Original Article

Efficacy of Sucralfate in Reflux Disease in comparison to H$_2$ – Receptor Antagonist: A Meta-Analysis of Randomized Trials

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ABSTRACT

Background and Aim: Reflux esophagitis is characterized by the erosions of esophagus due to gastric acids. H$_2$-Recptor antagonists are considered as effective therapy. We compared sucralfate with H$_2$-receptor antagonist for treatment of reflux esophagitis.

Methods: Seven studies are selected from different databases (PUBMED, MEDLINE, COCHRANE LIBRARY, CINAHL etc.) comparing the treatment of sucralfate with H$_2$-receptor antagonists (cimetidine and ranitidine). All studies selected are randomized controlled clinical trials. We applied inclusion and exclusion criteria for selection of studies. We also checked for heterogeneity and publication bias. We calculated odds ratio and 95% confidence interval for each study. We searched for national library of medicine's clinical trial registry for any unpublished data.

Results: Seven studies consisting of 319 patients finally selected for meta-analysis. We evaluated confidence interval and odds ratio for each study. None of the study show statistical significant result (p>0.05). The overall effect obtained by combining studies shows no statistical significant result (OR= 1.357, 95% CI=0.834 to 2.206, P-value=0.219, I^2=0) between sucralfate and H$_2$-recptor antagonist. There is no heterogeneity among the studies (I^2=0, χ^2 =4.8).

Conclusion: We can conclude that sucralfate is an effective alternate for treatment of reflux disease.

INTRODUCTION

Gastrointestinal reflux disease is a common gastrointestinal disorder prevalent in western world.[1] Esophagitis occurs when the gastric acid move back to the esophagus. Regular backing of gastric acid causes the burning and erosion of esophagus. Reflux esophagitis causes severe heartburn and regurgitation. If not given proper treatment for healing of esophagitis, it may result into chronic disorder. The other term to denote reflux esophagitis are gastroesophagal reflux disease (GERD), acid reflux disease etc. some of the common symptoms of reflux esophagitis includes heartburn, belching, upper abdominal pain, salivation,long term cough, vomiting etc. the failure of clearing the esophageal content is also responsible for reflux disease.[1,2]

H$_2$- receptor antagonists (cimetidine and ranitidine) are considered as most effective treatment for reflux disease since 1976 and these acts by reducing gastric acid secretion.[3,4] The other comparable drug sucralfate has the same symptomatic relief as that of H$_2$-receptor antagonist.[5] But certain studies give the inconsistent result. So, we obtained a combined effect of efficacy of sucralfate in gastrointestinal reflux disease by performing meta-analysis on eligible studies.[6] In this paper, we performed comparison of sucralfate and H$_2$-receptor antagonist by quantitative estimation technique called meta-analysis with R programming.

METHODS

Identification and selection of studies

We searched the English literature for our studies published during January 1985 to October 2014. The databases searched for meta-analysis are PUBMED, MEDLINE, CINAHL, Cochrane central library and EMBASE. The key terms included in search strategy are reflux esophagitis, sucralfate, ranitidine, and cimetidine and these are applied to each database in consideration. Reflux esophagitis fetches 33,500 articles. We got 17,300 articles with by search of sucralfate. By combining search by keyword reflux esophagitis and sucralfate, it gives 1760 articles. We only searched for double blind and single blind randomized trials. We checked title, abstracts, conclusion for identification of required study.

After the searching in all mentioned databases, 1760 relevant articles are found, and these are further evaluated for inclusion and exclusion criteria. We also discussed with experts for any relevant detail "

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for our studies as mentioned in Figure 1 (the flowchart for meta-analyis used in the study).

Inclusion and exclusion criteria

Selection criteria are applied to our selected studies, to include study of interest in meta-analysis. The inclusion criteria for study is

1. The study should be either double blind or single blind randomized control trial
2. The intervention treatment is with sucralfate.
3. The study is compared with H_2-receptor antagonist (ranitidine or cimetidine).
4. Patient involved in study should have manifestation of esophagitis before entering into the study.
5. The healing of esophagitis occurs at four, eight and twelve weeks.

Of 1760 identified trials, only eight trials met our inclusion criteria.[7-14] The one study from eight studies is excluded due to patient may not had esophagitis manifestation before entering into the study.[13] Finally, only seven trials included in our study (Table 1). The study selected for meta-analysis is all having same protocol for treatment. Information on healing of the symptoms of esophagitis is extracted from the trials. We have not applied any exclusion criteria. All the selected studies reviewed and obtained full texts for further evaluation in statistical analysis.

Extraction of data

From the selected studies, all data needed for the meta-analysis is obtained and feed to the statistical analysis. The data abstracted is

1. Name of studies
2. Number of patient (Number of men and women participants in study)
3. Year of publication
4. Location of studies
5. Study design
6. Age of patient
7. Alcohol consumption within patients
8. Smokers patients
9. Randomization ratio of patients.

This data used in the meta-analysis. We contacted to authors if data is seem to be insufficient. The data from different studies is compared to each other.

Outcome measures

We have designed the endoscopically healing of ulcers as our primary outcome. From different study, healing of ulcers is occurred at interval four, eight and twelve weeks. The complete healing measured by endoscopically is taken into consideration. We combined this data as our outcome measure for meta-analysis. There are also secondary outcomes such as epigastric pain, nausea, headache but these are not considered in this study.

Identification of heterogeneity and publication bias

All the studies selected for meta-analysis are subjected to the estimation of heterogeneity and publication bias measurement. Funnel plot is used for the assessment of the publication bias within the studies.[15] Asymmetry of funnel plot leads to the publication bias.[15,16] Heterogeneity measurement is done by chi-square (χ^2) statistics and I^2-statistics. P-value less than 0.10 are indication of significant heterogeneity. Heterogeneity in study is estimated using Cochrane's Q and I^2 statistics.[17] I^2 statistics is derived from the Cochrane Q.

$$I^2 = \frac{Q - df}{Q} \times 100$$

Where,

df = degree of freedom

I^2 greater than 50% represent significant heterogeneity in the study. If I^2 is equal to 0% then there is no heterogeneity among the studies.

RESULTS

The data extracted from study is subjected to meta-analysis. Dichotomous data calculated as odd ratio for the representation of effect size. The confidence is measured at 95% level. P-value is also measured for calculation statistical significant result. We have calculated weight for each study. Random effect model is applied to meta-analysis using DerSimonian and Laird method.[18]

A total of 375 patients are involved in analysis from seven different studies. The all studies are published during 1985 to October 2010. All patients are adults. A comparison of sucralfate is made with H_2-receptor antagonist in all studies. Elsborg and Jorgenesen (1991), Tytgat (1987), Hameeteman W. *et al.* (1987), Ros *et al.* (1991) compares sucralfate with cimetidine and Bremner (1991), Simon and Mueller (1987), B.K. chopra *et al* (1992) compares sucralfate with ranitidine.

Overall, the patient's clinical characteristics distributed among study as 55.31% men, 44.68% women, 59.67% smokers, 22.88% alcohol consumers. The trials are varied from four weeks to twelve weeks. The dosages used in the intervention are 1 gm. of sucralfate four times daily with exception of 6 gm. per day in Bremner (1991). The dosages of ranitidine are 150 mg of tablet twice a daily and those of cimetidine are 400 mg twice or four times daily.

As indicated in Table 2, the patients in sucralfate group are 176 (48.88%) and those in H_2- receptor antagonist group are 184 (51.11%) from overall 360 patients. When we analyzed the all studies there is no statistical significant difference is found in all study. All studies are having p-value greater than 0.05. Overall, we found that there is no clinical significant difference after combining all studies (odds ratio=1.283, 95% CI= 0.817-2.017, p-value=0.279). So, there is no statistical difference between the two treatments.

We checked heterogeneity among studies. The test for heterogeneity shows that there is no significant difference among studies (I^2=0% and χ^2=5.17, p-value=0.521). The chi-square statistics (χ^2) value obtained is 5.17 (less than degree of freedom) which indicate there is no significant heterogeneity among studies. P-value less than 0.10 suggest the heterogeneity. So heterogeneity is absent in the Meta analysis of these studies. The funnel plot for six studies shows that there is no publication bias as depicted in Figure 2. Studies are symmetrically distributed. The statistical calculations are performed using R packages. The packages used are "rmeta" and "meta" for forest plot as indicated in Figure 3. And funnel plot as shown in Figure 2.

DISCUSSION

Sucralfate and H_2-receptor antagonists are prescribed for the treatment of reflux esophagitis. The exaggerated movement of the gastric acid into the lower esophagus through lower sphincter causes the erosions to esophagus.[14] The reflux disease may lead to complex condition such as Barrett's epithelium and esophageal adenocarcinoma.[1] It is more common between 20 to 50 year patients and equally distributed in male and female. The drugs used for the treatment for common ulcers are ineffective in treating the esophageal erosions. The most common symptoms of reflux esophagitis are heartburn and regurgitation.[2] The available treatment for the treatment of reflux esophagitis are H_2-receptor

Table 1: Baseline characteristics and study design of seven selected studies for meta-analysis (the ratio is given as sucralfate to H_2-Receptor Antagonist, age is given in years)

	Elsborg and Jorgenesn	Bremner	Simon and Mueller	Tytgat	B K Chopra *et al.*	Hameeteman W. *et al.*	Ros *et al.*	Overall
Number of patient	68	98	41	40	40	40	48	375
Year of publication	1991	1991	1987	1987	1990	1987	1991	
Location of study	Denmark	South Africa	Germany	Netherlands	India	Netherlands	Spain	
Baseline Age (years)	49/51	60/60	60/60	62/59	39.9/39.1	62/59	58/54	
Male	29(48.33)	55(56.12)	25(60.97)	21(52.5)	27(67.5)	21(52.5)	25(52.08)	178
Female	31(51.66)	43(43.87)	16(39.02)	19(47.5)	13(32.5)	19(47.5)	23(47.91)	141
Smokers	64/56	16/14	9/11	6/8	4/4	6/8	4/9	105/101
Alcohol consumers	NA	8/11	12/15	5/10	4/4	5/10	NA	34/50
Study design	Double blind	Double blind	-	Single Blind	-	Single blind	Single blind	
Randomization ratio	32/28	43/55	22/19	19/21	20/20	19/21	23/25	178/189

Table 2: Odds ratio and confidence interval for each study

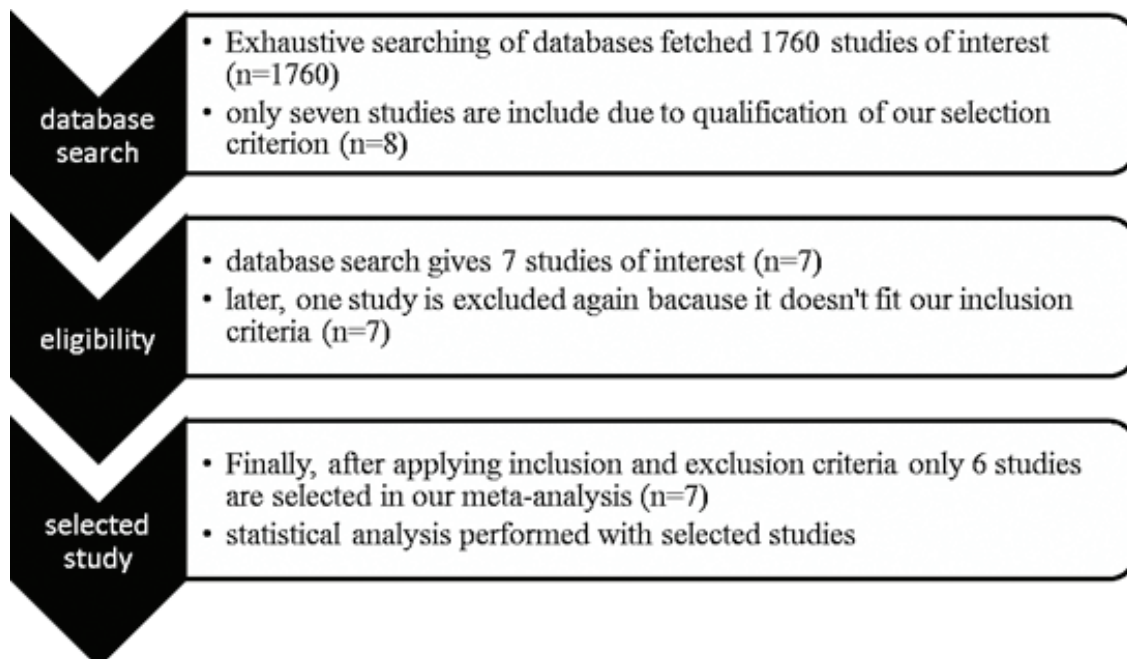| Study name	Sucralfate/H_2-Antagonist		Weight of study	Odds ratio	95% CI	p-value
	Participants	Events				
Elsborg and Jorgenesen	32/28	7/8	14.86%	0.700	0.217-2.261	0.551
Bremner	43/55	20/17	29.76%	1.944	0.849-4.450	0.116
Simon and Mueller	22/19	14/13	12.08%	0.808	0.220-2.964	0.747
Tytgat	19/21	6/3	8.41%	2.769	0.583-13.162	0.200
B.K.Chopra *et al.*	20/20	11/12	12.96%	0.815	0.232-2.860	0.749
W.Hameeteman *et al.*	19/21	6/3	8.41%	2.769	0.583-13.162	0.200
Ros *et al.*	21/20	11/11	13.53%	0.900	0.263-3.075	0.867
Total	176/184	75/67	100%	1.283	0.817-2.017	0.279

database search
- Exhaustive searching of databases fetched 1760 studies of interest (n=1760)
- only seven studies are include due to qualification of our selection criterion (n=8)

eligibility
- database search gives 7 studies of interest (n=7)
- later, one study is excluded again bacause it doesn't fit our inclusion criteria (n=7)

selected study
- Finally, after applying inclusion and exclusion criteria only 6 studies are selected in our meta-analysis (n=7)
- statistical analysis performed with selected studies
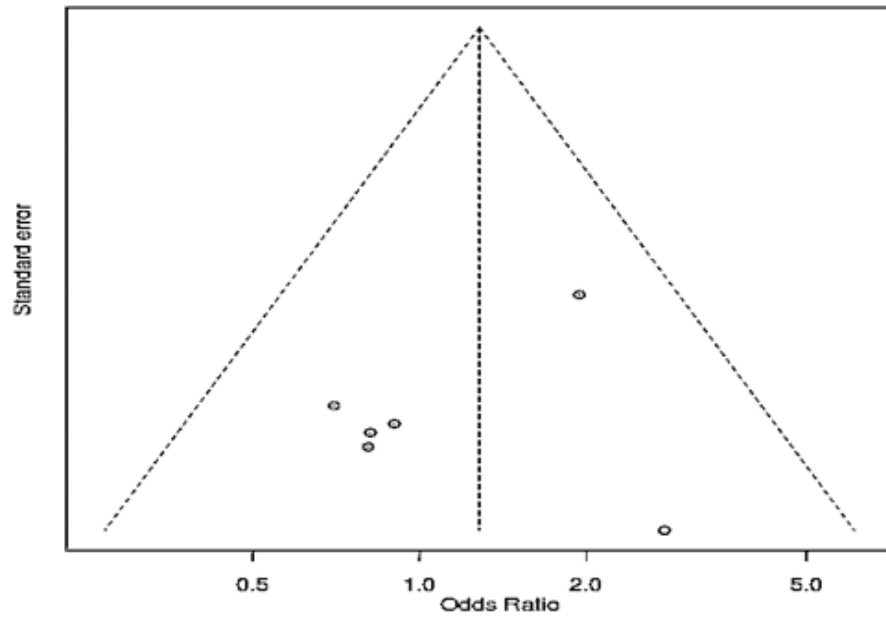
Figure 1: Flow chart for meta-analysis (n= number of studies).

Figure 2: Funnel plot for publication bias (funnel plot is showing equal distribution of studies indicating no publication bias).
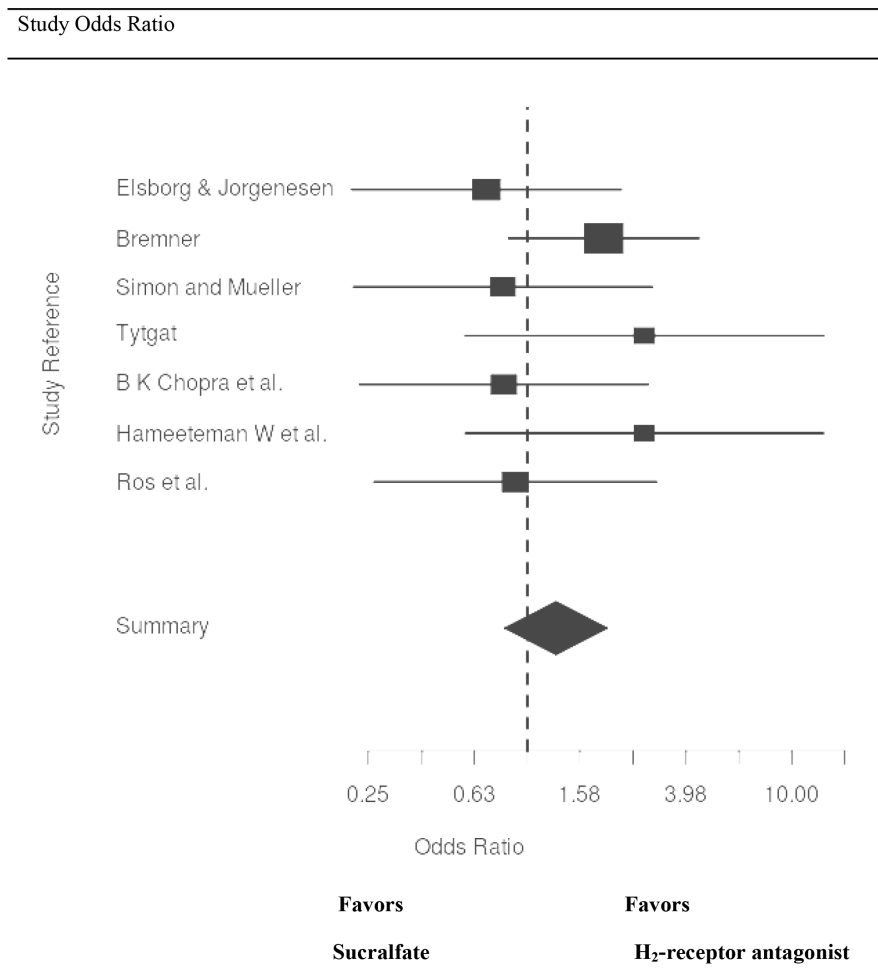

Study Odds Ratio

Figure 3: Effects of sucralfate and H_2-receptor antagonist (Forest plot of meta-analysis).

antagonist (cimetidine, ranitidine etc.), proton pump inhibitors (lansoprazole, omeprazole etc.), prokinetics (cisapride, domperidone etc.), sucralfate are commonly used.[19] Certain study didn't mention the use of sucralfate in treatment of reflux disease[1]. In contrast to these study, we evaluated two treatments sucralfate and H_2-receptor antagonist for the treatment of reflux esophagitis.

We compared the efficacy of both drugs using the technique meta-analysis. Meta-analysis is most effective approach for combining individual study. The meta-analysis performed for seven relevant studies containing more than 300 patient's shows that there is no statistical significant difference between the two treatments. We compared the seven different studies Elsborg and Jorgenesen (1991) (p=0.551), Bremner (1991) (p=0.116), Tytgat (1992) (p=0.200), Simon and Mueller (1987) (0.747), B.K. Chopra *et al.* (1992) (0.749), Hameeteman W *et al.* (1987) (p=0.700), Ross *et al.* (1991) (p=0.867). No study shows a statistical significant difference between the two treatments. Out of them, the studies, Elsborg and Jorgenesen (1991), Hameeteman W *et al.*(1987), Tytgat (1992), Ros *et al.* (1991) compares sucralfate with cimetidine (H_2-receptor antagonist) and remaining studies compares sucralfate with ranitidine (H_2-receptor antagonist). We have made this evidence stronger by combining all studies i.e. performing meta-analysis. The p-value obtained for each study is above 0.05.

Each study contains the different number of patients. We assess the effect of sucralfate on reflux disease in comparison to ranitidine and cimetidine. We compared the seven studies for meta-analysis involving more than 300 subjects. We considered the different baseline characteristic for each study. The numbers of male patients are more than the female patients. The combined p-value obtained is 0.279 which is more than 0.05. In this research, we included the publication bias and the heterogeneity to boost our result. We assessed the heterogeneity and publication bias for the study of interest. We obtained the positive result for the publication bias and the heterogeneity. The chi-square statistics (χ^2=5.17) and I^2=0% shows the absence of heterogeneity in the trials. Funnel plots are used for the assessing of publication bias. Funnel plot shows the scattered distribution of studies. The symmetry of funnel plot represents the absence of publication bias. We used odd ratio in calculating effect sizes rather than relative risk and hazard ratios. We also calculated the weight of each study. The meta-analysis is performed by using random effect model (DerSimonian and Laird method).

Thus analysis of seven clinical trials suggests that we can use sucralfate as potential drug for treatment in place of ranitidine or cimetidine for the gastrointestinal reflux disease. The H_2- receptor antagonists are considered the effective treatment for treating gastrointestinal reflux disease still now. Conclusively from the meta-analysis performed on trials comparing treatment of sucralfate and ranitidine or cimetidine, we found that there is no statistical significant between the two treatments for treating reflux disease. From our findings, we can conclude that sucralfate is an effective alternative treatment for treating gastrointestinal reflux disease. The clinical effectiveness of sucralfate and that of H_2-receptor antagonists

are comparable. So, we can focus our research on sucralfate for healing of the reflux esophagitis and gastrointestinal disorders. We can also relate sucralfate for other gastrointestinal disorders.

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