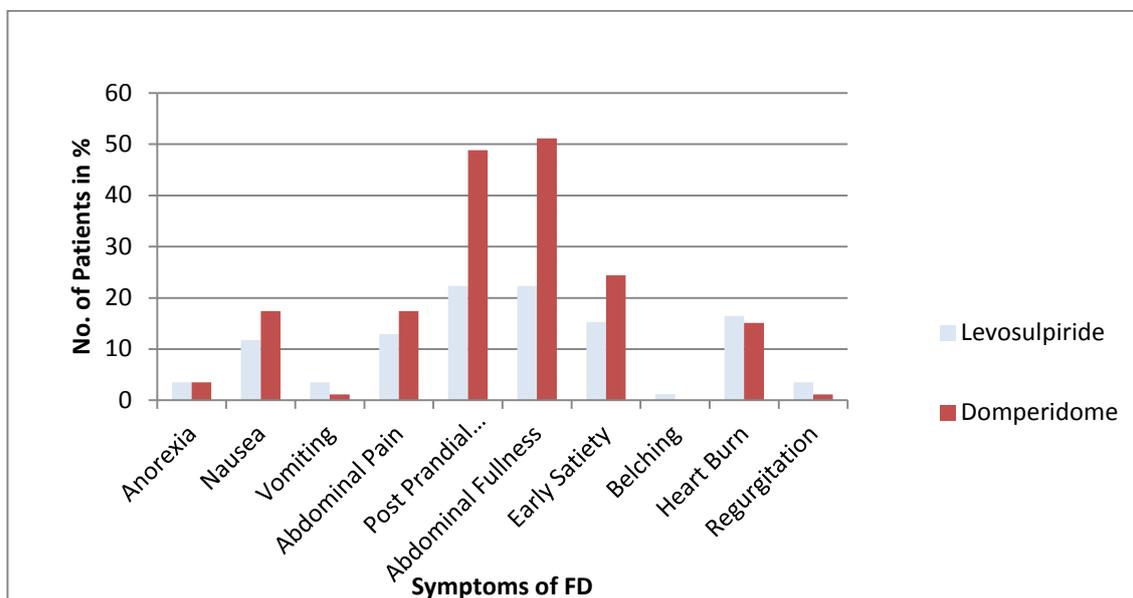
Severity of symptoms/control of symptoms after 4 week of therapy

	GROUP A	GROUP B
Excellent	69 (81.17%)	52 (60.46%)
Good	7 (8.23%)	28 (32.55%)
Nil	9 (10.58%)	6 (6.97%)

PP Bloating & Abdominal fullness were the symptoms which reappeared most and better controlled by levosulpiride while Vomiting, Belching and regurgitation were the symptoms which reappeared least and better controlled by domperidone, (as shown in the graph 2).

Graph 2

Comparison of efficacy among Group A and Group B in patients of FD (Based on reappearance of symptoms at the end of 8th week).

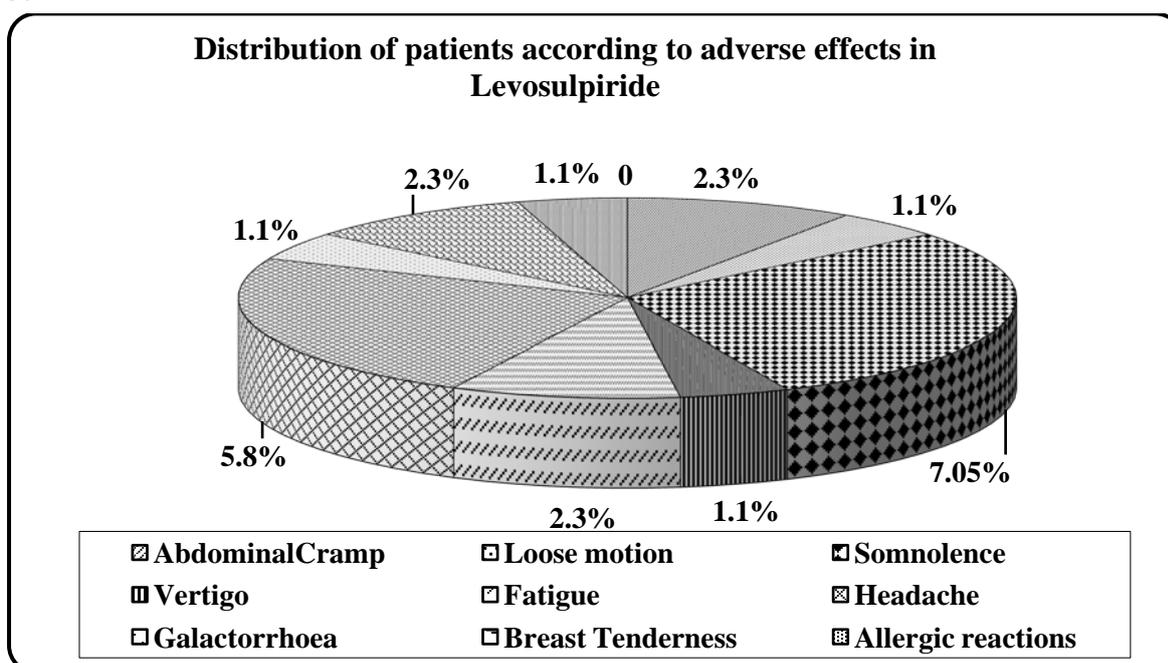


Levosulpiride & domperidone were well tolerated by patients, not a single patient discontinued the course due to adverse effects. Headache (5%) & somnolence (6%) were observed in patients on levosulpiride whereas galactorrhoea (3.5%) & breast tenderness (3.5%) were observed in patients on domperidone, (as shown in the graph 3).

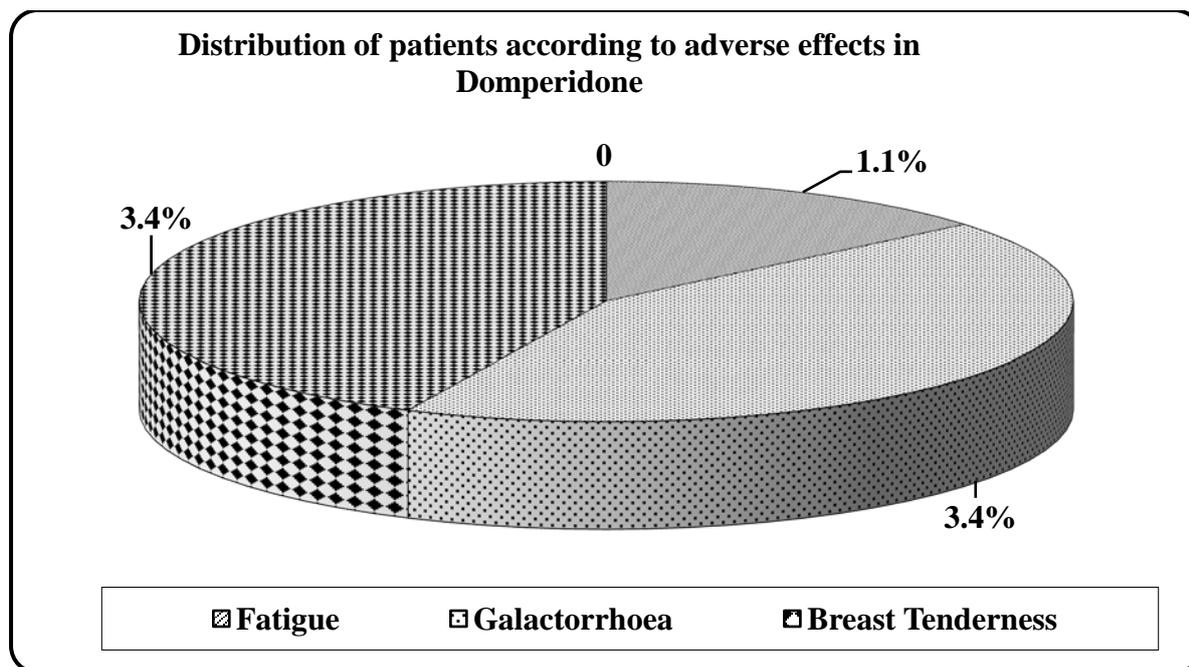
Graph 3

Comparison of adverse effects in Group A and Group B (3a/3b)

3a



3b



DISCUSSION

Demographic data of our study reveals 69% cases were in age group of 20-40 years while study done by Tougas G. et al. 2006 [14] survey showed that dyspepsia was not related to any particular age group. In a survey done in urban Mumbai, India it was found that FD was more prevalent in adults >40 years [15].

Male: Female ratio in our study is 2.45:1 i.e. male preponderance which is, in contrary to several studies in different population done by Koloski N. et al., 2000 [6] who noted consistent female preponderance with dyspepsia.

In our study most common presenting symptoms were abdominal fullness, post-prandial bloating, early satiety and nausea. These findings are similar to study done by Taugas et al. 2006 [14].

In our study we found highly significant ($p < 0.001$) improvement in PP Bloating (82%) and abdominal pain (81.63%) in levosulpiride group which was similar to study done by C.W. Song et.al 1998 [8] global efficacy was assessed which was excellent in levosulpiride as compared to placebo. It has also been documented in this study [8] that levosulpiride has been used for therapy of psychotic, depressive and somatoform disorders [14] and has also shown that it is able to influence gastric motor activity this suggests by its anti-psychotic property levosulpiride increase gastric motility and enhance prokinetic action.

In our study the incidence of adverse effects in levosulpiride Group, were 24%, most common Adverse effects were somnolence, vertigo, fatigue and headache, few cases had adverse effects like abdominal cramps, breast tenderness and galactorrhoea. While in a

study done by Corrazza GR et al 2000. [10] The incidence of adverse effects was 11%, with Levosulpiride, drowsiness/sedation was most frequent (2.5%) adverse effect.

In our study with Domperidone incidence of adverse effects was 7.9%. Most common adverse effects noted were breast tenderness and galactorrhoea it was similar to study done by Corrazza et al., 2000 [10].

CONCLUSION

Our study shows that levosulpiride cause more significant improvement in post prandial bloating and abdominal pain but more no of patients reported adverse effect as compared to domperidone hence the levosulpiride is more effective but less safer than domperidone in FD.

REFERENCE

1. William L. Hasler : Nausea, Vomiting and indigestion, principles of internal medicine. Harrison 17th edition, vol. 1 : 243-245
2. Talley N, Stanghellini V, heading R, et al. : Functional gastroduodenal disorders. Gut 45: 1137, 1999.
3. Frank L, Kleinman L, Ganoczy D, et al. : Upper gastrointestinal symptoms in North America: Prevalence and relationship to health care utilization and quality of life. Dig Dis Sci 45: 809, 2000.
4. Talley N, Verlinden M, Jones M : Quality of life in functional dyspepsia : Responsiveness of the Nepean Dyspepsia Index and development of a new 10-item short form. Aliment Pharmacol Ther 15 : 207, 2001.
5. Fass R, Fullerton S, Tung S, et al. : Sleep disturbances in clinic patients with functional bowel disorders. Am J Gastroenterol 95: 1195, 2000.
6. Koloski N, Talley N, Boyce P: The impact of functional gastrointestinal disorders on quality of life. Am J Gastroenterol 95: 67, 2000.
7. Brian E Lacy, Nicholas J Talley and Michael Camilleri: Functional Dyspepsia: Time to Change Clinical Trial Design. The American Journal of Gastroenterology 105, 2525-2529, 2010.
8. Song CW, Chun HJ, Kim CD et al. Effects of Levosulpiride in patients with functional dyspepsia accompanied by delayed gastric emptying. Korean J intern Med 1998; 13 (2) : 15-21.
9. Tonini M, Cipollina E, Poluzzi F, Crema GR, Corazza F, De Ponti. Review article : clinical implications of enteric and central D₂ receptor blockade by antidopaminergic gastrointestinal Prokinetics. Aliment Pharmacol Ther 2004; 19 : 379-390.
10. Corazza GR, Tonni M. Levosulpiride for Dyspepsia and Emesis : A review of its Pharmacology, Efficacy and Tolerability. Clin Drug Invest 2000; 19(2) : 151-162.
11. Tonini M : Recent advances in the pharmacology of gastrointestinal prokinetics. Pharmacol Res 1996; 33 : 217-226.

12. Brogden RN, Carmine AA, Heel RC, Speight TM, Avery GS : Domperidone. A review of its pharmacological activity, pharmacokinetics and therapeutic efficacy in the symptomatic treatment of chronic dyspepsia and as an anti-emetic. *Drugs* 1982; 24 : 360-400.
13. Harminder Singh, Ritu Bala, Kamalpreet Kaur ; Efficacy and Tolerability of Levosulpiride, Domperidone and Metoclopramide in Patients with Non-Ulcer Functional Dyspepsia: A Comparative Analysis : *J Clin Diagn Res.* 2015 Apr. 9(4)
14. Tally NJ, Locke GR 3rd, Lahr BD, Zinsmeister AR, Tougas G : Functional dyspepsia, delayed gastric emptying and impaired quality of life. *Gut* 2006 July; 55(7) 933-9.
15. Borovicka J, Kreiss C, Aral K, et al. : Role of cholecystokinin as a regulator of solid and liquid gastric emptying in humans. *Am J Physiol* 1996; 271 : G448-G453.