Comparative Study

A Parallel, Randomized, Comparative, Double-Blind, Double-Dummy Clinical Trial to Evaluate the Efficacy and Safety of Troxipide versus Rabeprazole in the Treatment of Gastritis

Prasan Kumar Hota, *Professor & HOD,*
Dept. of Surgery, Mamata Medical College, Khammam, Telangana.

Bhupesh Dewan, *Director Medical Services*

Deepashri Shah, *Assistant Manager,*

— Zuventus Healthcare Ltd., Mumbai, India.

Abstract

Aim of the study: To evaluate the efficacy and safety of Troxipide versus Rabeprazole in the Treatment of Gastritis. *Material and Methods:* A parallel, randomized, comparative, double-blind, double-dummy clinical trial was carried out on 50 endoscopically and histologically proven gastritis patients at department of "I.M.S. and SUM hospital", Bhubaneswar, India. All patients were randomized to receive either Troxipide (100mg, thrice a day) or Rabeprazole (20mg, once a day) for 4 weeks along with the dummy of the comparator. Endoscopy was performed at baseline and after week 4. The severity of clinical signs of gastritis i.e. abdominal pain, bloating, belching, nausea, vomiting, loss of appetite and regurgitation were assessed by the investigator at baseline, week 2 and week 4 using a Visual Analog Scale (VAS). Safety was assessed at each visit on the basis of the adverse event reported by the patients. *Results:* Troxipide showed significantly greater reduction in mean VAS score of abdominal pain (57.60 ± 13.92 vs 44.16 ± 10.59) and nausea (74.40 ± 10.44 vs 54.16 ± 18.15) than Rabeprazole at week 2. VAS scores improved for all clinical signs for both the groups ($P<0.05$) at week 4. Complete endoscopic healing of gastritis was observed at week 4 for both the groups except for one receiving Rabeprazole. Study medications were well tolerated and no adverse events were observed. *Conclusion:* Troxipide and Rabeprazole produce significant healing of gastritis with respect to resolution of clinical and endoscopic signs and both the drugs are well tolerated.

Keywords

troxipide, cytoprotective agents, gastritis, abdominal pain

Introduction

Gastritis is a heterogeneous pathological condition which is characterized by inflammation or swelling of the gastric mucosa, and is one of the most frequent reasons for medical consultation in Asian countries[1,2]. The causes of gastritis include infection (*H. pylori*), drugs (non steroidal inflammatory agents (NSAIDs), alcohol), stress, and autoimmune phenomena (atrophic gastritis)[3]. Gastritis can be classified as acute (predominantly neutrophilic infiltration) or chronic (with predominant infiltration by lymphocytes, plasma cells and macrophages) which leads to symptoms like abdominal pain, nausea and vomiting. Acute gastritis is in many cases similar to erosive gastritis whereas chronic gastritis implies some degree of atrophy

Address for correspondence: Dr. Bhupesh Dewan, Director Medical Services, Zuventus Healthcare Ltd., 5119, 'D' Wing, Oberoi Garden Estate, Chandivilli, Mumbai - 400 072. E-mail: bhupesh.dewan@zuventus.com

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or metaplasia. Although no typical clinical manifestation of gastritis has been reported, endoscopic examinations show the mucosa as reddened or inflamed. Small tissue samples (biopsy) removed from suspicious area helps in the confirmation of gastritis and the presence of *H. pylori* in the stomach lining by laboratory examination[4,5].

In gastritis, several necrotizing agents including NSAIDs and alcohol decrease gastric mucosal blood flow with loss of the mucosal protective barrier. NSAIDs inhibit prostaglandin production, whereas alcohol promotes depletion of sulfhydryl compounds in gastric mucosa[6]. In addition, Helicobacter pylori infection increases mucosal permeability by inducing a severe inflammatory response with gastric mucin degradation, which is cytotoxic to the gastric epithelium[7]. These evidences support that diminished mucosal barrier and dominance of noxious agents over defensive factors are responsible for the pathophysiology of gastritis.

The use of acid suppressants usually gives symptomatic relief in gastritis but the gastric mucosal damage still remains untreated[1]. Thus strengthening the mucosal defensive factors by the use of cytoprotective agents in the treatment of gastritis would be appropriate. Cytoprotective agents are known to stimulate mucus production and strengthen the mucosal barrier, thereby balancing aggressive factors (acid, pepsin, bile salts etc.) and defensive factors (mucin secretion, cellular mucus, bicarbonate secretion, mucosal blood flow, and cell turnover) in the gastrointestinal tract[8,9].

Troxipide is a systemically acting gastric mucosal protective agent that has been clinically proven to treat gastritis and ulcer. It neither inhibits acid secretion nor has acid neutralizing activity[10-12]. Troxipide causes increase in mucus production[13] and cytoprotective prostaglandin secretions, and inhibits inflammatory responses and mucosal injury mediated by neutrophils[14] which results in gastroprotection. Troxipide enhances the gastric mucosal metabolism[15] and microcirculation[16], independent of pH and content of the gastric juice[18], and promotes ulcer repair by increasing collagen regeneration of the ulcer base[17]. Further, Troxipide has been reported to be more efficacious than the prototype cytoprotectants (gefarnate, cetraxate and sucralfate)[15-18] and acid suppressants (famotidine and ranitidine) in various *in vivo* animal studies[20,21]. In clinical studies, Troxipide was not only found to be effective in the resolution of clinical symptoms associated with different acid peptic disorders (gastritis, dyspepsia, gastroesophageal reflux disease and ulcers), but was also found to be more effective than Ranitidine (300 mg/day) in controlling the subjective symptoms and improving the endoscopic findings in gastritis and gastric ulcers[21-22].

At present there are no clinical studies comparing safety and efficacy of Troxipide with proton pump inhibitors (PPIs) in patients with acid peptic disorders. The present parallel, randomized, comparative, double-blind, double-dummy clinical trial was carried out to compare the efficacy and safety of Troxipide 100mg given thrice a day (t.i.d.) with Rabeprazole 20 mg given once a day (o.d.) in the treatment of gastritis in Indian population.

Materials and Methods

Study Design

This was a parallel, randomized, comparative, double-blind and double-dummy study carried out on 50 patients between at the outpatient department of I.M.S. and SUM hospital, Bhubaneswar, India. The study was conducted in accordance with ICH-GCP and Indian regulatory guidelines for the conduct of clinical trials (schedule Y), and was approved by Independent Ethics Committee (Jagruti Independent Ethics Committee). Written informed consent was obtained from all patients. The trial has been registered with the Clinical Trial Registry of India (CTRI/2012/12/003264).

Patients

The study included patients with acute gastritis or acute exacerbation of chronic gastritis, evaluated on the basis of clinical symptoms and endoscopic diagnosis of gastric mucosal injury (erosion, oozing, redness or edema). Patients with history of pathological conditions of the intestine including inflammatory bowel disease, malabsorption syndromes, gastrointestinal malignancy, gastric or intestinal surgery including vagotomy, Barrett's esophagus or scleroderma; patients showing alarming features of unintentional weight loss, persistent vomiting, dysphagia, haematemesis, melaena, fever, jaundice, anaemia or serious concomitant disease; patients with signs of significant or massive gastrointestinal bleeding; patients unsuitable for pharmacotherapy e.g. patients with gastrointestinal perforation or pyloric stenosis, esophageal stricture or

intestinal obstruction; patients with major hematological, renal, cardiac, pulmonary or hepatic abnormalities were excluded from the study. Elderly patients and pregnant women, and those who test positive for *H. pylori* were also not included in the study.

Treatment

Patients were screened prior to enrollment and eligibility was assessed according to the specified inclusion and exclusion criteria. All the patients underwent a complete physical examination and the relevant demographic details were noted (**Table 1**). Endoscopic examination and laboratory investigations, which included complete blood count, hemoglobin, hepatic and renal function tests, were carried out in all the patients. The eligible patients received treatment with either Troxipide (100mg, t.i.d.) or Rabeprazole (20mg, o.d.), and second tablet of masking placebo similar in appearance to the other arm as per the computer generated randomization chart.

Assessment

Diagnosis of gastritis was based on the patient's description of his or her symptoms and verification was done using endoscopy along with biopsy of the suspicious area, to check for stomach lining inflammation and *H. pylori* status. The clinical profile of all the patients was recorded at baseline (visit 1), after 2 weeks (visit 2) and 4 weeks of treatment (visit 3). The severity of seven prominent clinical

Table 1
Baseline demographic & clinical characteristics of study population

	Troxipide (N=25)	Rabeprazole (N=25)
Sex (n, %)		
Male	14 (56)	15 (60)
Female	11 (44)	10 (40)
Age (yrs), (mean ± S.D.)	37.6 ± 11.05	43.72 ± 15.88
Body mass index (kg/m^2), (mean ± S.D.)	22.14 ± 1.8	22.21 ± 1.8
Endoscopic site of Gastritis (n, %)		
Antrum	5 (20)	6 (24)
Corpus	1 (4)	1(4)
Antrum & Corpus (Pangastritis)	18 (72)	19 (76)
Type of Gastritis		
Erosive Gastritis	10 (40)	7 (28)
Non-specific Gastritis	15 (60)	18 (72)
Gastritis clinical symptoms (n, %)		
Abdominal Pain	25 (100)	24 (96)
Bloating	9 (36)	8 (32)
Belching	18 (72)	13 (52)
Nausea	25 (100)	24 (96)
Vomiting	14 (56)	12 (48)
Loss of appetite	18 (72)	18 (72)
Heartburn	23 (92)	16 (64)

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signs of gastritis i.e. abdominal pain, bloating, belching, nausea, vomiting, loss of appetite and heartburn/ regurgitation were assessed at baseline and at every visit, using a Visual Analog Scale (VAS), a scoring system ranging from 0 to 100, where 0 represented lack of the symptom while 100 represented high severity. Endoscopy was performed at baseline and at the end of 4weeks of therapy in all patients to determine the effect of the treatment.

At the final visit of the trial, the patients were queried on the overall effect of the study medication, which was rated on a six -point Likert scale: 1 (The treatment made me a lot worse); 2 (The treatment made me slightly worse); 3 (The treatment made no change to my symptoms); 4 (The treatment made me slightly better); 5 (The treatment made me a lot better) and 6 (The treatment completely relieved my symptoms). Any adverse event, either reported by patient or observed by the investigator, was recorded at each visit.

Statistical Analysis

Comparative evaluations for the reductions in mean VAS score between the two groups and within the groups were performed by independent t-test and paired t-test, respectively. All data are presented as mean ± standard deviation (S.D.) unless stated otherwise. P value less than 0.05 was considered significant. Resolution of clinical symptoms and endoscopic signs of gastritis, and patient perspective on symptom relief are represented as percentage. Statistically analysis was performed using Microsoft excel and Analyse-it software.

Observations

Fifty patients with endoscopically proven gastritis were randomized into two groups; 25 patients received Troxipide (100mg, t.i.d.) while 25 patients received Rabeprazole (20 mg, o.d.).

Demographic and baseline characteristics

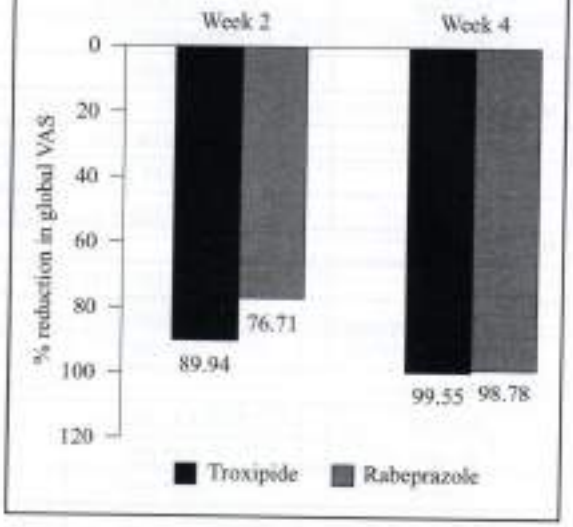
There were no clinically significant differences between the groups in baseline characteristics. Endoscopic examination and biopsy revealed that 34% (17/50) and 66% (33/50) patients had erosive gastritis and non-specific gastritis, respectively at baseline. The demographic profile and baseline clinical characteristics of the patients are as shown in **Table 1**.

Reduction in global VAS score

The percent reduction in the global VAS scores on day 14 and day 28 in Troxipide and Rabeprazole treated patients (n=50) is depicted in **Fig. 1**. At the end of the treatment, both, Troxipide and Rabeprazole significantly reduced the global VAS scores in all patients. A significant reduction in global VAS scores was observed in Troxipide treated patients as compared to Rabeprazole treatment group (89.94% vs 76.71%; P<0.001), after 2 weeks treatment but there was no difference observed between them after completion of 4 weeks treatment.

Fig. 1

Percent reduction in global VAS scores in patients treated with Troxipide and Rabeprazole (n=50)



Improvement in Clinical Symptoms

Troxipide showed significantly greater improvement (P<0.05) in VAS scores for abdominal pain and nausea compared to Rabeprazole at the end of 2 weeks of therapy (**Table 2**). The mean reduction in VAS score of abdominal pain from the baseline was 79.85% with Troxipide compared to 61.16% with Rabeprazole, while that of nausea was 99% with Troxipide compared to 78.50% with Rabeprazole at the end of 2 weeks of therapy.

The improvement in mean VAS scores for all other parameters was not observed to be significantly different (P>0.05) at week 2.

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Table 2
Improvement in VAS score of clinical symptoms associated with gastritis at different time points

	Troxipide Mean VAS score ± S.D (n)	Rabeprazole Mean VAS Score ± S.D (n)	p-value for difference between treatments
Abdominal Pain			
Baseline	74.4 ± 14.16 (25)	73.33 ± 11.67 (24)	
Week 2	16.8 ± 18.42* (13)	29.16 ± 12.12* (22)	S
Week 4	0.8 ± 2.78* (2)	0.83 ± 2.82* (2)	NS
Bloating			
Baseline	54.44 ± 14.24 (9)	58.75 ± 11.25 (8)	
Week 2	5.55 ± 11.3* (2)	10.0 ± 18.51* (2)	NS
Week 4	0.0* (0)	0.0* (0)	NS
Belching			
Baseline	67.22 ± 14.06 (18)	63.84 ± 8.87 (13)	
Week 2	3.33 ± 8.40* (3)	8.33 ± 14.03* (4)	NS
Week 4	0.0* (0)	0.83 ± 0.0* (1)	NS
Nausea			
Baseline	75.2 ± 10.04 (25)	70.41 ± 11.2 (24)	
Week 2	0.8 ± 0.0* (1)	16.25 ± 19.7* (11)	S
Week 4	0.0* (0)	1.25 ± 4.48* (2)	NS
Vomiting			
Baseline	58.57 ± 11.67 (14)	56.67 ± 18.74 (12)	
Week 2	0.0* (0)	5.83 ± 20.2* (1)	NS
Week 4	0.0* (0)	0.0* (0)	NS
Loss of Appetite			
Baseline	55.0 ± 12.48 (18)	51.11 ± 11.82 (18)a	
Week 2	0.0* (0)	3.88 ± 9.16* (3)	NS
Week 4	0.0* (0)	0.55 ± 0.0* (1)	NS
Heartburn			
Baseline	73.91 ± 13.39 (23)	67.5 ± 10.64 (16)	
Week 2	15.21 ± 13.43* (16)	18.12 ± 17.96* (9)	NS
Week 4	0.86 ± 2.88* (2)	1.25 ± 3.41* (2)	NS

*Note: NS (not significant, p>0.05) and S (significant, P<0.05); p-value for difference in mean VAS score within treatment groups is also provided (*p<0.001)*

The mean reduction in VAS scores at week 2 and week 4 with Troxipide and Rabeprazole treatment is presented in **Table 3**.

Clinical symptom resolution

Resolution of clinical symptoms was defined as proportion of patients achieving zero VAS score for the clinical symptoms evaluated (**Table 4**). At the end of two weeks, clinical resolutions of abdominal pain and nausea were significantly higher with Troxipide compared to Rabeprazole. Both treatments found to be equivalent in resolution of the clinical symptoms at the end of the treatment period.

Table 3
Mean reduction in VAS scores at week 2 and week 4 with Troxipide and Rabeprazole treatment

Clinical Symptoms	Mean reduction in VAS scores at week 2			Mean reduction in VAS scores at week 4		
	Troxipide* (Mean ± SD)	Rabeprazole* (Mean ± SD)	p-value for difference between treatments	Troxipide* (Mean ± SD)	Rabeprazole* (Mean ± SD)	p-value for difference between treatments
Abdominal pain	57.60 ± 13.92	44.16 ± 10.59	S	73.60 ± 14.10	72.50 ± 11.51	NS
Bloating	48.88 ± 12.69	48.75 ± 14.57	NS	54.44 ± 14.24	58.75 ± 11.25	NS
Belching	63.88 ± 15.73	55.00 ± 11.67	NS	67.22 ± 14.06	62.50 ± 7.53	NS
Nausea	74.40 ± 10.44	54.16 ± 18.15	S	75.20 ± 10.04	69.16 ± 11.76	NS
Vomiting	58.57 ± 11.67	50.83 ± 18.31	NS	58.57 ± 11.67	56.66 ± 18.74	NS
Loss of appetite	55.00 ± 12.48	47.22 ± 13.19	NS	55.00 ± 12.48	50.55 ± 11.61	NS
Heartburn	58.69 ± 13.91	49.37 ± 17.68	NS	73.04 ± 13.62	66.25 ± 12.04	NS

NS: Not significant (P>0.05); S: Significant (P<0.05)

**Significant difference was observed for mean reduction in VAS scores at week 2 and week 4 in both Troxipide and Rabeprazole groups, as compared to baseline.*

Table 4
Clinical resolution with Troxipide and Rabeprazole

Clinical Symptoms	Baseline		Clinical Resolution at week 2			Clinical Resolution at week 4		
	Troxipide N	Rabeprazole N	Troxipide* N (%)	Rabeprazole* N (%)	p-value for difference between treatments	Troxipide* N (%)	Rabeprazole* N (%)	p-value for difference between treatments
Abdominal pain	25	24	12 (48.00)	2 (8.33)	S	23 (92.00)	22 (91.66)	NS
Bloating	9	8	7 (77.70)	6 (75.00)	NS	9 (100)	8 (100)	NS
Belching	18	13	15 (83.33)	9 (69.23)	NS	18 (100)	12 (92.30)	NS
Nausea	25	24	24 (96.00)	13 (54.16)	S	25 (100)	22 (91.66)	NS
Vomiting	14	12	14 (100)	11 (91.66)	NS	14 (100)	12 (100)	NS
Loss of appetite	18	18	18 (100)	15 (83.33)	NS	18 (100)	17 (94.44)	NS
Heartburn	23	16	7 (30.43)	7 (43.75)	NS	21 (91.30)	14 (87.50)	NS

NS: Not significant (P>0.05); S: Significant (P<0.05)

** Significant difference was observed in clinical resolution at week 2 and week 4 in both Troxipide and Rabeprazole groups, as compared to baseline.*

Resolution of Endoscopic signs of Gastritis

As per endoscopic diagnosis, the signs of gastritis were limited to the antrum in 22% of the patients and corpus in 4% of the patients, while pangastritis was found in 74% of the patients (**Table I**). All patients, except one receiving Rabeprazole, showed a complete endoscopic healing of gastritis at the end of the treatment period.

Patients' perspective on Symptom Relief

At the end of 4 weeks of therapy, a higher proportion

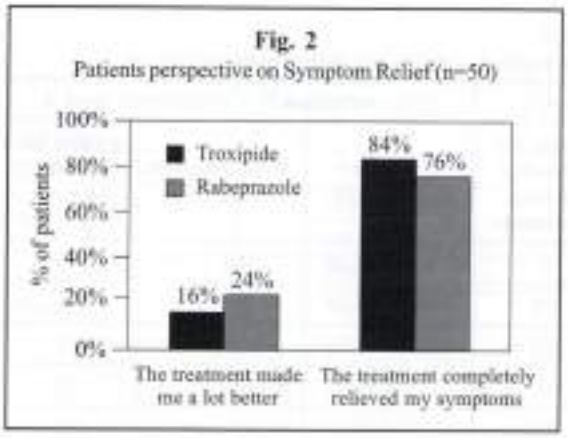

Fig. 2
Patients perspective on Symptom Relief (n=50)

of patients reported complete symptom relief with Troxipide as compared to Rabeprazole (84% vs 76 %; **Fig. 2**).

Safety and Tolerability Profile

There were no adverse events reported with either of the study medications. The laboratory parameters evaluated did not show any statistically significant change during the treatment period with both the drugs.

Discussion

Troxipide is a novel cytoprotective agent and has been clinically proven to be useful in the treatment of acid peptic diseases, like gastritis, and gastric and duodenal ulcers[21]. In order to compare its efficacy and safety with PPI, we planned a randomized, double blind, clinical trial of Troxipide versus Rabeprazole in the treatment of gastritis. The result of present study demonstrated that both, Troxipide and Rabeprazole significantly resolved the clinical and endoscopic symptoms associated with gastritis after completion of 4 weeks treatment. We did not find any significant difference in VAS score reduction between the groups at the end of the study period, however, Troxipide showed a statistically significant improvement ($P<0.05$) in VAS scores for abdominal pain and nausea as compared to Rabeprazole at the end of 2 weeks of therapy.

Acute gastritis is presented with sudden onset of abdominal pain, nausea, and vomiting, along with occasional infiltration of neutrophils with edema and hyperemia. If not treated, this condition evolves further into chronic gastritis. Histologically, chronic gastritis is characterized by an inflammatory cell infiltrate consisting of lymphocytes and plasma cells, with the involvement of neutrophils. These infiltrated inflammatory cells extend deeper into the mucosa, with progressive distortion and destruction of the glands. Endoscopically, the mucosa may become substantially thin, permitting clear visualization of the underlying blood vessels[4, 11]. Troxipide has ability to prevent mucosal inflammation induced by interleukin stimulated neutrophil migration, and inhibits xanthine oxidase and myeloperoxidase induced oxidative stress[14, 23]. Thus, treatment with Troxipide results in an overall decrease in gastric mucosal inflammation. Troxipide also increases gastric mucus production along with cytoprotective prostaglandin secretion like PGE_2 and PGI_2, and further provides protection against acid induced tissue injury[14]. Considering the pharmacodynamics of Troxipide, the superior efficacy of Troxipide in the resolution of abdominal pain and nausea at week 2 may be attributed to its rapid mucosal protective action.

We assessed the effect of Troxipide in both erosive and non-specific gastritis patients. It was found to be effective in controlling clinical symptoms and endoscopic findings in these patients. Erosive gastritis occurs when the inner lining of the stomach gets inflamed, and starts to erode away. This condition can occur suddenly due to the use of certain drugs (such as NSAIDs), alcohol and acute stress. Less common causes include radiation, viral infections, blood vessel injury and trauma. These injuries may decrease blood circulation to the stomach, which in turn decreases mucus formation[4]. As reported previously, Troxipide enhances gastric mucosal blood flow and metabolism, thereby increasing mucus production as well as tissue regeneration[15-17]. Troxipide restrains NSAID induced generation of porphyrins, tissue peroxidation and gastric lesion formation[24]. Troxipide also inhibits *H. pylori* derived urease, thereby suppressing further inflammatory responses[18]. Moreover, in a previously conducted clinical trial, Troxipide showed an overall amelioration rate of 82.9% and 79.4% in acute/chronic gastritis and gastric ulcer, respectively[11], suggesting good efficacy of Troxipide in erosive gastritis.

In the present study all the patients treated with Troxipide showed complete endoscopic healing of gastritis at the end of the treatment period. Global assessment for efficacy by patients towards the therapy showed that 84% patients got

completely relieved after Troxipide treatment as compared to 76% patients with Rabeprazole, suggesting higher efficacy of Troxipide in the treatment of gastritis. However, there was no significant difference observed between the two treatment groups. No adverse events with either of the study medications were observed, confirming the safety profile of Troxipide.

The study limitations included lower patient population and assessment of clinical symptoms on the basis of subjective VAS scale. Beside these limitations, the study furnishes the real life comparison between Troxipide and Rabeprazole in the treatment of gastritis. Further studies on larger population are required to confirm the results.

Conclusion

At the end of 4 weeks of treatment, both Troxipide and Rabeprazole effectively resolved the clinical and endoscopic signs of gastritis. Troxipide showed a better reduction in abdominal pain and nausea associated with gastritis as compared to Rabeprazole at the end of week 2; however, after 4 weeks of treatment, there was no significant difference between Troxipide and Rabeprazole treatment groups. No adverse events were reported with either of the study medications.

Summary

The aim of the study was to evaluate the efficacy and safety of Troxipide versus Rabeprazole in the Treatment of Gastritis. All patients were randomized to receive either Troxipide (100mg, thrice a day) or Rabeprazole (20mg, once a day) for 4 weeks. Endoscopy was performed at baseline and after week 4. The severity of clinical signs of gastritis i.e. abdominal pain, bloating, belching, nausea, vomiting, loss of appetite and regurgitation were assessed by the investigator at baseline, week 2 and week 4 using a Visual Analog Scale (VAS). Safety was assessed at each visit on the basis of the adverse event reported by the patients. Troxipide and Rabeprazole produced significant healing of gastritis with respect to resolution of clinical and endoscopic signs and both the drugs were well tolerated.

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