A Systematic Review on the Efficacy of Common Antacid Components

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Abstract: Gastroesophageal Reflux Disease (GERD) is a common health issue worldwide that utilizes antacids to mitigate its symptoms such as chest pains and burning sensations. However, the most common component used in antacids, Aluminum Hydroxide, has a high toxicity level as it builds up in the body. Thus, this study aims to determine whether Alginate, an organic compound, and Calcium Carbonate, which is considered an age-friendly component, are suitable antacid component alternatives to Aluminum Hydroxide in terms of their corresponding Acid Neutralization Capacity (ANC) and adverse effects. The researchers utilized a systematic review approach, guided by the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P), to accomplish the study objectives. The study results suggest that Calcium Carbonate has the highest ANC while Alginate has the second-highest ANC and has fewer adverse effects than placebo. These results support the claim that Alginate and Calcium Carbonate are suitable alternatives to Aluminum Hydroxide.

Key Words: antacid; gastroesophageal reflux disease; calcium carbonate; alginate; systematic review

1. INTRODUCTION

Gastroesophageal Reflux Disease (GERD) occurs when there are backflows of stomach acid in the esophagus, irritating its walls (Yamamichi et al., 2012). People with GERD have been more prevalent in the Philippines over the years (Sollano et al., 2007). One problem with treating GERD is that the majority of medications contain Aluminum; allergic reactions, such as exposure to xenobiotics, may occur when it is ingested or vaccinated (Crisponi et al., 2013). Though branded safe for usage as Aluminum Hydroxide, Aluminum has a record of toxicity (Jensen-Jarolim, 2015).

Due to this, researchers sought out an organic compound called Alginate derived from algae and Calcium Carbonate, which are also used to formulate antacids (Szekalska et al., 2016). Alginate is in recent antacid formulations because it is organically derived. Additionally, it also develops rafts that help maintain stomach acidity (Hampson et al., 2010). Calcium Carbonate is widely used in antacid formulations because it is suitable for all ages (Li et al., 2018). In comparison to the level of toxicity obtained by consuming Calcium Carbonate, the toxicity of Aluminum Hydroxide is significantly higher (Salisbury & Terrell, 2020). Adverse side effects of Calcium Carbonate are dizziness, nausea, and constipation.

Antacids are formulated to mitigate GERD symptoms, but a problem with this is that one of the most common antacid components is Aluminum Hydroxide, which can be toxic to humans when it builds up in the body (Crisponi et al., 2013). Thus, this research aims to determine, via a systematic review, if Alginate and Calcium Carbonate are effective alternative antacid components to Aluminum Hydroxide so that this toxic component may eventually be removed in antacids for GERD patients.

The paper is a systematic literature review on the efficacy of common antacid components present in the formulation of over-the-counter medications. The identified components are Alginate and Calcium Carbonate. The collected journals only focused on the properties of these compounds. Different parameters, acid neutralization, and adverse effects were identified and used to evaluate the two chemical components' efficacy. Also, the findings were based on the gathered data; no theoretical computations and primary data were presented. This study will help fill the research gaps in the academic and medical community and will help to further improve antacid formulations.

2. METHODOLOGY

2.1. Study Design

The methodology is composed of three phases as seen in Figure 1. First is the selection process of literature according to predetermined eligibility criteria. Second is the data collection process and the risk of bias assessment of the eligible papers. Last is the generalization of the collected data to determine a suitable alternative to Aluminum Hydroxide based on

Acid Neutralization Capacity or adverse effects. The study's methods were guided by the protocols for reporting systematic reviews adapted from the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) website. Subsections: Eligibility Criteria, Information Sources, Search Strategy, Study Records, ROB assessment, and Data Synthesis, were kept and modified accordingly in this study (Shamseer et al., 2015).

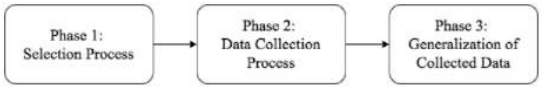

Figure 1. Flowchart of the Main Methodology

2.2. Eligibility Criteria

A literature search was performed where every title of a paper that the researchers read was considered a viewed paper and the papers that met the requirements of the eligibility criteria were considered accepted papers. The eligibility criteria include:
acceptability - if the paper was published by a reputable publisher and the paper's academic affiliations
study design - if the paper was quantitative study design
compound assessed - if the papers studied Alginate or Calcium Carbonate
parameter for evaluation - if the papers studied Acid Neutralization Capacity or adverse effects

2.3. Information Sources

The researchers prioritized sources such as Google Scholar, JSTOR, Science Direct, and ResearchGate. The researchers used these databases during the initial search period, including the use of the eligibility criteria. Afterward, the researchers branched out to different databases such as school repositories.

2.4. Search Strategy

In searching for literature through different recognized databases, a search strategy using specific keywords and search techniques was applied to set a guided framework for the researchers.

2.5. Study Record

To manage the literature and information, the researchers utilized the software Mendeley, OneDrive Microsoft Excel, and Risk of Bias Visualizer (ROBVis). The selection process in Figure 2 involved the literature search protocol for systematic reviews, which began with utilizing the search strategy. The criteria for filtering the literature according to its relevance to the study involved reading: title, publisher, and abstract during the search. In the title, the researchers sought out Alginate and Calcium Carbonate, then accepted papers with recognized publishers before scanning the abstract for quantitative study designs mentioning Acid Neutralization Capacity and adverse effects. Journals that did not meet the criteria were not eligible for the study. The researchers viewed a total number of 750 journals.

Figure 2. Flowchart of the Selection Process

2.6. Risk of Bias in Individual Studies

In the Cochrane Review Handbook, Higgins & Green (2011) defined bias as a systematic error that must be assessed by considering the Risk of Bias (ROB). This study's objectives require data collection from experimental trials that do not necessarily involve participants. Thus, the researchers modified the criteria from the Cochrane Handbook to suit the study's needs better.

After performing an individual ROB assessment, a general assessment was done by assigning number values for each risk (High = 2; Low = 1; None = 0) and computing for the average of each bias of the paper. The ROB Visualizer for systematic reviews was used to make a visual summary. The general assessment was utilized to justify the conclusions of the study.

Table 1. Risk of Bias Criteria

Bias	Risk	Criteria
Generated Source Type	Low	Primary source
	High	Secondary source Tertiary source
	Unclear	Not Enough Data (NED)
Randomized Testing of Market Antacids	Low	Random selection of market antacids
	High	Specific or non-random selection of market antacids
	Unclear	NED
Number of Trials	Low	5 or more trials
	High	4 or less trials
	Unclear	NED
Declaring the Control Variables	Low	All factors aside from the independent variable are controlled
	High	One or more factors aside from the independent variable are not controlled
	Unclear	NED
Generalizable Outcome Data	Low	Used statistics to determine the significance of results
	High	Did not use statistics to determine the significance of results
	Unclear	NED
Selective Reporting	Low	Specified expected outcomes, reported all of the results
	High	Specified outcomes, selective reporting of results
	Unclear	NED
Other Biases	Low	None
	High	1 or more
	Unclear	NED

2.7. Data Synthesis

The researchers collected information under Acid Neutralization Capacity (ANC) and adverse effects, then categorized the data in Microsoft Excel. Results that agreed with the same hypothesis and have similar implications on the efficacy of the compound were under the same category. The categorized data were used to make generalizations on the ANC and adverse effects of the compounds. These generalizations were the basis for determining whether Alginate and Calcium Carbonate are suitable alternatives to Aluminum Hydroxide for treating Gastroesophageal Reflux Disease (GERD).

3. RESULTS AND DISCUSSION

3.1 General Assessment of Risk of Bias

Figure 4 and Figure 5 present the summary of all risk of bias assessment in terms of the criteria. Generated source type, generalizable outcome data, selective reporting, and other biases had a low risk of bias in total, while the number of trials and declaring the controlled variables had a majority summation of low risk of bias. The overall summary of the risk of bias in the accepted papers is a low risk of bias.
Figure 4 is the traffic plot which is prescribed by Cochrane in presenting the ROB assessment. Green represents a low risk of bias, red for a high risk of bias, and yellow for an unclear risk of bias. The traffic plot's purpose is to illustrate which study and criterion of that study had a different risk of bias judgment from the majority. It was observed that the only high risk of bias came from the randomized testing of market antacids in Tytgat and his team's paper. This implies that in general, the accepted papers are considered to have a low risk of bias.

Figure 4. General ROBVis Assessment Traffic plot

Figure 5 presents the summary of all risk of bias assessment in terms of the criteria. Generated source type, generalizable outcome data, selective reporting, and other biases had low risk of bias in total, while the number of trials and declaring the controlled variables had a majority summation of low risk of bias. Randomized testing of market antacids, although it was observed to have a high risk of bias in one of the papers, resulted in a low risk of bias in the summary. The overall summary of the risk of bias in the accepted papers is a low risk of bias. Meaning, for all accepted papers, no other possible sources of bias were observed.

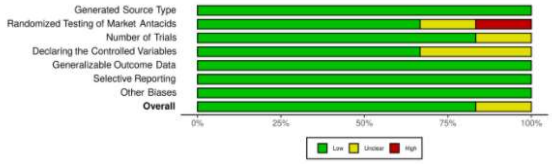

Figure 5. General ROBVis Assessment Summary plot

3.2 Antacid Component with Highest Acid Neutralization Capacity

The Acid Neutralizing Capacity (ANC) was used to test the amount of acid neutralization and the duration of the antacid maintaining the pH level of above 3.5 (Dhawal & Barve, 2020). According to Ayensu et al. (2020), antacid efficacy can be determined according to neutralizing capacity. The information synthesized, as seen in Table 2, implies that Calcium Carbonate, present in the antacid brand Rennie Duo, is a suitable alternative to Aluminum Hydroxide in terms of ANC. This is because Calcium Carbonate shows the highest ANC among the comparators' components, excluding Aluminum Hydroxide. Calcium carbonate, an inorganic salt, neutralizes Hydrochloric acid in gastric secretions when it is dissolved in the stomach, which is why the preferred formulation of Calcium Carbonate is in a compressed powder tablet. Additionally, the collected data supports the claim that Alginate is another suitable alternative to Aluminum Hydroxide since it has the second-highest ANC, below Calcium Carbonate.

Table 2. Resulting Efficacy of Antacids and their components based on ANC

Study	Year Published	Parameters Identified (ANC, adverse effects)	Results (Highest to Lowest Parameter)	Components (of the corresponding antacids)
Hampson, F. C., et al.	2005	ANC	1. Gaviscon Extra Strength (liquid) 2. Mylanta Heartburn Relief (liquid) 3. Algicon (liquid) 4. Rennie Duo (liquid) 5. Gaviscon Regular Strength (liquid) 6. Gaviscon Original (liquid) 6. Peptac (liquid) 7. Gastrocote (liquid) 8. Gaviscon Advance (liquid)	1. Aluminum Hydroxide 2. Calcium Carbonate 3. Magnesium Alginate 4. Calcium Carbonate 5. Magnesium Carbonate 6. Sodium Alginate 7. Sodium Alginate 8. Sodium Alginate
Tytgat, G. & Simoneau, G.	2005	ANC	1. Rennie Duo (liquid) 2. Gaviscon Original (liquid) 3. Placebo (liquid)	1. Calcium Carbonate 2. Sodium Alginate 3. not mentioned
Dettmar, P. W., et al.	2017	ANC	1. Rennie Duo (liquid) 2. Gaviscon Double Action (liquid) 3. Gaviscon Original (liquid) 4. Peptac (liquid) 5. Mylan Liquid Suspension (liquid) 6. Maalox RefluRAPID (liquid)	1. Calcium Carbonate 2. Sodium Alginate 3. Sodium Alginate 4. Sodium Alginate 5. Sodium Alginate 6. Sodium Alginate 7. Alginic Acid
Mahmood, D., et al.	2020	ANC	7. Algicon (solid) 1. Moxal Plus (solid) 2. Rennie Duo (solid) 3. Gaviscon Original (solid) 4. Gaviscon Advance (liquid) 5. Moxal (solid) 6. Gaviscon Original (liquid) 7. Moxal Plus (liquid) 8. Epicogel (liquid) 9. Moxal (liquid) 10. Mucogel (liquid) 11. Fawar lemon (effervescent powder)	1. Aluminum Hydroxide 2. Calcium Carbonate 3. Sodium Alginate 4. Sodium Alginate 5. Aluminum Hydroxide 6. Sodium Alginate 7. Aluminum Hydroxide 8. Aluminum Hydroxide 9. Aluminum Hydroxide 10. Aluminum Hydroxide 11. Sodium Bicarbonate

3.3 Antacid Component with Less Adverse Effects

The information collected, tabulated in Table 3, implies that in addition to Alginate being a suitable alternative to Aluminum Hydroxide in terms of high Acid Neutralization Capacity (ANC), Alginate also causes fewer adverse effects when taken by patients. Meaning, Alginate is also a suitable alternative to Aluminum Hydroxide and Calcium Carbonate for patients who choose to intake a more organic antacid component. Alginate is considered organic because it has Alginic Acid that is derived from brown seaweeds. Organic compounds contain more carbon and oxygen than inorganic compounds, these elements are already present within the biochemical makeshift of a human. Sodium Alginate is a raft-forming agent that

floats on top of the stomach which traps carbon dioxide. This raft stops incoming acidic gases that may worsen gastric pH. The raft gives gastric acid time to normalize before it eventually dissolves and gets digested.

Table 3. Resulting Efficacy of Antacids and their components based on Adverse Effects

Study	Year Published	Parameters Identified (ANC, adverse effects treatment)	Results (Highest Parameter to Lowest Parameter)	Components (of the corresponding antacids)
Sun, J., et al.	2015	Adverse effects	1. Gaviscon Double Action (solid) 2. Placebo (solid)	1. Sodium Alginate 2. not mentioned
Wilkinson, J., et al	2019	Adverse effects	1. Gaviscon Double Action (liquid) 2. Placebo (liquid)	1. Sodium Alginate 2. not mentioned

3.4 Alginate and Calcium Carbonate as an alternative to Aluminum Hydroxide

The researchers evaluated the most effective chemical component, excluding Aluminum Hydroxide, in treating Gastroesophageal Reflux Disease (GERD) based on the resulting Acid Neutralization Capacity (ANC) and Adverse Effects among the accepted papers. Finding an alternative to Aluminum Hydroxide is significant because Aluminum Hydroxide can become toxic if built up in the body when intaking antacids. According to Dettmar et al., Hampson et al., Mahmood et al., and Tytgat & Simoneau, the most effective chemical component in treating GERD based on ANC is Calcium Carbonate. It is then followed by Alginate, more specifically Sodium Alginate. According to the studies of Sun et al. and Wilkinson et al., the most effective antacid component in treating GERD based on Adverse effects is Alginate. Overall, both Calcium Carbonate and Alginate are suitable alternatives to Aluminum Hydroxide.

4. CONCLUSIONS

The research aims to find the best alternative antacid component to Aluminum Hydroxide through a systematic literature review. Results from the eligible papers indicate that Calcium Carbonate has the highest Acid Neutralization Capacity (ANC), while Alginate, specifically Sodium Alginate, has fewer adverse effects than placebos. These results support the claim that either Alginate or Calcium Carbonate are suitable alternative components to Aluminum Hydroxide in terms of ANC and adverse effects. The research findings suggest that Alginate and Calcium Carbonate can be an alternative to Aluminum Hydroxide. However, the potential of these components to completely replace Aluminum Hydroxide can be further looked into by future researchers. Also, it is recommended for future studies to explore other antacid components and different efficacy parameters to expand the scope of the study.

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