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A Prospective, Multicentric, Post Marketing Surveillance to Evaluate Efficacy & Safety of Ranitidine HCl (150 & 300 mg IR/CR) in Indian Patients with Gastroesophageal Reflux Disease (PROGRADE)

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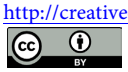
Abstract

Purpose: Ranitidine hydrochloride (HCl) remains an important medication for treating acid-peptic ailments such as Gastroesophageal reflux disease (GERD). The main objective of this Post Marketing Surveillance (PMS) clinical study was to test the efficacy and safety of Ranitidine HCl in Indian patients suffering from GERD. **Patients and Methods:** Data of 2446 patients (1307 males; 1121 females) from 21 centers across India were analyzed. Patients received either of the three treatments: Ranitidine HCl 150 mg twice a day (BID) (ARM-A), Ranitidine HCl 300 mg once daily (OD) or BID (ARM-B), and Ranitidine HCl 300 mg OD (ARM-C). Gastroesophageal Reflux Disease Symptom Assessment Scale (GSAS) score and Heartburn Severity score were used to assess the drug's efficacy. The adverse events reported by patients or investigators were analyzed to assess the safety profile of Ranitidine. **Results:** Of the 2446 subjects screened, 2428 were enrolled. There was a significant reduction in GSAS scores from baseline to the end of the study visit in all



three ARMs. The GSAS scores reduced from 2.02 to 0.23 in ARM-A, 2.01 to 0.24 in ARM-B, and 2.07 to 0.26 in ARM-C patients. In ARM A, 72.82% had 24 hours heartburn-free days, and 66.89% had 7 consecutive heartburn-free days, which was more significant than the other two ARMs. 128 (5.27%) patients reported ADRs due to Ranitidine HCl at different doses. The most frequently reported ADR was constipation (17.18%), followed by oliguria (14.06%), cold (13.28%), and dysuria (12.5%). Of 128 ADRs, 113 (88.28%) were mild, and only 11 (8.59%) ADRs were related to the study drug. No severe ADRs were reported during the study. **Conclusion:** Ranitidine HCl 150/300 mg tablet was found to be an effective and safe H2-receptor antagonist for treating GERD in Indian Patients.

Keywords

Ranitidine Hydrochloride, GERD, Heartburn, H2-Receptor Antagonists

1. Introduction

Gastroesophageal reflux disease (GERD) is a common clinical problem that presents with reflux of gastric contents into esophagus, due to transient opening of the lower esophageal sphincter (LES). [1] Most individuals might experience normal gastroesophageal reflux to some degree around once every hour, which is usually not much bothersome. [2] The prevalence of GERD is as high as 10%-38% in the Western population, with cases rising, every year. In the United States, 20% of adults show GERD-related signs weekly, and 7% experience them daily. [3] Life-threatening consequences, such as Barret's esophagus, esophageal strictures, and cancer, are associated with GERD [4].

Although GERD is accompanied by eight key symptoms such as heartburn, food regurgitation, flatulence, belching, dysphagia, nausea, vomiting, and acid regurgitation, GERD is commonly characterized by heartburn. [5] Typical GERD symptoms are often recognizable; however, extraesophageal manifestations though widespread are not consistently diagnosed [6].

Screening patients for alarm symptoms associated with GERD is critical, and an endoscopic evaluation should be performed as there could be an underlying malignancy. For typical GERD symptoms, upper endoscopy is not required. [7] However, endoscopy is recommended in patients at high risk for complications like Barrett's esophagus, individuals with chronic and recurrent indications, aged > 50 years, central obesity and Caucasian race [8].

The selective histamine type 2 receptor antagonists/blockers (H2 blockers) remain an important class of medications for the treatment of acid-peptic disorders such as GERD, duodenal and gastric ulcers, Zollinger-Ellison syndrome, etc. [9] Since its introduction in 1981, Ranitidine HCl, an H2-receptor antagonist, has been extensively employed in GERD, and it reduces both baseline gastric secretion and acid secretion generated by histamine, pentagastrin, and other secretagogues. Ranitidine HCl is administered intravenously, intraduodenally, and

orally. The maximum effect is achieved with a daily oral dose of 300 mg. [10] Ranitidine HCl has been extensively evaluated in several studies. Since its inception, clinical development programs investigating new uses or different formulations have continued, making Ranitidine HCl as one of the most widely studied drugs. [11] The primary goal of GERD is symptom relief and Ranitidine HCl helps to achieve significant relief from symptoms with faster healing rates.

In this paper, we report the results of an open-label study that compares the efficacy and safety of Ranitidine HCl in different doses in patients with GERD. This Post Marketing Surveillance (PMS) clinical study aims to test the efficacy and safety of Ranitidine HCl in patients suffering from GERD.

2. Materials and Methods

An open-label, prospective, multicenter, Post Marketing Surveillance (PMS) clinical study was carried out to assess the safety, tolerability, and efficacy of Ranitidine HCl 150/300 mg tablet (Rantac® 150/Rantac® 300/Rantac® OD 300) (PROGRADE TRIAL) of J B Chemicals and Pharmaceuticals Ltd. in Indian patients with GERD. (CTRI No: CTRI/2021/10/037668). The Post Marketing Surveillance (PMS) clinical study was conducted in the year 2021-2022.

Inclusion criteria:

Patients of either gender aged between 18 years and 65 years suffering from GERD were included in the study. The presence of at least one typical symptom of GERD (acid regurgitation, heartburn, or pain in swallowing) led to the enrollment of the subject into the study. Subjects with symptoms of GERD or who had a history of episodes of heartburn for more than or equal to one month before screening were considered. Patients who experienced heartburn at least four out of seven days of the screening period were also included.

Exclusion criteria:

Patients were excluded if they had peptic ulcer, Zollinger-Ellison syndrome, irritable bowel disease, and concomitant diseases like cardiovascular, respiratory, Central Nervous System (CNS) disorders, or renal disorders. Patients receiving non-steroidal anti-inflammatory drugs (NSAIDs), prokinetic drugs, proton pump inhibitors (PPIs), H2-receptor antagonists, and allergic drug reactions were also excluded. Pregnant and lactating women were also excluded from the study.

Interventions and assessments:

The study recruited 2446 patients, of which 2415 patients completed the study. 18 patients failed during the screening, and 13 lost to follow-up (**Figure 1**).

2.1. Study Design

The total study duration was 28 ± 2 days. Inclusion/Exclusion criteria were checked on the screening visit (Visit 1) Subject fulfilling all inclusion criteria were enrolled in the study. Enrolment day was considered as visit 2. At day 14 ±

2, follow-up visit was performed. The end of study visit was done on day 28 ± 2 (Visit 4). 2446 subjects were screened during the study out of which 2428 were enrolled and further 2415 subjects completed the study.

Enrollment:

Subjects enrolled in this Open Label study were assigned to one of the three treatment groups, namely, Ranitidine HCl tablets 150 mg BID (ARM-A), Ranitidine HCl tablets 300 mg OD or BID (ARM-B), and Ranitidine HCl CR tablets 300 mg OD (ARM-C) (Table 1). Four visits were planned for all the patients, and the first visit was a screening visit (V1) on day 3, in which a physical examination was done before treating the patient with the study drug. The second was an enrolment visit (V2) on day 1, and the third visit (V3) was on day 14 ± 2. The study visit (V4) ended on day 28 ± 2. The entire period of treatment was 28 ± 2 days. The first subject was screened on 21-Oct-2021 and enrolled on 23-Oct-2021.

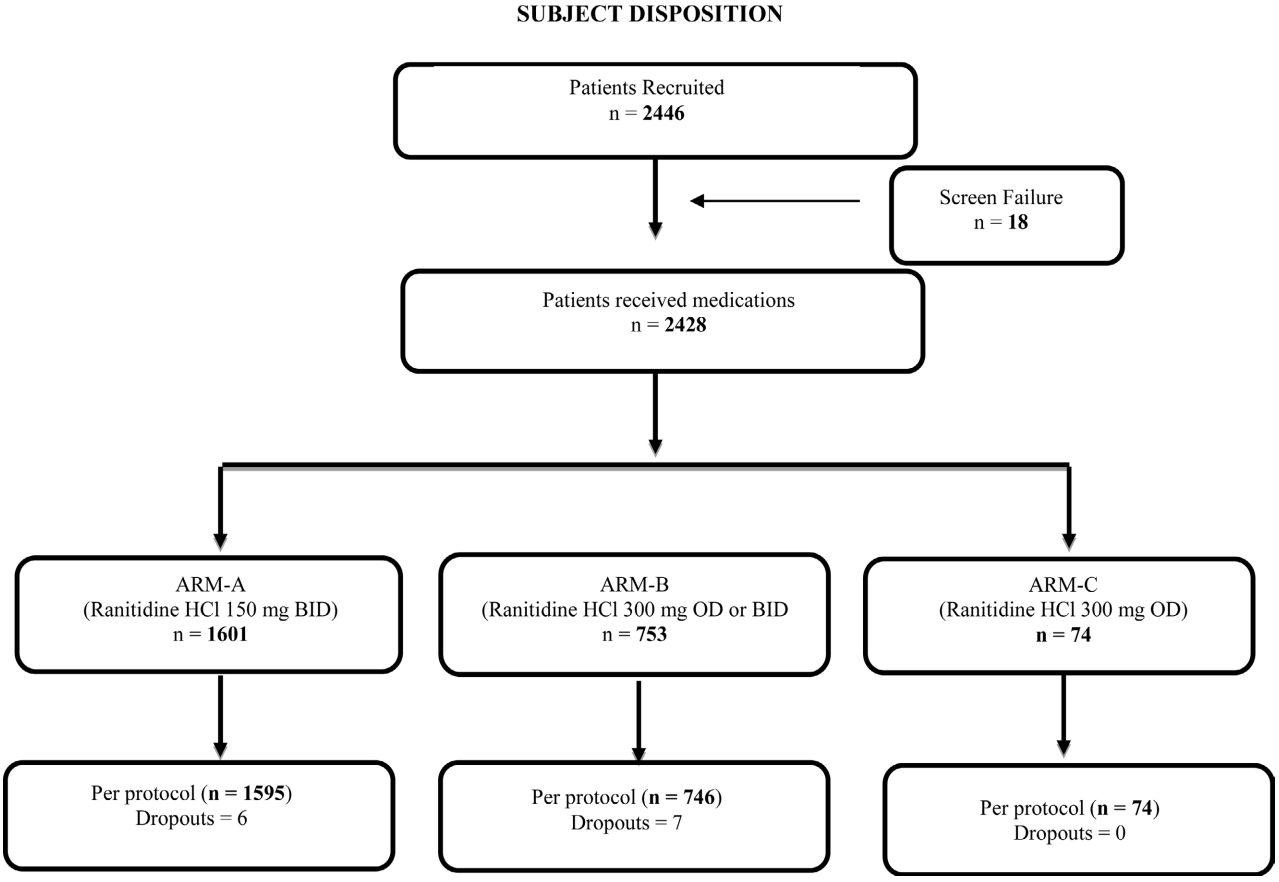


Figure 1. Flow chart of trial subject selection.

Table 1. Treatment ARMs.

Strength	Dose	No. of patients received
Ranitidine HCl 150 mg	BID	1601
Ranitidine HCl 300 mg	OD or BID	753
Ranitidine HCl 300 mg	OD	74

The final subject was screened on 05-Feb-2022 and enrolled on 07-Feb-2022. The first subject finished the study on 19-Nov-2021 and the last subject on 07-Mar-2022. The overall length of the study was 138 days.

Assessment of patient's symptoms GSAS is a GERD-specific scale that involves uni-dimensional and multidimensional questionnaires to assess the patient's symptoms, severity, and frequency in patients with GERD. It has fifteen elements, such as bloating, nausea, early satiety, etc. However, it does not encompass all atypical and nocturnal symptoms. It has been validated and demonstrated to have acceptable reliability and sensitivity to changes in symptom severity across time. GSAS scores were assessed on day 14 and 28 [12].

Safety evaluations: All ADRs (adverse drug reactions) observed by the investigator or treating physician were noted in detail in the ADR reporting form. According to the World Health Organization (WHO)-defined causal relationships to the study medications, the ADRs were categorized as related or not related. [13] The ADR severity was assessed using the HARTWIG scale as mild, moderate, and severe [14].

2.2. Statistical Analysis

GraphPad Prism version 9.0 was used for data analysis. All the data was captured into the MS Excel sheet, and all the study results were mentioned in percentages, frequency, or mean ± SD values. Comparisons were made between the baseline and end of the visit of the three ARMs for assessing the symptom relief using a student t-test. The number of patients relieved from 8 key symptoms was compared to know which dose is effective in relieving symptoms using Cochran-Mantel-Haenszel odds ratio analysis at 95% CI. Patients of three ARMs were compared at two endpoints such as 24 hours and after 7 consecutive days for heartburn-free days. The incidence, severity, and causality of ADRs were summarized. For analysis, P-value < 0.001 was considered statistically significant.

2.3. Ethics Considerations

This study was submitted to and approved by the Ethics Committee of shah lifeline hospital and heart institute ethics committee and by Ethicare ethics committee under number CTRI No: CTRI/2021/10/037668.

2.4. Respect for Autonomy

Written, signed, and dated informed consent was acquired from patients willing to comply with the protocol requirements.

2.5. Confidentiality

Participants were given codes instead of using their names for identification.

3. Results

Of the 2446 subjects screened, 2428 were enrolled in the study, 18 failed during

the screening, and none withdrew consent after enrolment. After 13 subjects were lost to follow-up, 2415 subjects completed the study. All patients were given the same drug but at different doses. 1601 subjects were given Ranitidine HCl 150 mg BID (ARM-A), 753 received 300 mg OD or BID (ARM-B), and 74 were taken 300 mg OD (ARM-C). None of the patients were terminated from the study owing to any adverse events per the protocol. A total of 1595 subjects in Arm A, 746 subjects in Arm B, and 74 subjects in Arm C completed the study. The demographic characteristics of the subjects registered in the study are mentioned in Table 2.

3.1. Efficacy Analysis

Heartburn, food regurgitation, flatulence, belching, dysphagia, nausea, vomiting, and acid regurgitation are the primary symptoms of GERD. After 2 weeks, 60.96% of ARM-A, 53.91% of ARM-B, and 52.7% of ARM-C were completely relieved from the 8 key symptoms of GERD. After 4 weeks, the corresponding cumulative results raised to 75.95% in the ARM-A group, 61.88% in ARM-B, and 58.10% in the ARM-C group. The percentage of patients relived from the 8 key symptoms was higher in ARM-A when compared to the other two groups (ARM-B, ARM-C), and it was significant ($P < 0.001$), and there was not much difference between ARM-B and ARM-C (Figure 2). There was a significant reduction in GSAS scores from baseline to the end of the study visit in all three ARMs. The GSAS score reduced from 2.02 to 0.23 in patients under ARM-A, 2.01 to 0.24 in patients of ARM-B and 2.07 to 0.26 in ARM-C patients (Table 3). The heartburn-free days were assessed for 24 hours and 7 consecutive days. In ARM-A, 72.82% had 24 Hours heartburn-free days, and 66.89% had 7 consecutive heartburn-free days, which was more significant than the other two ARMs. There was a drastic reduction in the percentage of patients under ARM-C from 24 Hours of heartburn-free days to 7 consecutive heartburn-free days (70.27% vs. 52.70%) (Table 4).

3.2. Safety Analysis

There were 128 clinical adverse events notified in 128 subjects. The most frequently reported ADR was constipation (17.18%), followed by oliguria (14.06%), cold (13.28%), and dysuria (12.5%) (Table 5). A total of 128 (5.27%) patients had been affected by ADRs due to Ranitidine HCl of different doses. Among

Table 2. Demographic characteristics.

Variable	Ranitidine HCl 150 mg BID (n = 1601)	Ranitidine HCl 300 mg OD or BID (n = 753)	Ranitidine HCl 300 mg OD (n = 74)
Male	862 (53.84%)	400 (53.12%)	45 (60.81%)
Female	739 (46.15%)	353 (46.87%)	29 (39.18%)
Mean Age (years)	37.39 ± 8.76	38.23 ± 6.35	38.20 ± 13.21

Table 3. Gastroesophageal Symptom Assessment Scale (GSAS).

GSAS Questions	ARM-A			ARM-B			ARM-C		
	Baseline Visit	End of Study Visit	P-Value	Baseline Visit	End of Study Visit	P-Value	Baseline Visit	End of Study Visit	P-Value
Heart burn or burning pain in Chest region	2.04 (0.19)	0.66 (0.48)	<0.0001	2.05 (0.21)	0.65 (0.48)	<0.0001	2.07 (0.25)	0.65 (0.48)	<0.0001
Chest Pressure or Discomfort	2.25 (0.55)	0.66 (0.47)	<0.0001	2.23 (0.54)	0.66 (0.47)	<0.0001	2.30 (0.54)	0.66 (0.48)	<0.0001
Food coming back into the mouth	2.07 (0.55)	0.74 (0.44)	<0.0001	2.08 (0.57)	0.74 (0.44)	<0.0001	2.08 (0.49)	0.74 (0.44)	<0.0001
Acidic or Sour Taste in mouth	2.02 (0.34)	0.68 (0.46)	<0.0001	2.02 (0.34)	0.66 (0.48)	<0.0001	2.04 (0.31)	0.62 (0.49)	<0.0001
Frequent Stomach Gurgling	2.30 (0.54)	0.68 (0.46)	<0.0001	2.29 (0.53)	0.68 (0.47)	<0.0001	2.41 (0.59)	0.61 (0.49)	<0.0001
Pressure Or Lump in the Throat	2.13 (0.62)	0.63 (0.48)	<0.0001	2.09 (0.63)	0.61 (0.49)	<0.0001	2.22 (0.67)	0.59 (0.49)	<0.0001
Nausea	1.84 (0.37)	0.62 (0.49)	<0.0001	1.82 (0.39)	0.59 (0.49)	<0.0001	1.92 (0.27)	0.61 (0.49)	<0.0001
Burning throat Pain	1.94 (0.23)	0.70 (0.46)	<0.0001	1.94 (0.24)	0.74 (0.44)	<0.0001	1.97 (0.16)	0.73 (0.45)	<0.0001
Bloating	1.98 (0.58)	0.76 (0.43)	<0.0001	1.96 (0.59)	0.73 (0.44)	<0.0001	2.14 (0.51)	0.81 (0.39)	<0.0001
Belching	2.04 (0.60)	0.79 (0.41)	<0.0001	2.02 (0.62)	0.77 (0.42)	<0.0001	2.09 (0.55)	0.78 (0.41)	<0.0001
Flatulence	2.07 (0.56)	0.76 (0.43)	<0.0001	2.03 (0.55)	0.76 (0.43)	<0.0001	2.09 (0.53)	0.82 (0.38)	<0.0001
Early satiety	1.98 (0.40)	0.70 (0.46)	<0.0001	1.99 (0.40)	0.71 (0.45)	<0.0001	1.99 (0.39)	0.78 (0.41)	<0.0001
Halitosis	1.85 (0.42)	0.71 (0.45)	<0.0001	1.87 (0.41)	0.74 (0.44)	<0.0001	1.88 (0.37)	0.76 (0.43)	<0.0001
Cough	1.86 (0.35)	0.56 (0.50)	<0.0001	1.85 (0.36)	0.58 (0.49)	<0.0001	1.88 (0.33)	0.59 (0.49)	<0.0001
Hoarseness	1.89 (0.31)	0.08 (0.27)	<0.0001	1.89 (0.31)	0.08 (0.28)	<0.0001	1.95 (0.23)	0.08 (0.27)	<0.0001
GSAS Score	2.02 (0.23)	0.23 (0.42)	<0.0001	2.01 (0.23)	0.24 (0.43)	<0.0001	2.07 (0.20)	0.26 (0.44)	<0.0001

Table 4. Percentage of patients who achieved sustained resolution of heartburn.

Endpoint	Ranitidine HCl 150 mg BID n (%)	Ranitidine HCl 300 mg OD or BID n (%)	Ranitidine HCl 300 mg OD n (%)
24 hours heartburn free days	1161 (72.82)	511 (68.49)	52 (70.27)
7 consecutive heartburn-free days	1067 (66.89)	415 (55.63)	39 (52.70)

these 128, 53 (7.03%) received Ranitidine HCl 300 mg OD or BID, 5 (6.75%) received Ranitidine HCl 300 mg OD, and 70 (4.37%) received Ranitidine HCl 150 mg BID. ADRs incidence was high in ARM-B (Ranitidine HCl 300 mg OD or BID). Of 128 ADRs, 113 (88.28%) were mild, 15 (11.71%) were moderate in severity, and no severe ADRs were reported during the study according to the Hart wig severity assessment scale. Causality assessment was done using the WHO scale, which showed only 11 (8.59%) ADRs were related to the study drug. No

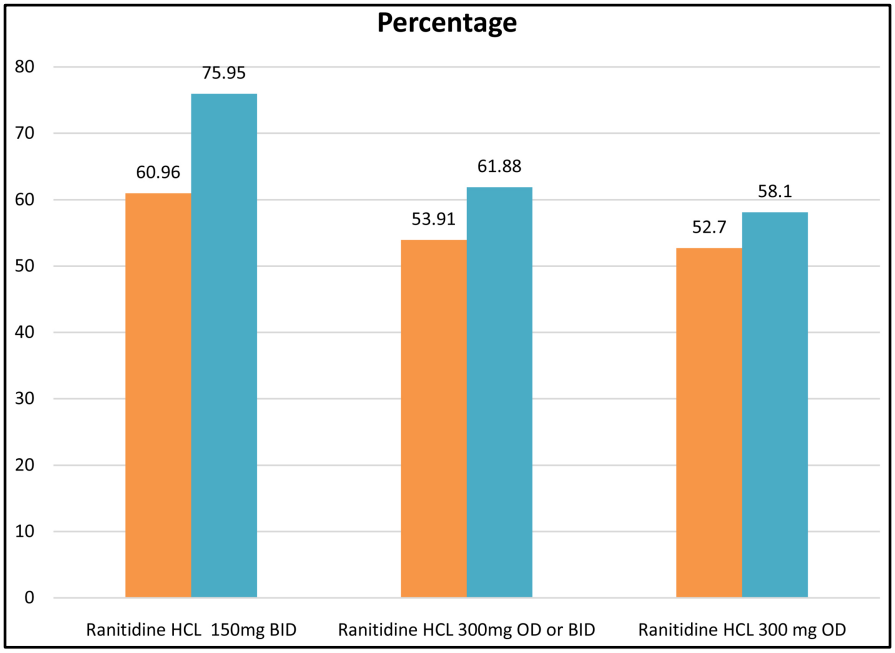


Figure 2. Percentage of patients free from the eight key symptoms of GERD [Clinical data presented for 2 weeks (Orange bar) and 4 weeks (Blue bar)].

Table 5. Percentage of ADR-experienced patients.

S. No	Description of ADR	No. of ADRs n = 128 (%)	No. of Patients N = 2248 (%)
1	Constipation	22 (17.18)	22 (0.91)
2	Oliguria	18 (14.06)	18 (0.80)
3	Cold	17 (13.28)	17 (0.75)
4	Dysuria	16 (12.5)	16 (0.71)
5	Fever	14 (10.93)	14 (0.62)
6	Arthralgia	8 (6.25)	8 (0.35)
7	Blurred vision	8 (6.25)	8 (0.35)
8	Insomnia	6 (4.68)	6 (0.26)
9	Myalgia	5 (3.90)	5 (0.22)
10	Back pain	2 (1.56)	2 (0.08)
11	Diarrhea	1 (0.78)	1 (0.04)
12	Nausea	1 (0.78)	1 (0.04)
13	Abdominal pain	1 (0.78)	1 (0.04)
14	Flatulence	1 (0.78)	1 (0.04)
15	GI Cramps	1 (0.78)	1 (0.04)
16	Headache	1 (0.78)	1 (0.04)
17	Vertigo	1 (0.78)	1 (0.04)
18	Malaise	1 (0.78)	1 (0.04)
19	Skin rash	1 (0.78)	1 (0.04)
20	Pruritus	1 (0.78)	1 (0.04)
21	Hair Loss	1 (0.78)	1 (0.04)
22	Urticaria	1 (0.78)	1 (0.04)

mortalities or hospitalizations were reported in treatment groups throughout the trial period (Table 6).

4. Discussion

GERD is a fairly common disorder and has shown a rising prevalence in recent years due to lifestyle changes. The backflow of stomach acid from the stomach to the esophagus causes GERD. This acid reflux can irritate the lining of the esophagus. GERD negatively impacts the daily lives of affected individuals, as it undermines social functioning, disturbs sleep, reduces productivity at work, and interferes with physical activity. An important clinical and research goal is to prevent the progression of GERD. [15] Ranitidine HCl, a H2-receptor antagonist, inhibits gastric acid secretion induced by histamine, pentagastrin, and other secretagogues. In this study, Ranitidine HCl 150/300 mg tablet (Rantac® 150/Rantac® 300 OD or BID/Rantac® OD 300) was found to be safe and effective in subjects with GERD [16].

Although several symptoms accompany GERD, it mainly exhibits 8 key symptoms: heartburn, food regurgitation, flatulence, belching, dysphagia, nausea, vomiting, and acid regurgitation. The current study assessed all the patients for complete relief of these 8 key symptoms after 2 weeks and 4 weeks of treatment. Most patients (75.95%) relieved from the 8 key symptoms were of ARM-A. This is consistent with the data published by Hotz*et al*., which reported that Ranitidine HCl 150 mg BID led to the reduction of acid-related and general dyspeptic symptoms in 66% of patients.[10] Another placebo-controlled study in pregnant women carried out by Larson J *et al*. reported that Ranitidine HCl 150 mg taken twice daily showed better results than Ranitidine HCl 300 mg taken once daily. [17] The GSAS score measures 15 specific symptoms, distress, and quality of life of patients with GERD. The GSAS scores were significantly reduced in

Table 6. Incidence of adverse events in the study population.

Variable	Ranitidine HCl 150 mg BID	Ranitidine HCl 300 mg OD or BID	Ranitidine Hydrochloride 300 mg OD	Total N (%)
Patients enrolled in the study	1601	753	74	2428
Patients with AE n (%)	70 (4.37)	53 (7.03)	5 (6.75)	128 (5.27)
Severity n (%)				
Mild	62 (88.57)	47 (88.67)	4 (80)	113 (88.28)
Moderate	08 (11.43)	06 (11.32)	01 (20)	15 (11.71)
Severe	00	00	00	00
Causality n (%)				
Related	05 (7.14)	05 (9.43)	01 (20)	11 (8.59)
Not Related	65 (92.85)	48 (90.56)	04 (80)	117 (91.4)

all three ARMs from baseline to after 4 weeks. Statistically significant differences in the mean GSAS scores were observed with Ranitidine HCl 150 mg twice daily taken for 6 weeks [18].

GERD is predominantly characterized by heartburn. Heartburn is recurrently accompanied by a sour aftertaste, with or without regurgitation of the refluxate. GERD may induce chest pain (non-cardiac) [19].

Patients administered with Ranitidine HCl 150 mg BID achieved good results in 24 hours and 7 consecutive days. Ranitidine HCl can reduce both the frequency and severity of heartburn. [20] Ranitidine HCl safety profile remained comparable to that observed in previously reported study. Ranitidine HCl, 150 mg twice a day, not only reduced heartburn but also improved the endoscopic changes of the esophagus mucosa in patients with GERD [21].

H2-receptor antagonists have better safety profile with acceptable tolerability. The safety profile of Ranitidine HCl was validated by a review of data from a vast number of controlled clinical trials, post-marketing monitoring studies, and spontaneously reported adverse events [22]. The safety of Ranitidine HCl over a wide range of doses and different dosage forms has been well documented which was observed in our study as well. The safety parameters of the current clinical study were the number of adverse events and serious adverse events reported during the clinical study. Only 5.27% of patients in our study reported to have mild-to-moderate ADRs. The most frequently reported ADR was constipation, followed by oliguria, cold, and dysuria. ADRs were high in patients receiving Ranitidine HCl 300 mg OD or BID and low in patients receiving Ranitidine HCl 150 mg twice daily. This is consistent with the study published by Simon et al., which reported fewer adverse events with Ranitidine HCl 150 mg BID than with 300 mg OD. [23] No severe ADRs were reported, and most of the ADRs were mild in severity and not related to the study drug.

In one of the reported 6-week clinical trial, ranitidine 150 mg was compared with the placebo in patients with GERD. 284 patients with GERD were evaluated before, during, and after six weeks of treatment with either ranitidine (150 mg twice daily) or placebo. Ranitidine treatment was significantly more effective than placebo treatment at reducing the frequency and the severity of heartburn during both daytime and nighttime assessment periods. The significant correlation was found between improvement in heartburn symptoms and reduction in antacid consumption. Patients receiving ranitidine consumed significantly fewer antacid tablets. The ranitidine-treated group had less erosions and ulcerations as well as better healing. This study concluded that, in patients with gastroesophageal reflux disease, ranitidine therapy, 150 mg twice daily, markedly reduced the heartburn symptoms of reflux disease and significantly improved the endoscopic appearance of the esophageal mucosa [21].

4.1. Limitations

There are few limitations in our study. Sample size was not sufficient to detect rare and very rare side-effects. Secondly, the study lacks a control arm and lastly

subjects were not followed up beyond 4 weeks.

4.2. Implications

This study suggests that Ranitidine hydrochloride 150/300 mg tablets can be beneficial to the patients with GERD and it will be helpful to improve their quality of life with minimal side-effects.

5. Conclusion

Ranitidine hydrochloride 150/300 mg tablet showed a favorable efficacy and safety profile. There was a significant reduction in GSAS scores from the baseline to the end of the study period. It also showed a significant increase in the percentage of patients who achieved sustained resolution of heartburn (7 consecutive heartburn-free days) and the percentage of 24-hour heartburn-free days. Ranitidine hydrochloride was well tolerated, with a safety profile comparable to previously reported studies in subjects with GERD. The study confirmed that Ranitidine hydrochloride is still a very effective and clinically significant drug for the management of various acid-peptic disorders.

Authors' Contributions

All authors made a significant contribution to the work reported.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this manuscript.

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