

Efficacy of Zinc Sulfate in Peptic Ulcer Disease: A Randomized Double-Blind Clinical Trial Study

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ABSTRACT

Introduction: Peptic ulcer is a common disease that affects millions of people worldwide. Considering its global prevalence finding new approach for treating is important.

Aim: The aim of this study was to investigate the effect of zinc sulfate on gastric and duodenal ulcer treatment.

Materials and Methods: This double-blind clinical trial study was done on 90 patients who were admitted to the gastrointestinal endoscopy clinic of Tohid hospital in Sanandaj, Iran. All patients were diagnosed with gastric and duodenal ulcers. They were randomly divided into two-intervention and control groups, using block randomization with block sizes of 4. Patients and researcher were unaware of the grouping. To assess the level of zinc, blood samples were taken. In case of positive Rapid Urease Test (RUT), triple therapy regimen including amoxicillin, clarithromycin and omeprazole was administered for two weeks. For intervention group in addition to "triple therapy", an oral

dose of Zinc Sulfate 220mg capsules were administered daily, while the control group received placebo capsules.

Results: A total of 54.5% and 57% of the patients in the intervention and control groups had gastric ulcer respectively. The Rapid Urease Test (RUT) result of 72.7% of intervention group and 83.3% of control group was positive ($p = 0.24$). Serum zinc level of 20.9% of intervention group and 35.7% of control group was lower than the normal level ($p = 0.13$). The mean of serum zinc level of intervention group and control group were 81.9 and 78.9 mg dL respectively ($p = 0.4$). After intervention, peptic ulcer in 81.8% of the intervention group and 83.3% of the control groups were improved ($p = 0.85$). Response to treatment were higher in patients with normal zinc levels compared to patients with abnormal levels (77.5% vs. 22.5%, $p = 0.019$).

Conclusion: A daily dose of 220mg zinc sulfate was not significantly effective on peptic ulcer. However, patients with normal zinc levels had better ulcer treatment.

INTRODUCTION

Peptic ulcer has plagued mankind for centuries. The first suggested description of gastric hemorrhage attributed to an ulcer is in the Egyptian Papyrus Ebers [1]. Gastric and duodenal ulcers significantly affect millions of people worldwide [2]. Of adult US residents, 10% reported having physician-diagnosed ulcer disease, and one third of these individuals reported having an ulcer in the past year. The disease is responsible for 15,000 deaths annually. The annual direct and indirect costs of the disease are estimated to be more than \$10 billion [3]. A meta-analysis has reported that 95% of all hospitalized ulcer cases in the USA were attributable to *H pylori* infection, main risk factors are-use of non-steroidal anti-inflammatory drugs (NSAIDs), minor tranquilisers and tobacco smoking [4,5]. Over the past few decades, dietary factors are taken into consideration as effective factors on digestive diseases including peptic ulcer [6].

Zinc is an essential mineral for optimal development of human body. It is ubiquitous within cells in contrast to iron, which is contained in defined cellular components and has defined physiological roles. The role of zinc in biology can be grouped into three general functional classes, namely catalytic, structural and regulatory functions [7]. Furthermore, zinc is an important metabolic requirement for growth and repair of squamous tissue [8]. Numerous aspects of cellular metabolism are dependent on zinc. It is required for the function of approximately 100 enzymes and it plays a role in immune function, protein synthesis, wound healing, DNA synthesis and cell division [7-10].

Effect of zinc on peptic ulcer treatment has been described in animal studies. Moreover, other studies have shown the protective action of zinc ions on the gastric mucosa [9,10]. Frommer [11]

Keywords: Gastro duodenal ulcer, Mineral nutrients, Treatment

showed zinc effectiveness on gastric ulcers, but Yazdanpanah et al., in their study found no significant association between zinc supplementation and peptic ulcer treatment [12]. They recommended further studies with higher doses of zinc to determine effective dose. The aim of this study was to investigate the effect of zinc sulfate on gastric and duodenal ulcer treatment.

MATERIALS AND METHODS

This randomized, double-blind clinical trial study was done on 90 patients who referred to the Digestive Endoscopy Center of Sanandaj Tohid Hospital from 2013 to 2014. Inclusion criteria were peptic ulcer during endoscopy and age above 20 years. Exclusion criteria were clear symptoms indicating malignancy, malignancy in pathology, patient reluctance to endoscopy, unwillingness in continuing medication, discontinuation of the medication for more than two days and diseases that impair absorption (cirrhosis, celiac disease).

Endoscopy was performed for patients by subspecialist of gastroenterology using Olympus 160 Video Endoscope Endoscopy System. Then patients with gastric and duodenal ulcers were enrolled in the study. After explaining the procedure, written informed consent was taken from participants.

Total of 90 patients were divided in two-intervention and control groups using the randomized block method. Based on study variables clinical interview was performed for each patient and data were documented in questionnaires. Blood samples were taken and sent to the laboratory to measure the level of zinc. Standard treatment was started for both groups according to the results of RUT. Triple therapy regimen including amoxicillin, clarithromycin, and omeprazole was administered for two weeks if the RUT test

was positive. Based on ulcer size, triple therapy regimen was prescribed for 2 weeks followed by 4 weeks of omeprazole for 3 cm ulcers. If the ulcer was less than 3 cm triple therapy regimen was prescribed for 2 weeks followed by 2 weeks of omeprazole. In the case of negative RUT test, treatment was performed only with omeprazole.

H pylori AB-I was checked in false negative RUT cases such as in patients with gastrointestinal bleeding, consumption of Proton Pump Inhibitors (PPI), or in history of antibiotic use in previous 2 weeks. Depending on the positive or negative RUT, patients were treated as RUT positive or RUT negative respectively. In addition to triple therapy, a daily dose of zinc sulfate 220mg (Alhavi Pharmaceutical Co.) were prescribed in the intervention group orally. In the control group only placebo was given to the patients. After intervention the ulcers were assessed by second endoscopy performed by the same physician and their size were documented.

From 90 cases who were participated in the study 4 patients were excluded from the study (2 patients underwent surgery due to bleeding and 2 of them had no desire to continue with the study) [Table/Fig-1].

STATISTICAL ANALYSIS

Data were analysed by Statistical Package for Social Sciences (SPSS) software version 18.0. To compare the improvement of peptic ulcer, descriptive statistics, chi-square, and fisher exact

test were used. T-test was used for quantitative variables such as age, ulcer size and level of zinc in both intervention and control groups.

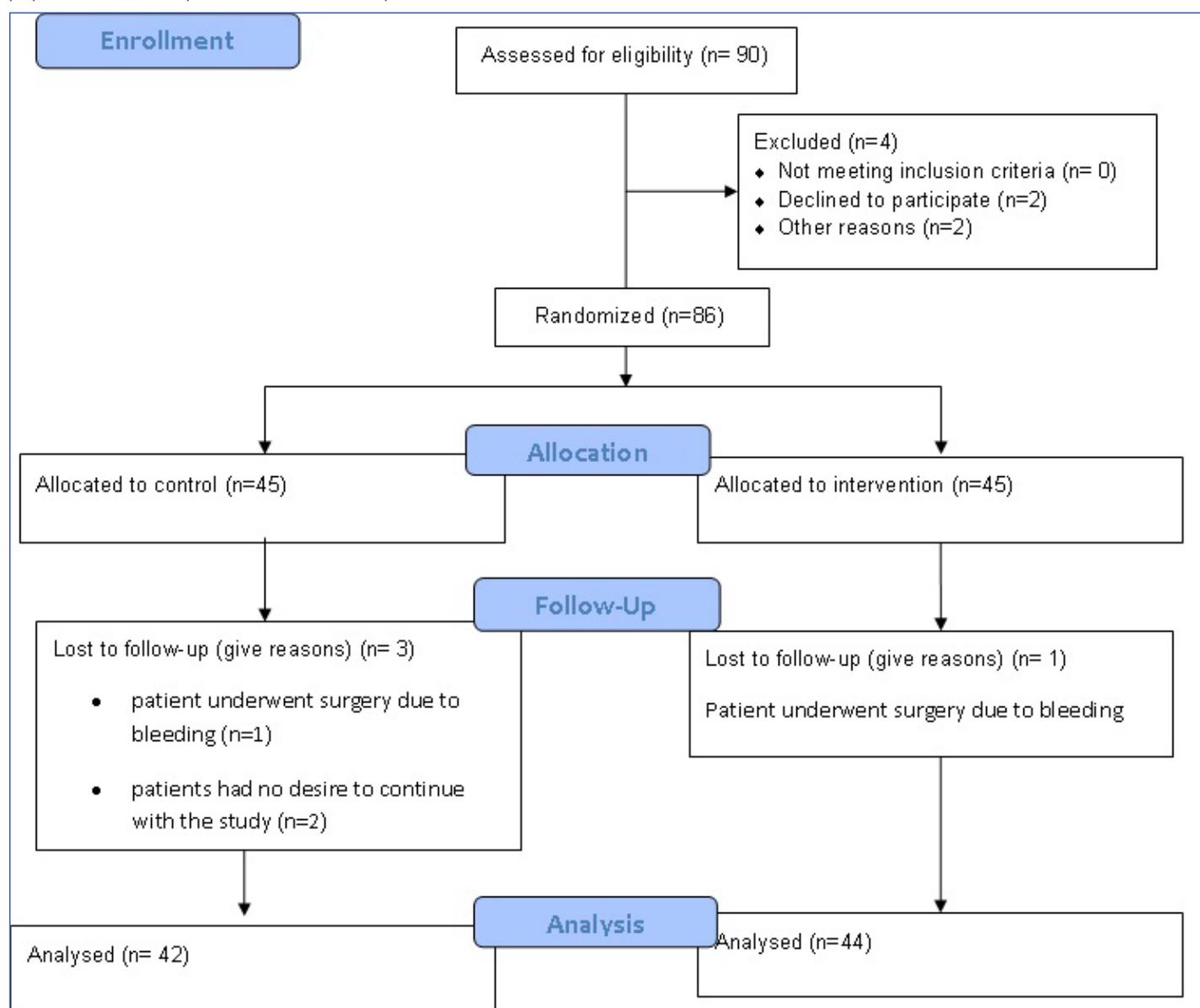
This study has been approved by the ethics committee of Kurdistan University of Medical Sciences and also has been registered in Iranian Registry for Clinical Trials with code no. IRCT2014062212789N4.

RESULTS

Findings of this study showed that, male population in the intervention and control group was 81.8% and 81% respectively. Mean age of the patients in the intervention and control group was 47.5 ± 17.2 years and 52.6 ± 18.4 years, respectively ($p=0.02$). In both groups, use of NSAIDs was the same (52.3 % vs. 54.8%).

In the intervention group 55.5% of the ulcers were located in the stomach and 45.5% of them were found in duodenum. However, in the control group, 59.6% of the ulcers were located in the stomach and 40.4% of them were found in the duodenum ($p>0.05$). The result of RUT and IgG was similar in both groups. RUT was positive in 72.7% of the intervention and 83.3% of the control group ($p= 0.24$) [Table/Fig-2].

There was no significant difference between both groups for epigastric pain, night pain, epigastric burning, nausea, vomiting, melena, and rectorrhagia ($p>0.05$). However, frequency of immediate pain after meal in the intervention and control groups



[Table/Fig-1]: Flow diagram of the progress through the phases of a two-group parallel randomized trial.

Variable	Group	Intervention	Control	p
		No. (%)	No. (%)	
Gender	Male	36 (81.8)	34 (81.0)	0.92
	Female	8 (18.2)	8 (19.0)	
Smoking	Yes	19 (43.2)	11 (26.2)	0.1
	No	25 (56.8)	31 (73.8)	
Alcohol	Yes	3 (6.8)	1 (2.4)	0.62 Fisher
	No	41 (93.2)	41 (97.6)	
Use of Non-steroidal anti-inflammatory drugs	Yes	23 (52.3)	23 (54.8)	0.82
	No	21 (47.7)	19 (45.2)	
Ulcer site	Stomach	24 (55.5)	25 (59.6)	0.64
	Duodenum	20 (45.5)	17 (40.4)	
RUT	Positive	32 (72.7)	35 (83.3)	0.24
	Negative	12 (27.3)	7 (16.7)	
IgG	Positive	32 (72.7)	34 (81.0)	0.45
	Negative	12 (27.3)	8 (19.0)	

[Table/Fig-2]: Comparison of two groups in terms of different variables.

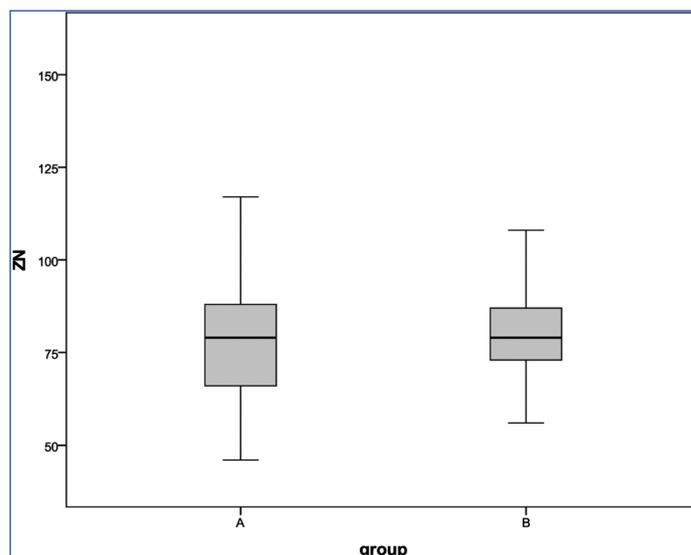
was 54.5 % and 28.6% respectively ($p=0.015$). Pain with interval after meal, was 36.4% in the intervention group and 61.9% in the control group ($p=0.018$) was significant [Table/Fig-3].

The mean of peptic ulcer size in the intervention and in the control groups were 11.1 ± 3.6 and 15.4 ± 7.3 mm ($p=0.0001$). The mean of zinc level in the intervention group was 81.9 ± 16.4 mg/dl also for 79.1% of them the level of zinc was normal. The mean of zinc level in the control group was 78.9 ± 17.4 mg/dl. For 64.3% of the patients in control group the level of zinc was normal ($p=0.4$) [Table/Fig-4].

The response to treatment in the intervention and control groups did not show a significant difference statistically ($p=0.85$) [Table/Fig-5]. However, in intervention group positive response was 81.8% and patients with normal zinc serum levels had better ulcer treatment (77.5% Vs 22.5%, $p=0.019$) [Table/Fig-6].

Variable	Group	Intervention		Control		p
		No.	(%)	No.	(%)	
Epigastric pain	Yes	39	88.6	36	85.7	0.68
	No	5	11.4	6	14.3	
Pain immediately after meal	Yes	24	54.5	12	28.6	0.015
	No	20	45.5	30	71.4	
Pain with interval after meal	Yes	16	36.4	26	61.9	0.018
	No	28	63.6	16	38.1	
Night pain	Yes	26	59.1	22	52.4	0.53
	No	18	40.9	20	47.6	
Stomach pain relieved by antacids	Yes	24	54.5	17	40.5	0.19
	No	20	45.5	25	59.5	
Epigastria burning	Yes	24	54.5	23	54.8	0.98
	No	20	45.5	19	45.2	
Nausea	Yes	29	65.9	28	66.7	0.94
	No	15	34.1	14	33.3	
Vomiting	Yes	25	56.8	22	52.4	0.68
	No	19	43.2	20	47.6	
Hematemesis	Yes	14	42.9	18	42.9	0.29
	No	30	57.1	24	57.1	
Melena	Yes	30	45.5	23	54.8	0.39
	No	14	54.5	19	45.2	
Rectorrhagia	Yes	8	18.2	3	7.1	0.2 Fisher
	No	36	81.8	39	92.9	

[Table/Fig-3]: Frequency of symptoms in the intervention and control groups.



[Table/Fig-4]: Comparison of the level of zinc in the intervention (A) and control (B) groups.

Group	Intervention		Control		p
Response to Treatment	No.	(%)	No.	(%)	
Positive	36	81.8	35	83.3	0.85
Negative	8	18.2	7	16.7	

[Table/Fig-5]: Response to treatment in the two groups.

Response to Treatment/	Yes		No		p
Zinc serum level	No.	(%)	No.	(%)	
Lower than normal	16	22.5	8	57.1	0.019
Negative	55	77.5	7	42.9	

[Table/Fig-6]: Relationship between the results of treatment and zinc serum level in the two groups.

DISCUSSION

Helicobacter pylori is the main cause of peptic ulcer disease. Physiologically essential elements; Fe, Zn, and Cu are of great clinical concern in medicine. Their deficiencies are among the important health problems [13]. The studies have recently been focused on the possible anti-*Helicobacter pylori* effects of dietary metals [14-17].

In our study the treatment response in the intervention and control groups were 81.8% and 83.3% respectively which showed no significant difference. The study results revealed that zinc sulfate had no statistically significant effect on peptic ulcer. In a study by Yazdanpanah et al., zinc sulfate administered every other day, after intervention, the ulcer size in the intervention group was less than the control group; however, the difference was not statistically significant [12]. In our study also the ulcer size in the intervention group was less than the control group and difference was statistically significant. It seems that zinc sulfate can reduce the ulcer size and for better result the more dose of zinc sulfate is required. Zinc sulfate o.d was given to the patients in the present study. In Frommer's study zinc sulfate 220mg was given orally three times a day for three weeks in intervention group. The ulcer healing rate was three times that of control group. This difference was significant [11]. Also, Pories revealed that oral medication with zinc sulphate is safe at the level of 220mg. t.i.d. for periods up to 61 days and it accelerate wound healing as well as systemic therapy with zinc is beneficial during tissue repair in man just as it is in rats [18]. Rodrigues et al., conducted a study to demonstrate the protective action of zinc ions on the gastric mucosa of rats. The results showed that zinc had positive effect on the healing of gastric ulcer [10].

In our study, there was no difference between groups in terms of the serum zinc level, but the number of cases with lower level in the intervention group was less than the control group. In a study by Bandyopadhyay et al., a significant increased value ($p < 0.01$) of zinc content in gastric mucosa of patients with peptic ulcer diathesis was noted. They concluded that the low serum zinc level of the peptic ulcer patients is possibly due to the positive shift for the zinc from serum to the gastric mucosa [19]. Plasma and gastroduodenal levels of zinc reflect the stage of the pathological process in peptic ulcer [20].

Previous studies have indicated the positive effect of zinc on ulcer healing in animal models [21,22]. In a study conducted by Garcia, a daily dose of 600mg zinc sulfate was more effective than Famotidine in the treatment of duodenal ulcers [23]. Findings of study by Troskot et al., indicated that zinc plays an important cytoprotective role in duodenal ulcer disease [24].

In the present study in terms of the epigastric pain, night pain, pain relief with antacids, epigastric burning, nausea, vomiting, haematemesis, melena and rectorrhagia there was no significant difference between the intervention and control groups. However, there was statistically significant difference between the two groups in terms of pain immediately after meal and pain with interval after meal. Frequency of pain immediately after meal was higher in the intervention group; whereas, pain with interval after meal was higher in the control group. Incidence of gastric ulcers (57%) was higher than duodenal ulcers; however, there was no statistical difference between the two groups in terms of location of the ulcer.

In a study conducted by Barazandeh et al., on North West's population of Iran incidence of gastric ulcer was 3.3% and duodenal ulcer has been reported as 4.9% [25]. This rate was lower than the reported prevalence in previous studies in Asia which were based on endoscopy in the general population [26-28]. In a systematic review by Li et al., incidence of gastrointestinal ulcer, gastric ulcer and duodenal ulcer in china were 17.2%, 1.6%, and 13.3% respectively [29]. According to medical examination and assessment of hospitalized patients, annual global incidence of gastric ulcer was 0.1 -0.19% and 0.03 -0.17%, respectively [30]. Results of this study is similar to the results of epidemiologic studies conducted in Europe which showed a prevalence of 4.1% (2% gastric ulcer and 2.1% duodenal ulcer) [31] to 6.2% (gastric ulcer 2.3% and duodenal ulcers 3.9%) [32]. In all of these studies prevalence of gastric ulcers was less than duodenal ulcer. In our study, incidence of gastric ulcer was more than duodenal ulcer which could be explained by different statistical population. Another reason could be that other studies were conducted in the general population, while our study was conducted on patients with gastrointestinal symptoms referring for endoscopy.

Mean age of patients in this study was 47.5 and 52.6 years in the intervention and control groups respectively. In the studies conducted in Iran, mean age was between 40 and 53.3 year [33,34]. In other international studies mean age was between 48-57 years [35,36]. Studies which conducted in Iran showed that with promotion of public health, mean age increased.

RUT result for the detection of *Helicobacter pylori* were the same in both groups and was about 78%. In a study conducted on 200 patients, 82% of the patients were infected with *Helicobacter pylori* [37]. Many studies on biological microscopy in China revealed high prevalence of *Helicobacter pylori* [30]. In 73% to 100% of the patients with duodenal ulcer and 65% to 100% of the patients with gastric ulcers, high infection rate with *Helicobacter pylori* were reported [38,39]. In a 10-year study in Korea, by Jang et al., incidence of peptic ulcer and especially duodenal ulcer had decreasing trend [40]. Good management and promotion of community health in the west lead to the eradication of *H. pylori* followed by decrease in the rate of duodenal ulcer [41].

LIMITATION

The limitation of our study was that; some patients who were treated during the study did not follow-up.

CONCLUSION

Daily administration of 220mg of zinc sulfate reduced peptic ulcer size and also patients with normal levels of serum zinc had better healing processes. It seems that for better effect high dose of zinc sulfate is required.

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