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The Efficacy of Cisapride in Infants with GERD-Meta-Analysis

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Cisapride; Efficacy; Gastroesophageal reflux; Infants

1. Abstract

1.1. Background: Infants often have gastroesophageal reflux disorder (GERD), and Cisapride is prescribed for treatment. This study aimed to assess the effectiveness of Cisapride in treating GERD in newborns, while considering its adverse effects and its removal from the market.

1.2. Methods: A meta-analysis is performed on randomized clinical trial studies conducted on Cisapride over the period 1987 to 2000, using the fixed-effect and random-effect models. Twelve clinical trials, with 512 infants (284 Cisapride treated and 228 Control Group) were chosen.

1.3. Results: According to a clinical score with a -0.72 weighted mean difference (WMD), a 2.94 quantile difference, and a P-value of 0.78, there is no evidence that Cisapride reduces the risk of vomiting, arrhythmia, or esophagitis compared with alternative treatments. 24-hour esophageal pH measurements found that the mean reflux rate was somewhat lower in Cisapride-treated neonates. Two trials indicated that Cisapride therapy was ineffective, with a WMD value of 5.34 and a confidence interval (CI) ranging between -8.41-4.81. Six studies indicated the same efficacy of Cisapride and Control with WMD -0.42 and CI value of 0.47.

1.4. Conclusion: There was no significant variance in unfavourable conditions. Cisapride showed no clinically significant effects in infants with GERD.

1.5. Author Contributions: AM: Assisted in the data collection, prepared and drafted the manuscript, contributed to the analysis and interpretation of data for the manuscript and revised the work for critically important intellectual content.

2. Introduction

Gastroesophageal reflux (GER) and gastroesophageal reflux disease (GERD) are typical disorders in the first four to five months of infancy GER may be a major gastrointestinal movement problem, or may be caused by other disorders, such as bovine milk protein hypersensitivity [1]. GER frequently occurs in a variety of children with bronchopneumonia syndrome, and these infants have reduced esophageal clearing. Gastroesophageal reflux disease (GERD) is a common intestinal problem [2]. It increases gastrointestinal mortality in infants, with substantial morbidity and mortality risks [3-5]. Specific signs of GERD include episodes of regurgitation, and failure to develop, as well as persistent reduced gastrointestinal motility and reflux disorders such as reactive airways, systemic dyspepsia, gastroparesis, pneumonia, and atelectasis. In preterm infants, reflux syndrome often triggers pneumonia and bronchopulmonary dysplasia (BPD). [6]. However, GER may normally occur naturally after meals, but irregular GER occurs in the presence of elevated acidity, reducing the pH level to < 4.0, which persists for more than 1.2 hours over 20 h calculated by intra-esophageal pH testing [7, 8]. Standard treatments include adjusting the posture of the infant while eating, the use of gastrointestinal sedation chemicals, and thickening of feeds. GERD therapy may involve a range of treatments, including anti-reflux measures, histamine (receptor type 2) antagonists (, either normal or strong dosage), proton pump inhibitors, Cisapride, and surgical procedures, including Nissen fundoplication and partial posterior hemi-fundoplication.

Preliminary research in the 1990s suggested that Cisapride, a gastrointestinal prokinetics agent, is effective for the treatment of

GERD in infants and young children [9, 10]. Gaviscon, another antacid compound [11], has been shown to minimize reflux in two-fold visually challenged patients with GERD [12]. Nonetheless, in response to various clinical studies showing the efficacy of Cisapride, its efficacy has been reduced owing to its negligible adequacy. Cochrane analysis of Cisapride following its removal concluded that there was no proof that Cisapride reduced the symptoms of GERD and showed a strong marketing prejudice against trials with good results following Cisapride. [13]. As a consequence, we aim to assess the effectiveness of Cisapride on scientifically appropriate knowledge of its usage in GERD and to address the issue we performed the meta-analysis of clinical trials investigating the short, medium, and long-term effects of Cisapride on infants suffering from GERD.

3. Material and Methods

Cisapride has already been removed from the market owing to its low adequacy and is not in use against GERD in infants. This study provided a comprehensive meta-analysis of the efficacy of Cisapride in the management of GER disease in infants. This review of the World Journal is reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines.

3.1. Search Criteria

Clinical studies on Cisapride were found by searching: PubMed, EMBASE, Google Scholar, and the Cochrane Library. All reports published between 1987 and 2014 were included in the search, without any language constraints. Several keywords used were: “Gastro-esophageal,, “Gastro-esophageal reflux”; “Reflux disease”; “Infants”; “Efficacy”, “Cisapride”; “Cisapride clinical study”; “Young children”; “Premature infants”; “Intestinal motility”; “morbidity”; “Postganglionic nerve endings”; “Pneumonia”; “Esophagitis”; “Bronchopulmonary dysplasia”; “Children”; “Gastrointestinal tract”. “We narrowed our scope to randomized clinical trials (RCTs), systematic reviews, and meta-analyses of RCTs. We manually scanned the reference lists of systematic reviews to ensure that they were included in our study.

3.2. Selection of Studies

Randomized clinical trials and experiments performed to assess the efficacy of Cisapride alone and to equate its regimens with other medications in infants and premature infants with GERD were included in this meta-analysis. Patients aged 1st month to the 30th month of age were chosen. Kids above 2.5 years of age were removed from the sample to reduce the possibility of prejudice. In all reported studies, Cisapride was administered either alone or in combination with placebo or antacid agents.

The validity of the research tests and experiments was determined in case of disparity., and eligibility was adjudicated. The types were derived, and the methods of abstraction and possibility of bias were measured.

3.3. Quality Assessment

The consistency of the chosen studies was measured, and their internal validity was evaluated using the Cochrane risk-bias tool [14]. These papers were then graded as good, moderate, or poor, by methodological consistency, using the kappa statistic (k) to quantify the agreements between studies beyond chance.

3.4. Assessment of Outcomes

Data on all outcomes were analyzed, with primary outcomes described as improvements in the degree and frequency of symptoms, including diarrhea, arrhythmia, esophagitis, weeping, regurgitation, and irritability, following Cisapride_treatment. However, adverse events, emergence of certain dangerous illnesses, and occurrence of clinical conditions have been listed as secondary. All findings were evaluated using fixed and random effects method.

3.5. Statistical Measures and Analysis

For Statistical analysis, the data were divided into two groups: 1- the Cisapride and 2- control group. The control category included only the control results, but infants diagnosed with certain antacid medications or non-surgical therapies other than Cisapride were also included in the control group. The means and standard deviations (STDs) were defined as having a significant p-value of< 0.05. When standard deviations were not accessible, as they were calculated from the test statistics or using the p-value in the SPSS software, similar differences were recognized in both the treatment and control groups.

Statistical analyseis were performed using the Meta-Mar server. software (http://www.meta-mar.com/). The effect sizes based on standardized mean differences as well as correlation coefficients and risk ratios, the weight of each effect, and the heterogeneities of the experiments were determined using the fixed-effect model and random effect model, as well as forest and funnel plots. Statistical significance was set at an alpha threshold of 0.05. Heterogeneity among the studies was analyzed using I2 statistics; the larger the I2 value the greater the heterogeneity. P values < 0.10 and I2 > 50% howed substantial proof of heterogeneity in such cases, the random-effect model was employed. When the P values were > 0.10 I2 was identified as less than 50%, no apparent heterogeneity was observed, and the concept of a fixed-effect model was used.

4. Results

A total of 64 literature studies were reported from various sources: 10 clinical trial studies and 13 review studies on the use of Cisapride in the treatment of GERD were retrieved from the PubMed database, seven studies were collected from EMBASE, three reviews and one clinical trial were located in the Cochrane library archives, and more than 30 studies were retrieved from Google Scholar. Of 64 studies, 29 were selected for the first approach. After reading titles and abstracts, 35 duplicates were removed. A description of the trials and evaluation studies omitted from this meta-analysis is available upon request. After a thorough evaluation of the remain-

ing 29 studies, only 12 trials involving 516 infants (284 Cisapride group, 228 Control group) with k=0.99 were included in the final analysis, 7 were recognized as references and reports from other meta-analyses, and 10 were considered irrelevant. The study selection process is illustrated in (Figure 1).

The characteristics of the 12 selected trials, including Cisapride alone and in combinnation with other antacid drugs (k= 0.73), are shown in (Table 1). Of the selected reports, seven were rated as fair standards and four as strong standards. In all other trials, primary and secondary outcomes were defined as improvements in post-treatment symptoms, whereas death, motility, and morbidity were defined as adverse outcomes. The outcomes of these therapies are summarized in (Table 2). (Table 1) shows the characteristics of the 12 included studies. The measures included clinical conclusions, age of the infants enrolled in the trials, Cisapride dosage, treatment days, and several treated infants. The side effects of the therapies were evaluated as primary and secondary outcomes in both studies. Five trials measured the rate of vomiting as a chronic variable, either as a ranking or frequency factor, and seven experiments measured the change in the vomiting situation as an actual variable. Arrhythmia and Esophagitis were found in 7 of the 12 studies. Adverse outcomes or side effects were recorded in four of the 12 trials (Table 2). A meta-analysis of these 12 trials, including 512 infants (284 Cisapride treated and 228 Control group), found that Cisapride was superior to non-pharmacological control, causing a reduction in the mean reflux index at the final follow-up (Figures 2 and 3).

According in (Figures 2 and 3), two of the three trials demonstrated the full benefit of Cisapride treatment over non-pharmacological control, and six indicated improved patient effects with Cisapride relative to others (weighted mean difference of 5.34; 95% CI 8.41 - 4.81). A meta-analysis of three trial studies found the same confirmation of the efficacy of both Cisapride and the Control, with a weighted mean difference of 0.42; 95% CI 0.47. Two studies measured no effectiveness parameters and found no observable essential benefit of Cisapride over other drugs, with a weighted mean difference of-0.72, demonstrating a 95 per cent confidence interval varying from-5 from 5; quantum discrepancy= 2.94 and a P-value of 0.78. The findings of this meta-analysis are summarized in (Table 3).

The sections listed in (Table 3) n1 and n2 show the samples. The standardized mean differences in Hedges' (adjusted g) as effect sizes were determined from theselected trials. The negative g values in (Table 3) indicate the inefficiency of the Cisapride treatment compared to the control treatment. However, positive g values <1 showed the same efficacy for both the Cisapride and Control treatments. g values >1 indicated the effectiveness of Cisapride treatment. An overview of the fixed- and random- effects models and the heterogeneity evaluation is presented in (Table 4).

The standardized mean difference (SMD) Hedges was used as a summary statistic in this meta-analysis study, because all trial studies measured the same outcome in various forms. It was also compulsory to standardize the findings of the trial studies to a uniform scale until they could be merged. The size of the intervention effect in every sample was represented by the SMD relative to the variable [24]. Heterogeneity was also determined (Table 4) to assess the degree to which experimental findings were consistent. The confidence interval (CI) was also determined if it had a low correlation with the tests, indicating significant heterogeneity. A statistically meaningful finding may suggest a problem with heterogeneity, and a non-significant result should not be considered as evidence of heterogeneity. Therefore, a P- value of 0.10, instead of 0.05, was used to assess statistical significance. The threshold value for I2 was 83.999999% using both fixed- effects and random-effects models, indicating significant heterogeneity (Table 4). Publication bias was tested using Rosenthal's (1979) and Rosenberg's Fail-N Secure (2005) file drawer approaches, as shown in (Table 5), and the Meta-Regression Results are shown in (Table 6). The negative values of both the fixed- and random- effects models in (Table 5) indicate a minimum degree of publication bias, rendering the results significant.

This meta-analysis revealed no significant changes in GERD. This meta-analysis revealed no significant changes in GERD. This may be attributed to the limited scale of the trials or the absence of an effective rate; therefore, no clinically important benefits were observed. The 95 % confidence interval of the pooled calculation indicated that Cisapride therapy could be effective in reducing many symptoms of GERD. There is still confusion regarding the therapeutic effects of Cisapride in infants, and multiple trials are expected until a clinically significant advantage can be dismissed. Using the details from the studies included in this meta-analysis, we found that Cisapride was effective in the management of GERD (Figures 2 and 3). In this meta-analysis, vomiting, esophagitis, and arrhythmia were selected as primary outcomes, rather than details of the esophageal pH test, as these are signs of GER. Seven [9, 10, 20-22] of the 12 experiments do not specify the primary outcome of the esophageal pH study, although only 5 [15-19] trials used the pH check criteria as the primary outcome.

Most of the identified trials demonstrated the benefit of Cisapride over placebo/non-pharmacological control over the length of the reaction to acid, as measured by the reflux index. The relevance of this meta-analysis is uncertain, provided that there has been no decrease in the recurrence of reflux episodes lasting longer than 5 min. and no decrease in esophagitis. Several authors have noted that pH test estimations are of unclear clinical significance, [25] and there is a weak correlation between arrhythmia on pH test estimations and histological esophagitis results.

Just 4 [12, 17, 22, 23] of the 12 trials in this meta-analysis indicate infants with severe GERD, and 7 trials involved infants undergoing significant regurgitation for first-line treatment. [26, 27] De-

spite the apparent heterogeneity in the trial studies, there was no significant variability in treatment outcomes among the trial studies, indicating that the outcome is sufficient for infants with GER of changing the severity. The data reported in this meta-analysis are not consistent with current recommendations regarding the use of Cisapride. In 2001, the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) suggested Cisapride as a treatment for recurrent severe GER resistant to therapy [28]. ESPGHAN's advice preceded the USA Food and Drug Administration's restrictions on the effectiveness of Cisapride and elevated the chances of potential side effects, and its utilization after its removal from the market in the last decade [29]. The current meta-analysis differs from the 2001 ESPGHAN survey because, it uses statistical analysis of details, measures the validity of the trials, and considers symptom improvement after Cisapride treatment as the primary outcome. The results of this meta-analysis are compatible with those of previous review studies and meta-analyses that have used a similar approach.

As there are possible problems with any review, evaluation of the consistencies of the studies was difficult because of the absence of experimentation in all trials. The removal of patients due to the severe side effects of medications or adverse outcomes has contributed to an unwillingness to obtain information regarding patients. In several studies, the procedure for distribution of concealment was indistinct. This is considered a significant source of publication bias that contributes to overestimation of the treatment effect [30]. However, as the meta-analysis did not show evidence of a treatment effect, the results were not adjusted regardless of whether allocation concealment was sufficient.

In certain cases, adverse conditions and side effects were not accurately measured. Only a few findings involved regurgitation, vomiting, and arrhythmia, and they could speak of treatment disappointments. Multiple trials included events, such as upper respiratory tract diseases, asthma, and dental growth, which are normal occurrences in most infants. The presence of these incidents made it impossible to prove a substantial change in the side effects between the Cisapride and control groups. A delayed QT interval causes sudden infant death syndrome. There is a great deal of anxiety over this result, which led to the proclamations by the North American Society for Pediatric Gastroenterology and Nutrition (NASPGN) [31] and the European Society for Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN) [32] and the prohibition on the use of Cisapride in the United States and the United Kingdom. The significance of the delayed QT interval is not evident, as addressed in NASPGN studies; there have been no records of patient mortality that may be related to Cisapride therapy. The limited number of patients included in the selected studies, in addition to inappropriate effects, limits the utility of the results.

Attempts were made to eliminate bias in this meta-analysis by identifying titles, abstracts, and papers, as per the priori-inclusion criteria. Publication bias, which could be due to a ban on unpublished investigations, cannot be dismissed as formal testing for publication bias. The use of a funnel plot was difficult due to the limited number of trials, and, the file drawer problem was used. Publication bias is likely to result in the overestimation of treatment effects [33]. However, this probably does not affect the findings of this meta-analysis, since no clear evidence of the benefit of Cisapride treatment was found over the control.

Table 1: Characteristics of the trial studies.

Study	Dosage	No of Patients	Mean Age	Treatment Duration (median)	Participants (severity of GER)	Reference
Jaime et al, 2000	0.2 mg/kg/dose 3 times/day	63	29 months	60 days	Not stated	15
Greally et al, 1992	0-8 mg/kg/day	50	9 months	28 days	Yes	12
Ronald et al, 2001	0.09 to 0.25 mg/kg every 6 hours	12	2.25 months	24 Hours	Yes	16
Ralph et al, 1999	0.2 mg/kg 4 times daily	50	6.3 months	14 days	Yes	17
Badriul et a, 2009	0.8 mg/kg/day, 3 doses/day	10	11 months	14 days	Not stated	18
Cucchiara et al, 1990	0-15 mg/kg intravenously	7	15.7 months	30 days	Yes	10
Cucchiara et al, 1987	0-3 mg/kg three times a day	11	26 months	60 days	Yes	9
Levine et al, 1999	0.8 mg/kg per day	10	1.5 months	30 days	Not stated	19
Levy et al, 2001	0.2 mg/kg dose three times daily	24	14.4 months	30 days	Yes	20
Rode et al, 1987	0.33 mg/kg in 2 mL water 6 hours daily	18	6.5 months	30 days	Yes	21
Lander et al, 1997	l.4–2.3 mg/kg/day	11	6 months	7 days	Not stated	22
Enriquez et al, 1998	0.2 mg/kg/dose four times daily	18	8 months	25 days	Not stated	23

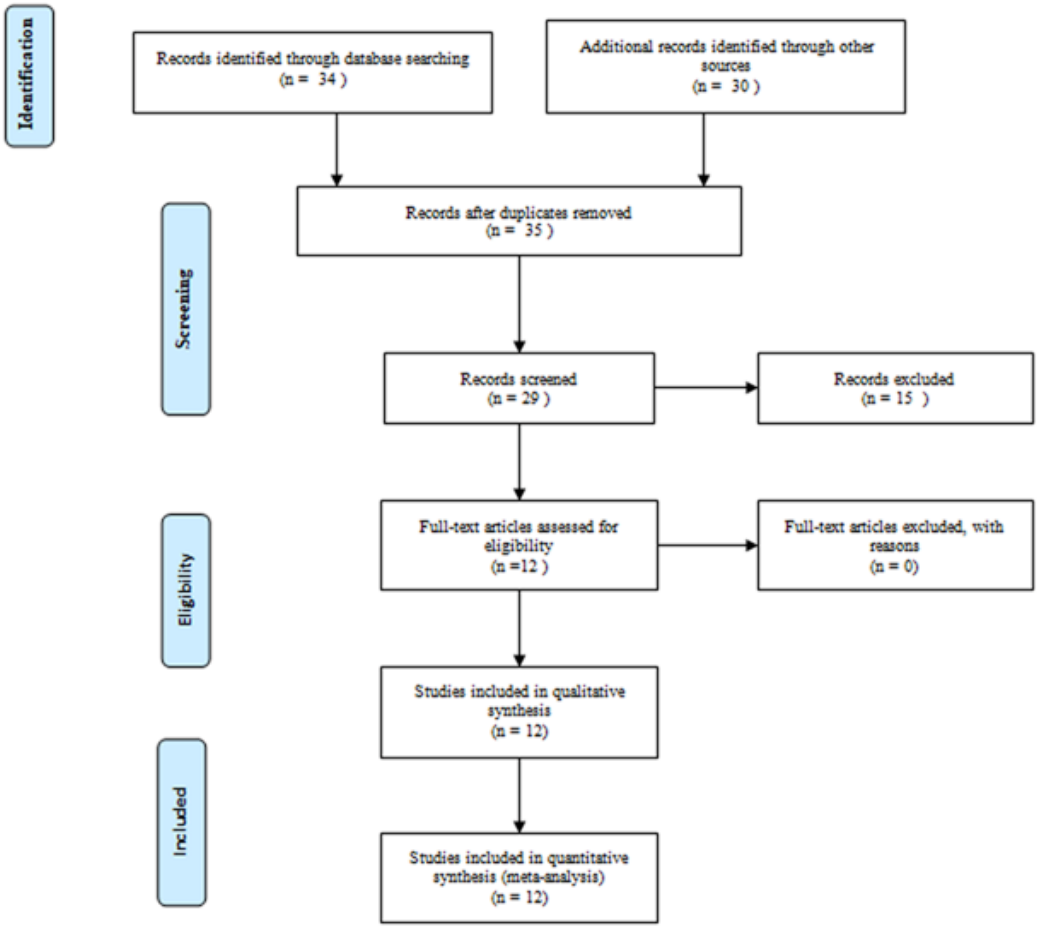

Figure 1: Flow chart of study selection according to PRISMA guidelines.

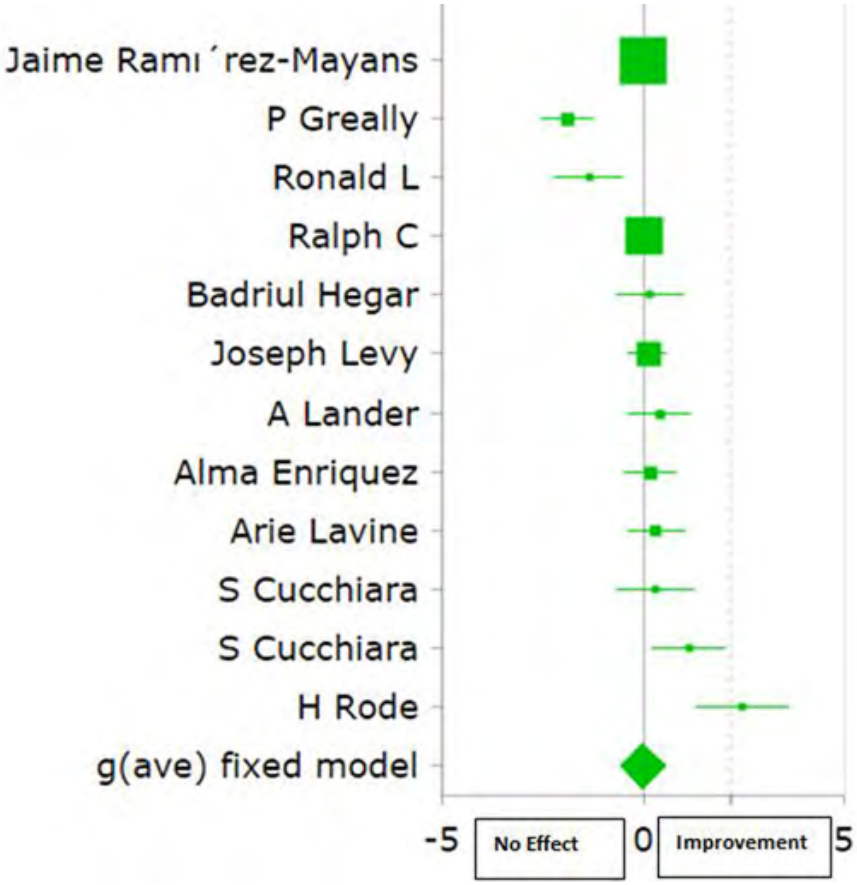

Figure 2: The Meta-analysis of trial studies using the Fixed effect model showing the efficacy of Cisapride treatment of Infants having GERD.

Table 2: The assessment of Primary and Secondary outcomes after the Cisapride Treatment

Study	Esophagitis	Arrhythmia	Vomiting	Adverse Effects	Reference
Jaime et al, 2000	X	X	✓	✓	15
Greally et al, 1992	✓	✓	X	✓	12
Ronald et al, 2001	✓	✓	X	X	16
Ralph et al, 1999	✓	✓	✓	✓	17
Badriul et al, 2009	X	✓	X	X	18
Cucchiara et al, 1990	✓	X	✓	X	10
Cucchiara et al, 1987	✓	X	✓	X	9
Levine et al, 1999	✓	X	✓	X	19
Levy et al, 2001	X	X	X	X	20
Rode et al, 1987	X	✓	X	X	21
Lander et al, 1987	✓	✓	X	✓	22
Enriquez et al, 1998	X	✓	X	✓	23

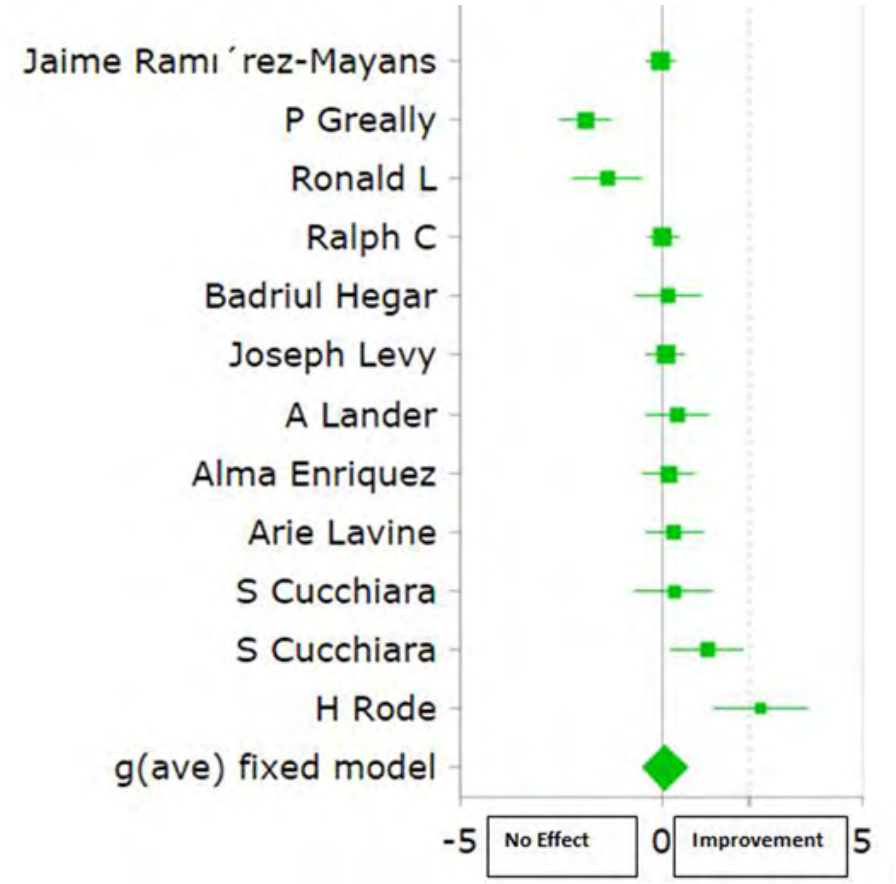

Figure 3: The Meta-analysis of trial studies using the Random effect model showing the efficacy of Cisapride treatment of Infants having GERD.

Table 3: The overall result summary of the Meta-analysis study of selected 12 Trials.

		Cisapride Group			Control Group			Meta-analysis Using Standardized mean difference Hedges' (adjusted) g statistics			
S. no	Study name	n1	Mean1	SD1	n2	Mean2	SD2	G	SEg	weight(%)-fixed model	weight(%)-random model
1	Jaime Ramı´rez-Mayans	63	412	38	57	411	38	-0.02615	0.181646	24.62965	10.02649
2	P Greally	26	15.3	5.3	24	6.3	3.9	-1.89218	0.3368	7.164181	8.753274
3	Ronald L	12	79.5	6.5	12	70.9	5.7	-1.3583	0.440236	4.193147	7.767694

4	Ralph C	50	8.9	6.6	45	9.1	6.6	0.030058	0.203831	19.56018	9.873809
5	Badriul Hegar	10	5.13	2.17	10	5.6	2.8	0.179705	0.429259	4.410352	7.872967
6	Joseph Levy	24	406	21	44	408	18	0.103523	0.251022	12.89697	9.510289
7	A Lander	11	10.4	3.8	12	12.3	4.9	0.415216	0.406967	4.90674	8.087015
8	Alma Enriquez	18	9.1	5.2	16	10.2	8.2	0.158555	0.336026	7.19722	8.760476
9	Arie Lavine	11	0.371	0.02	19	0.38	0.03	0.326022	0.371023	5.903503	8.430871
10	S Cucchiara	7	13.8	7.7	7	17.5	14.1	0.304914	0.503711	3.20294	7.166182
11	S Cucchiara	11	7.87	7.05	9	16.25	7.1	1.134844	0.466375	3.736296	7.518107
12	H Rode	9	25.1	6.7	9	54.6	14.7	2.459485	0.607941	2.198818	6.232822

Table 4: The result summary of Fixed and Random Effect Models

Models	Hedges'g (SMD)	SEg	95%Confidence Interval (CI)	z score	p-value	Heterogeneity (I2)
Fixed Effect Model	-0.01	0.09	[-0.191,0.162]	-0.161	0.872038	83.40%
Random Effect Model	0.09	0.235	[-0.373,0.55]	0.376	0.706649	83.39999999999999%, T2=0.52

Table 5: The publication bias analysis of the selected trials

The Bias of the Analysis Regarding the File-Drawer Problem	Fixed Model	Random Model
Orwin's Fail-N Safe (1983), based on Rosenthal (1979)		
Fail-safe for the critical effect size of:		
Small (critical g = 0.2)	-12.87	-6.68
Medium (critical g = 0.6)	-12.29	-10.23
Large (critical g = 0.8)	-12.22	-6.35
Rosenberg's Fail-N Safe (2005)		
Fail-safe for the critical Z score of:		
α = 0.05 two-tailed	-12.99	-9.7
α = 0.05 one-tailed	-13.18	-9.25
α = 0.01 two-tailed	-12.75	-10.25
α = 0.01 one-tailed	-12.83	-10.06

Table 6: Results of Meta-regression for this meta-analysis

OLS Regression Results						
Dependant. Variable:	G	**R-squared:**	0.079			
Model:	OLS	**Adjusted. R-squared:**	0.08			
Method:	Least Squares	**F-statistic:**	Nan			
Date:	Sun, 19 Apr 2020	**Prob (F-statistic):**	Nan			
Time:	12:50:28	**Log-Likelihood:**	-17.472			
No. Observations:	12	**AIC:**	36.94			
Df Residuals:	11	**BIC:**	37.43			
DF Model:	0					
Covariance Type:	Non-robust					
	Coefficient	**STD error**	**T**	**P>|t|**	**[0.025**	**0.975]**
Constant	0.153	0.313	0.489	0.635	-0.536	0.842
7	0	0	Nan	Nan	0	0

5. Conclusion

This randomized controlled study comparing Cisapride and other antacids or non-pharmacological treatment groups has not provided proof of the clinically relevant value of Cisapride in infants with GER. According to this meta-analysis, only two studies reported the full efficacy of Cisapride over Control, although 6 of the 12 studies verified the equivalent efficacy of Cisapride and Control. A broad randomized controlled study, that includes infants with recurrent chronic GER resistant to traditional therapy, is required. Considering its far-reaching historical use, there are continuing questions about damage, and the weakness of its usability.

6. Availability of Data and Materials

All trial studies were available in PUBMED, EMBASE, and Cochrane Library. The Statistical software Meta mar is available online at www.metamar.com, and SPSS can be downloaded from www.softpedia.com. The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

7. Acknowledgements

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8. Competing Interests

None of the authors has any competing Interests.

9. Funding

No funding was provided for this study.

10. Ethical Approval

This study does not involve any human or animal subject.

11. Ethical Compliance

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

References

1. Maret-Ouda J, Markar SR, Lagergren J. Gastroesophageal reflux disease: a review. Jama. 2020; 324(24): 2536-47.
2. Katz PO, Dunbar KB, Schnoll-Sussman FH, Greer KB, Yadlapati R, Spechler SJ, et al. ACG clinical guideline for the diagnosis and management of gastroesophageal reflux disease. The American journal of gastroenterology. 2022; 117(1): 27-56.
3. Jung HK, Tae CH, Song KH, Kang SJ, Park JK, Gong EJ, et al. 2020 Seoul consensus on the diagnosis and management of gastroesophageal reflux disease. Journal of Neurogastroenterology and Motility. 2021; 27(4): 453.
4. Hamel C, Ahmadzai N, Beck A, Thuku M, Skidmore B, Pussegoda K, et al. Screening for esophageal adenocarcinoma and precancerous conditions (dysplasia and Barrett's esophagus) in patients with chronic gastroesophageal reflux disease with or without other risk factors: two systematic reviews and one overview of reviews to inform a guideline of the Canadian Task Force on Preventive Health Care (CTFPHC). Systematic reviews. 2020; 9(1): 20.
5. Manning MA, Shafa S, Mehrotra AK, Grenier RE, Levy AD. Role of Multimodality Imaging in Gastroesophageal Reflux Disease and Its Complications, with Clinical and Pathologic Correlation. RadioGraphics. 2020; 40(1): 44-71.
6. Cheng J, Ouwehand AC. Gastroesophageal Reflux Disease and Probiotics: A Systematic Review. Nutrients. 2020; 12(1): 132.
7. Ge S, Mendley SR, Gerhart JG, Melloni C, Hornik CP, Sullivan JE, et al. Population Pharmacokinetics of Metoclopramide in Infants, Children, and Adolescents. Clinical and Translational Science. 2020; 13(6): 1189-1198.
8. Kopsaftis Z, Yap HS, Tin KS, Hnin K, Carson-Chahhoud KV. Pharmacological and surgical interventions for the treatment of gastro-oesophageal reflux in adults and children with asthma. Cochrane Database of Systematic Reviews. 2021; 17: 5(5).
9. Cucchiara S, Staiano A, Capozzi C, Di Lorenzo C, Boccieri A, Auricchio S, et al. Cisapride for gastro-oesophageal reflux and peptic oesophagitis. Archives of disease in childhood. 1987; 62(5): 454-7.
10. Cucchiara S, Staiano A, Boccieri A, De Stefano M, Capozzi C, Manzi G, et al. Effects of cisapride on parameters of oesophageal motility and on the prolonged intraoesophageal pH test in infants with gastro-oesophageal reflux disease. Gut. 1990; 31(1): 21-5.
11. Wilkinson J, Abd-Elaziz K, Den Daas I, Wemer J, Van Haastert M, Hodgkinson V, et al. Two placebo-controlled crossover studies in healthy subjects to evaluate gastric acid neutralization by an alginate–antacid formulation (Gaviscon Double Action). Drug Development and Industrial Pharmacy. 2019; 45(3): 430-8.
12. Greally P, Hampton FJ, MacFadyen UM, Simpson H. Gaviscon and Carobel compared with cisapride in gastro-oesophageal reflux. Archives of disease in childhood. 1992; 67(5): 618-21.
13. Mt-Isa S, Tomlin S, Sutcliffe A, Underwood M, Williamson P, Croft NM, et al. Prokinetics prescribing in paediatrics: evidence on cisapride, domperidone, and metoclopramide. Journal of pediatric gastroenterology and nutrition. 2015; 60(4): 508-14.
14. Boutron I, Page MJ, Higgins JP, Altman DG, Lundh A, Hróbjartsson A, et al. Cochrane Bias Methods Group. Considering bias and conflicts of interest among the included studies. Cochrane handbook for systematic reviews of interventions. 2019; 177-204.
15. Ramírez-Mayans J, Garrido-García LM, Huerta-Tecanhuey A, Gutierrez-Castrellón P, Cervantes-Bustamante R, Mata-Rivera N, et al. Cisapride and QTc interval in children. Pediatrics. 2000; 106(5): 1028-30.
16. Ariagno RL, Kikkert MA, Mirmiran M, Conrad C, Baldwin RB. Cisapride decreases gastroesophageal reflux in preterm infants. Pediatrics. 2001; 107(4): e58.
17. Cohen RC, O'Loughlin EV, Davidson GP, Moore DJ, Lawrence DM. Cisapride in the control of symptoms in infants with gastroesophageal reflux: a randomized, double-blind, placebo-controlled trial. The Journal of pediatrics. 1999; 134(3): 287-92.

18. Hegar B, Alatas S, Advani N, Firmansyah A, Vandenplas Y. Domperidone versus cisapride in the treatment of infant regurgitation and increased acid gastro-oesophageal reflux: a pilot study. Acta Paediatrica. 2009; 98(4): 750–5.
19. Levine A, Fogelman R, Sirota L, Zangen Z, Shamir R, Dinari G, et al. QT interval in children and infants receiving cisapride. Pediatrics. 1998; 101(3): e9.
20. Levy J, Hayes C, Kern J, Harris J, Flores A, Hyams J, et al. Does cisapride influence cardiac rhythm? Results of a United States multicenter, double-blind, placebo-controlled pediatric study. Journal of pediatric gastroenterology and nutrition. 2001; 32(4): 458-63.
21. Rode H, Stunden RJ, Millar AJ, Cywes S. Esophageal pH assessment of gastroesophageal reflux in 18 patients and the effect of two prokinetic agents: cisapride and metoclopramide. Journal of pediatric surgery. 1987; 22(10): 931-4.
22. Lander A, Redkar R, Nicholls G, Lawson A, Choudhury SR, Corkery JJ, et al. Cisapride reduces neonatal postoperative ileus: randomised placebo controlled trial. Archives of Disease in Childhood-Fetal and Neonatal Edition. 1997; 77(2): F119-22.
23. Enriquez A, Bolisetty S, Patole S, Garvey PA, Campbell PJ. Randomised controlled trial of cisapride in feed intolerance in preterm infants. Archives of Disease in Childhood-Fetal and Neonatal Edition. 1998; 79(2): F110-3.
24. Schünemann HJ, Vist GE, Higgins JP, Santesso N, Deeks JJ, Glasziou P, et al. Cochrane GRADEing Methods Group. Interpreting results and drawing conclusions. Cochrane handbook for systematic reviews of interventions. 2019; 23: 403-31.
25. Vieira MC. GER and Prokinetics. InGastroesophageal Reflux in Children 2022 (pp. 319-325). Cham: Springer International Publishing.
26. Chevalier I, Beck CE, Doré-Bergeron MJ, Orkin J. Medical management of gastro-esophageal reflux in healthy infants. Paediatrics & Child Health. 2022; 27(8): 503-6.
27. Báez PT, Arévalo AH. Pathological gastroesophageal reflux management in newborns and infants with osteopathy. Colombian Journal of Physical Medicine and Rehabilitation. 2016; 26(1): 75-84.
28. Mt-Isa S, Tomlin S, Sutcliffe A, Underwood M, Williamson P, Croft NM, et al. Prokinetics prescribing in paediatrics: evidence on cisapride, domperidone, and metoclopramide. Journal of pediatric gastroenterology and nutrition. 2015; 60(4): 508-14.
29. Mccarthy ME, Ross JS. 4 The FDA and Health Canada: Similar Origins, yet Divergent Paths and Approaches to Transparency. Transparency, Power, and Influence in the Pharmaceutical Industry: Policy Gain or Confidence Game?. 2021.
30. Mathur MB, VanderWeele TJ. Sensitivity analysis for publication bias in meta-analyses. Journal of the Royal Statistical Society. Series C, Applied Statistics. 2020; 69(5): 1091.
31. Simon M, Levy EI, Vandenplas Y. Adverse Effects of GER Medication Except Anti-Acid Drugs. InGastroesophageal Reflux in Children 2022 (pp. 327-333). Cham: Springer International Publishing.
32. Levy EI, Salvatore S, Vandenplas Y, Dde Winter JP. Prescription of acid inhibitors in infants: an addiction hard to break. European journal of pediatrics. 2020; 179: 1957-61.
33. Wagner III JA. The influence of unpublished studies on results of recent meta-analyses: Publication bias, the file drawer problem, and implications for the replication crisis. International Journal of Social Research Methodology. 2022; 25(5): 639-44.