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## Anti-ulcer effect of Sodium cromoglycate in NSAID and ethanol induced ulcer in comparison with ranitidine in rats

**Marpu Raghava Sravani and Avula Naveen**

### Abstract

**Objective:** To evaluate the antiulcer effect of Sodium Cromoglycate in comparison with Ranitidine in Ethanol induced and NSAID induced ulcer in rats.

**Background:** Peptic ulcer disease is a break in the lining of the stomach, first part of the small intestine, or occasionally the lower esophagus. An ulcer in the stomach is known as a gastric ulcer while that in the first part of the intestines is known as duodenal ulcer [1]. There are many anti-ulcer agents like H2-receptor antagonists, Proton pump inhibitors to alleviate the symptoms of peptic ulcer disease. Though these medications considered to be safe, some of the recent studies have shown that role of Proton pump inhibitors in aggravating myocardial infarction and other cardiac ailments. Therefore search for a new potent, safe and nontoxic drug continues.

**Materials and Methods:** This animal study was a cross sectional, observational in nature carried out in male Wistar rats. Animals were divided into four groups with six animals in each group. GROUP 1: Standard drug Ranitidine in Aspirin induced ulcer. GROUP 2: Test drug Sodium Cromoglycate in Aspirin induced ulcer. GROUP 3: Ranitidine in Ethanol induced ulcer. GROUP 4: Sodium Cromoglycate in Ethanol induced ulcer. Parameters like number of ulcers, severity of ulcers and Ulcer Index was calculated.

**Results:** In the present study, Mean number of ulcers with Group I is  $3.16 \pm 3.44$ , in Group II is  $4.83 \pm 2.32$ , ( $p < 0.05$ ). In Group III is  $2.33 \pm 2.72$  and in Group IV is  $3.83 \pm 2.32$ , ( $p < 0.05$ ) is statistically significant. Mean Grade of Severity of ulcers in Group I is  $1.13 \pm 1.12$ , in Group II is  $1.72 \pm 0.12$ , ( $p < 0.05$ ). In Group III is  $1.01 \pm 1.06$  and in Group IV is  $1.50 \pm 0.18$ , ( $p < 0.05$ ). Is statistically significant. Ulcer index in Group I – 12.62, Group II – 16.55, Group III – 11.67 and in Group IV – 15.33.

**Conclusion:** Sodium Cromoglycate is an effective agent in ulcer healing, in Ethanol induced and NSAID induced ulcers in rats but is less compared to that of Standard drug Ranitidine.

**Keywords:** Peptic ulcer, NSAID induced ulcer, Ethanol Induced ulcer, Sodium Cromoglycate, Ulcer index

### Introduction

Peptic ulcers are defects in the gastrointestinal mucosa that extend through the muscularis mucosae. It is an important cause of morbidity and health care costs and one of the most common causes of upper GI bleeding affecting 60% of cases. The risk factors being, H. pylori infection [1], use of NSAIDs, Smoking, Ethanol consumption etc.

Imbalance in mucosal offensive and defensive factors is the pathophysiological mechanism in peptic ulcer. Generation of reactive oxygen species free radicals also contribute to ulcer. Gastric mucosa can resist auto digestion although it is exposed to numerous endogenous noxious stimuli like aggressive secretion of hydrochloric acid, pepsin and reflux of bile. Exogenous agents like spicy food, alcohol [2], smoking, caffeine, drugs like aspirin, corticosteroids, indomethacin, and phenylbutazone are ulcerogenic. Diseases like Zollinger Ellison Syndrome (ZE syndrome) [3] cause chronic forms of gastric and duodenal ulcer. H. pylori infection is also an important risk factor in the pathogenesis of peptic ulcer [4]. It is found to be more common in males and in population with "O" positive blood group.

Since recognition of peptic ulcer is an important clinical entity, efforts have been made to find a suitable remedial measures to reduce acid secretion which have predominated the pharmacological basis of peptic ulcer therapy. In the last two decades the introduction of new drugs like H2 receptor antagonist, proton pump inhibitors and so on have been developed for the treatment of duodenal and gastric ulcer, but ulcer due to an increase in aggressive factors like acid and pepsin is found only in minority of the patients.

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Thus attention has been focused on gastrointestinal defense mechanism leading to the concept of cytoprotection. So, peptic ulcer disease can be prevented by strengthening the defense mechanism of gastric and duodenal mucosa [5]. Also these drugs are expensive, toxic and lead to many drug drug interactions, constant efforts have been made to find a suitable, palliative and curative agent for the treatment of peptic ulcer disease.

Cromolyn prevents the release of mediators which attract inflammatory cells and it also stabilizes the inflammatory cells [6]. Has stabilizing effect on mast cells with an anti-asthmatic effect [7].

Sodium Cromoglycate has already been used in the treatment of many gastric conditions like persistent diarrhea [8], as an adjuvant in the treatment of Inflammatory Bowel Disease especially Ulcerative Colitis [9]. It acts by mechanisms other than mast cell stabilization. Sodium cromoglycate inhibits the exaggerated neuronal reflexes and inhibits calcium influx, histamine and substance P mediated peptic ulcers. The present study was designed to investigate the beneficial effects of Cromoglycate in healing peptic ulcers in comparison with Ranitidine.

### Materials and Methods

Male wistar rats weighing 200 – 250 gms, were procured from Central animal house of Gandhi Medical College, Secunderabad after obtaining permission from the Institutional Animal Ethics Committee for the project. There are several animal models for evaluation of anti-ulcer agents. It includes acute chronic models. Acute models such as pylorus ligated ulcer in rats [10], Histamine induced ulcer in guinea pigs [11], cysteamine induced duodenal ulcer [12], Dimaprit induced duodenal ulcers [13], Stress ulcers models etc. In the present study we have chosen stress ulcer models with NSAIDs and Ethanol as triggering agents.

**Study design:** Animals were divided into 4 groups six animals in each group and given standard and test drugs as follows.

**Group 1:** Standard drug Ranitidine in Aspirin induced ulcer.

**Group 2:** Test drug Sodium Cromoglycate in Aspirin induced ulcer.

**Group 3:** Standard drug Ranitidine in Ethanol induced ulcer.

**Group 4:** Test drug Sodium Cromoglycate in Ethanol induced ulcer.

**Doses:** Dose of Standard drug Ranitidine 27mg/kgwt given intraperitoneally.

Test drug Sodium Cromoglycate 40mg/kgwt, given intraperitoneally.

Induction of ulcer with Aspirin 200mg/kgwt orally.

Induction of ulcer with 1ml of Ethanol orally.

Before initiation of the main study, a Pilot study was done for the induction of ulcer by Aspirin and Ethanol in two animals. The animals were fasted for 24 hours with free access to

water at libitum. After 24 hours Aspirin given in a dose of 200mg/Kg and 1 ml of Ethanol given orally via intragastric tube. Two hours after the treatment the animals were sacrificed by cervical dislocation under Ether Anesthesia. Abdomen incised and irrigated with normal saline. Stomach is identified and cut along the greater curvature and washed gently. They are placed in bottles with formalin and sent to Pathology department Gandhi Medical College for histopathological examination. The HPE reported as focal gastric erosions in NSAID induced model and gastritis in Ethanol induced model.

**In the main study:** After fasting for 24 hours, animals were divided into four groups. Group 1 & 3 are pre-treated with Standard drug Ranitidine. Group 2 & 4 are pre-treated with Test drug Sodium Cromoglycate. Two hours after the pre-treatment, ulcer is induced with Aspirin in group 1 & 3 and Ethanol in group 2 & 4. Two hours after the induction of ulcer, animals were sacrificed by cervical dislocation under ether anaesthesia. Anterior abdominal incision is given and irrigated with normal saline. Stomach is identified and the upper end and lower end is ligated, and cut along its greater curvature, washed gently in running tap water and examined for the following:

#### 1. Mean Number of ulcers

#### 2. Mean Grade of Severity of ulcers [14]: 0 – No ulcer

1 – Superficial ulcer

2 – Deep ulcer

3 – Perforation

After grading the severity of each ulcer in a single animal, the average severity has been taken out for analysis.

#### 3. Ulcer index

Ulcer index was calculated by adding the total number of ulcers plus severity of ulcers [15].

Lesion severity was determined by measuring ulcer index.

$$UI = U_N + U_S + U_P \times 10^{-1}$$

UI = Ulcer Index.

$U_N$  = Mean Number of ulcers.

$U_S$  = Mean grade of Severity of ulcers.

$U_P$  = Ulcer Probability (incidence) for each group.

Ulcer index calculated for each group separately by the above formula.

#### Histopathological examination

The tissue samples are fixed in 10% buffered formalin and processed with paraffin wax. For Histopathological examination, 5mm sections were stained with hematoxylin and eosin. The extent and depth of ulceration and hemorrhage are evaluated [16].

#### Statistical Analysis

This is carried out by using unpaired “t” test as it is a Quantitative data. All the results were expressed as mean  $\pm$  standard error of the mean. All the results obtained in the study were compared with each group.  $P < 0.05$  were considered statistically significant.

**Results**

**Table 1a:** Number of Ulcers – Aspirin Group

Animal No.	Ranitidine in Aspirin induced ulcer	Sodium Cromoglycate in Aspirin induced ulcer
1	4	6
2	3	5
3	5	3
4	3	4
5	0	5
6	4	6
MEAN	3.16	4.83
2 X S.D	2 X 1.72 = 3.44	2 X 1.16 = 2.32

*P*<0.05, Statistically significant

The mean number of ulcers in Aspirin group after treating with Ranitidine is  $3.16 \pm 3.44$  and the mean number of ulcers after treating with Sodium Cromoglycate is  $4.83 \pm 2.32$ . The difference between two means is 1.69. This difference is statistically significant (*p*<0.05).

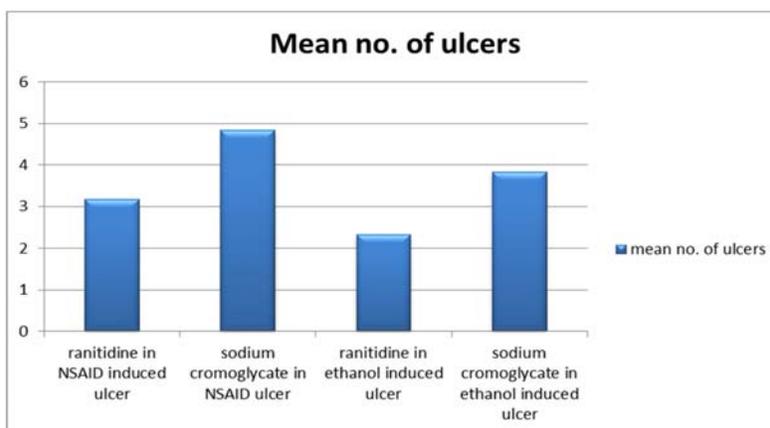
Sodium Cromoglycate also has significant ulcer healing property but not more than Ranitidine in Drug induced ulcers.

**Table 1b:** Number of Ulcers –Ethanol Group

Animal No.	Ranitidine in Ethanol	Sodium Cromoglycate in Ethanol
1	3	5
2	2	4
3	4	2
4	2	3
5	0	4
6	3	5
MEAN	2.33	3.83
2 X S.D	2 X 1.36 = 2.72	2 X 1.16 = 2.32

*P*<0.05, Statistically significant.

The mean number of ulcers in Ethanol group after treating with Ranitidine is  $2.33 \pm 2.72$  and the mean number of ulcers after treating with Sodium Cromoglycate is  $3.83 \pm 2.32$ . The difference between two means is 1.50, and this difference between two means is statistically significant. (*p*<0.05) Sodium Cromoglycate also has an ulcer healing property but not more than Ranitidine in treating Ethanol induced ulcers.



**Chart 1:** (Table: 1A & 1B): Bar diagram showing mean number of ulcers in Aspirin and Ethanol group after treating with Standard and Test drug.

X axis represent Mean Number of Ulcers.  
Y axis represent Groups.

**Table 2a:** Grade of Severity of Ulcer- Aspirin Group

Animal No.	Ranitidine in Aspirin induced ulcer	Sodium cromoglycate in Aspirin induced ulcer
1	1.5	1.6
2	1.3	1.8
3	1.4	1.6
4	1.3	1.7
5	1.25	1.8
6	0	1.6
MEAN	1.13	1.72
2 X S.D	2 X 0.56 = 1.12	2 X 0.06 = 0.12

*P*<0.05. Statistically significant

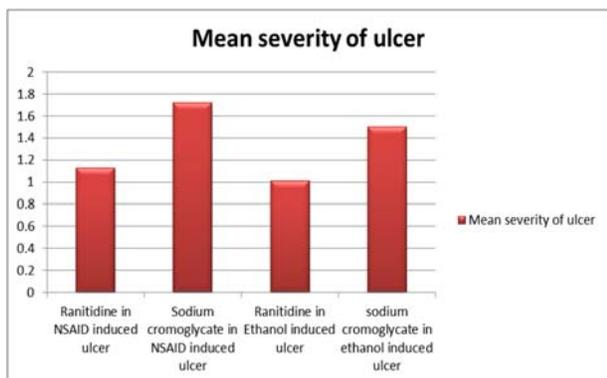
The Mean Grade of Severity of ulcer in Aspirin group after treating with Ranitidine is  $1.13 \pm 1.12$  and the Mean Grade of Severity of ulcer in Ethanol group after treating with Sodium Cromoglycate is  $1.72 \pm 0.12$ . The difference between two means is 0.59 and this difference is statistically significant. (*p*<0.05) Sodium Cromoglycate also efficacious in reducing the Severity of ulcer in Aspirin induced ulcer group, but not more than Ranitidine.

**Table 2b:** Grade of Severity of Ulcer - Ethanol Group

Animal No.	Ranitidine in Ethanol	Sodium cromoglycate in Ethanol
1	1	1.6
2	1.5	1.5
3	1.25	1.5
4	1	1.3
5	0	1.5
6	1.3	1.6
MEAN	1.01	1.5
2 X S.D	2 x 0.53 = 1.06	2 x 0.09 = 0.18

*P*<0.05, statistically significant.

The Mean Grade of Severity of ulcer in Ethanol group after treating with Ranitidine is  $1.01 \pm 1.06$  and the Mean Grade of Severity of ulcer in Ethanol group after treating with Sodium Cromoglycate is  $1.5 \pm 0.18$ . The difference between two means is 0.49 and this difference is statistically significant. (*p*<0.05) Sodium Cromoglycate also efficacious in reducing the Severity of ulcer in Ethanol induced ulcer group, but less than compared to Ranitidine.



**Chart 2:** (Table 2A & 2B): Bar diagram showing Mean Grade of Severity of ulcers in Aspirin and Ethanol group after treating with Standard and Test drug.

X axis represent Mean Severity of Ulcers.  
Y axis represent Groups.

**Analysis of Results**

**Mean number of ulcers:** The Mean Number of ulcers in Aspirin group after treating with Ranitidine is  $3.16 \pm 3.44$  and the Mean Number of ulcers after treating with Sodium Cromoglycate is  $4.83 \pm 2.32$ .

The Mean Number of ulcers in Ethanol group after treating with Ranitidine is  $2.33 \pm 2.72$  and the Mean Number of ulcers after treating with Sodium Cromoglycate is  $3.83 \pm 2.32$ .

**Mean Grade of severity of ulcers:** The Mean Grade of Severity of ulcer in Aspirin group after treating with Ranitidine is  $1.13 \pm 1.12$  and the Mean Grade of Severity of ulcer in Ethanol group after treating with Sodium Cromoglycate is  $1.72 \pm 0.12$ .

The Mean Grade of Severity of ulcer in Ethanol group after treating with Ranitidine is  $1.01 \pm 1.06$  and the Mean Grade of Severity of ulcer in Ethanol group after treating with Sodium Cromoglycate is  $1.5 \pm 0.18$ .

Ulcer index for each Group is calculated as follows:  
Ulcer Index (UI) = Mean Number of Ulcers ( $U_N$ ) + Mean Severity of Ulcers ( $U_S$ ) + Ulcer Propability ( $U_P$ )  $\times 10^{-1}$   
Group I:  $UI = U_N + U_S + U_P \times 10^{-1}$   
 $3.16 + 1.13 + 83.3 \times 10^{-1}$

$$3.16 + 1.13 + 8.33 = 12.62$$

$$\text{Group II: } UI = U_N + U_S + U_P \times 10^{-1}$$

$$4.83 + 1.72 + 100 \times 10^{-1}$$

$$4.83 + 1.72 + 10 = 16.55$$

$$\text{Group III: } UI = U_N + U_S + U_P \times 10^{-1}$$

$$2.33 + 1.01 + 83.3 \times 10^{-1}$$

$$2.33 + 1.01 + 8.33 = 11.67$$

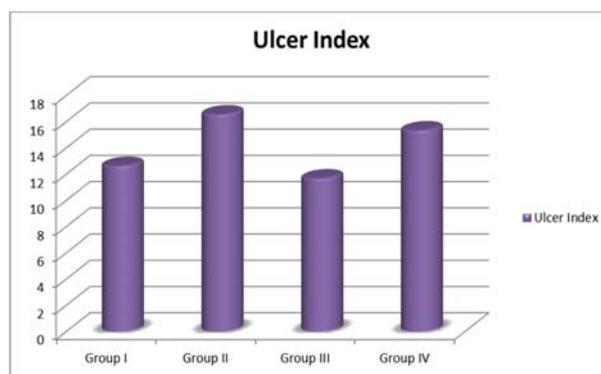
$$\text{Group IV: } UI = U_N + U_S + U_P \times 10^{-1}$$

$$3.83 + 1.5 + 100 \times 10^{-1}$$

$$3.83 + 1.5 + 10 = 15.33$$

**Table 3:** Ulcer Index in Different Groups:

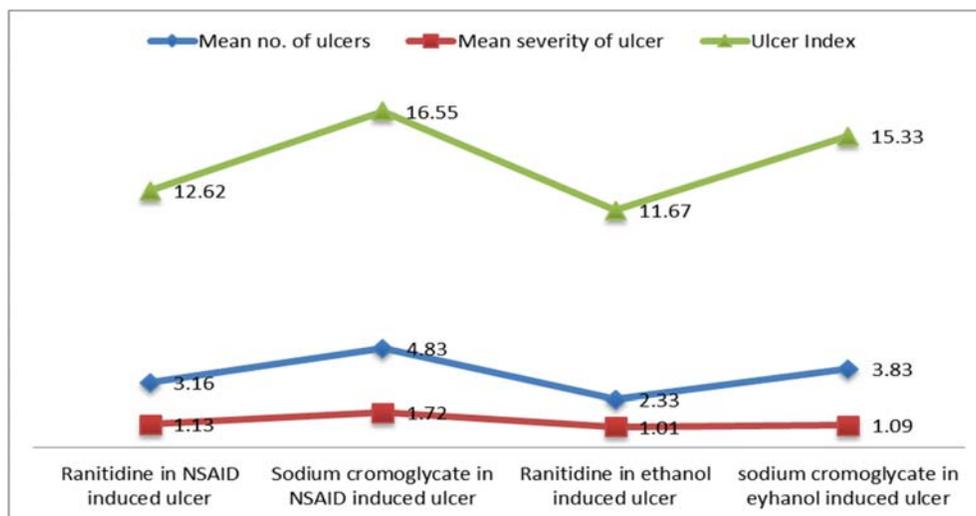
Group Number	Group Name	Ulcer Index
I	Ranitidine in Aspirin induced ulcer.	12.62
II	Sodium cromoglycate in Aspirin induced ulcer.	16.55
III	Ranitidine in Ethanol induced ulcer	11.67
IV	Sodium cromoglycate in Ethanol induced ulcer.	15.33



**Chart 3:** Bar graph showing ulcer index in different groups.

**Table 4:** Showing all three parameters of Number, Severity and Ulcer index.

Group no.	Mean no. of Ulcers	Mean Grade of Severity of Ulcers	Ulcer Index
I	3.16	1.13	12.62
II	4.83	1.72	16.55
III	2.33	1.01	11.67
IV	3.83	1.09	15.33



**Chart 4:** Line diagram showing Mean no. of ulcers, Mean Grade of Severity of ulcers and Ulcer index in different groups.

## Discussions and Conclusions

Sodium Cromoglycate is an anti-asthmatic drug, prevents release of histamine from mast cells. Commonly given as prophylaxis in combination with bronchodilators. It is given topically as eye drops for Allergic Vernal Conjunctivitis.

The present study demonstrated the anti-ulcer effect of Sodium Cromoglycate in Ethanol and NSAID induced ulcer in comparison with Ranitidine in experimentally induced ulcer in rats.

There is a significant ulcer healing property with the test drug Sodium Cromoglycate by reduction in the number of ulcers and the severity of ulcers, but less when compared to that of standard drug Ranitidine.

- In Paul L. Beck, *et al*, in Canadian Journal of Physiology and Pharmacology study in 1989, Sodium Cromoglycate was found to be effective in treating the Ethanol induced ulcer in a dose dependent manner.<sup>(73)</sup>
- In Mohammad Tariq *et al* study in 2006, Sodium Cromoglycate was proved to be effective in preventing water immersion restraint stress (WIRS) and Indomethacin induced ulcer than Ethanol and cysteamine induced ulcer.<sup>(74)</sup>
- In Vivek srivastav *et al*. study, efficacy of Sodium Cromoglycate was proved in pylorus ligated induced gastric ulcer was published in 2010.<sup>(75)</sup>

In the present study ulcer healing property of sodium Cromoglycate is compared with H<sub>2</sub> receptor antagonist Ranitidine and found to be effective in treatment of peptic ulcer in rats. Further clinical studies have to be conducted for the final assessment of ulcer healing property of Sodium cromoglycate.

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## Declarations

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Conflict of interest: None declared

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