ORIGINAL ARTICLE

A Systematic Review on the Efficacy and Safety of Alginate–based Liquid Formulations in Reducing Gastroesophageal Reflux in Neonates and Infants

Theodore Joseph J. Ablaza, MD, Erika A. Crisostomo, MD and Ma. Esterlita V. Uy, MD

Department of Pediatrics, Philippine General Hospital, University of the Philippines Manila

ABSTRACT

Background. Neonates and infants experience gastroesophageal reflux as manifested through vomiting, reflux, and coughing. The complaint from many caregivers begins around the 2nd or 3rd month of life and subside around the 6th month of infancy. The standard of care has not been established and treatment options are limited owing to the pharmacological interventions that are deemed safe and effective. Alginate-based formulations, a widely used product in adults such as Gaviscon™, have been explored as another option to treat gastroesophageal reflux.

Objectives. To determine the safety and efficacy of alginate-based formulations in reducing symptoms of gastroesophageal reflux in neonates and infants.

Methods. An electronic search was conducted for randomized control trials in MEDLINE via PubMed, Herdin Plus, Cochrane Central Register of Controlled Trials, SCOPUS, and Clinical Trials Registry. The search terms were "gastroesophageal reflux," "acid reflux," "neonates," "newborn," "infants," "baby," "babies,", and "alginate." Two review authors independently assessed the available full text articles and a third author intervened to settle the discussion.

Results. Two studies were identified and included in this study. Due to the difference in the period of measurement of the trials, a meta-analysis was not pursued. However, a systematic review was still conducted. The two studies suggest a significant improvement of symptoms with alginate-based liquid formulations as intervention. No significant adverse events have been noted making this treatment option generally safe for use in infants.

Conclusion. There is insufficient evidence to conclude that alginate-based formulations ultimately help decrease gastroesophageal reflux in neonates and infants, but initial trials show promising results. There is also insufficient data to conclude the safety profile of this treatment option given the small sample.

Keywords: gastroesophageal reflux, neonate, infant, alginates

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Corresponding author: Theodore Joseph J. Ablaza, MD
Department of Pediatrics
Philippine General Hospital
University of the Philippines Manila
Taft Avenue, Ermita, Manila 1000, Philippines
Email: tjablaza@gmail.com

INTRODUCTION

Background of the Study

Infants experience some problems during feeding in their first few months of life. Gastroesophageal reflux (GER) presents as one of the more common complaints in infancy, especially in the first six months – even in the healthy population.[1] Seen in both the preterm and term population, it equally presents as a challenge for both age groups. Implications to feeding and other related problems such as apnea make this a cause of concern.

Gastroesophageal reflux has been noted in infants from 0-12 months. This was noted at least once a day in the first three months, peaked at four months, and decreased from six months onwards.[2] In a similar study, it has been seen that

50% of 0–3-month-old infants experienced GER while 67% were noted in 4-month-old infants. Likewise, only 5% has been reported in 12-month-old infants.[3] Intuitively, preterm infants are more likely to experience symptoms of GER due to physiological immaturity compared to term infants but a study by Jeffery[4] has proven otherwise.

GER pertains to the involuntary passage of contents from the stomach into the esophagus. This is a physiologic occurrence that happens all throughout the day but mostly after feeding. Although considered a normal process, it is characterized as regurgitation with occasional vomiting episodes. This occurs even in healthy children and acts as a protective mechanism to decompress the abdomen. On the other hand, Gastroesophageal Reflux Disease (GERD) can be considered pathologic when more severe symptoms arise such as failure to thrive or when morphological changes have been observed such as metaplasia of the mucosa. The latter is also characterized by excessive regurgitation. Even though considered physiologic, GER still causes parents to consult. The quality of life of both parents and infants have been noted.[5]

The North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN) have come up with a Clinical Practice Guideline regarding Pediatric Gastroesophageal Reflux. Non-pharmacologic recommendations include thickening of feeds, more frequent feedings, and extensively hydrolyzed-based formula. Pharmacologic interventions also explore the possibility of use of alginates, although not extensively studied yet. The use of Proton Pump Inhibitors (PPI) as first-line treatment and an alternative of Histamine-2 Receptor Antagonist (H2RA) in cases where the former is not available or contra-indicated.[6]

The American Academy of Pediatrics (AAP) have likewise recommended lifestyle modifications such as positional therapy and even changing the maternal diet.[7] On top of PPIs and H2RA drug classes, antacids, and prokinetics have been considered as possible treatment options as well.

The treatment of Gastroesophageal Reflux in adults include symptomatic relief through medications readily available over the counter – such as that of Gaviscon™ and Gaviscon Double Action™ – where sodium alginate comprises most of its active ingredients, along with Sodium Bicarbonate, and Calcium Carbonate. A couple of clinical trials, on top of case control studies, have begun exploring the use of these liquid preparations in the younger age group of neonates to children.

Significance of the Study

The study on the prevalence of the GER among infants have been documented poorly. There is no local available data in the Philippines, but few studies made in Asia showed differences in trends. In contrast to Western data, a study in Thailand[8] showed a peak incidence at two months old while a similar study in Japan reported peak incidence at one month of life.[9] A study comparing 6- and 9-month-old infants in Indonesia also showed decreasing trends with increase in age.[10] Across these populations, a need to address regurgitation is emphasized but a short-term solution could probably address this problem that eventually resolves sooner in life.

Regurgitation leads to possible complications such as the case of apnea, which has been found to increase both short and prolonged frequencies.[11] Laryngeal chemoreflex, described as a reflex following exposure of the larynx to acid stomach contents, can lead to episodes of apnea as well.[12] In adults, it has been shown that esophageal reflux has worsened status asthmaticus demonstrating how airway hyperresponsiveness is further aggravated by increased acid content in the esophagus.[13]

The current standard of care in the treatment of gastroesophageal reflux in neonates and infants have not been uniform across hospitals, more so in households. The need to address this issue has provided more treatment options such as these alginate-based formulations for infants. In a cross-over study done by Baldassarre[14] in infants, the use of magnesium-alginate formulation has reduced symptoms while also proving to be less expensive than thickened formulas.

Review of Related Literature

Pathophysiology of GER in neonates and infants

The pathophysiology of GER varies with age. It is a predominantly physiologic process[15] in most infants. However, GER is also associated with esophageal airway problems. Due to factors such as a small aerodigestive tract, a supine posture, and differences in neuromotor responses, increased frequency in GER may be noted.[16]

Diagnosis and documentation of GER

Esophageal pH monitoring is considered as the first line in doing investigation for GER.[17] Another method is that of multiple intra-luminal impedance (MII). Other diagnostic examinations such as ultrasonography, barium studies, manometry, and scintigraphy have all been discouraged.[6]

Mechanism of Action of Alginate-based formulations

Alginate-based formulation works by forming a gel once it comes in contact with gastric acid. These formulations produce bicarbonate which in turn becomes carbon dioxide producing a relatively pH-neutral barrier. The onset of action sets in within seconds of administration. These do not have systematic effects and do not interfere with the normal secretory patterns in the stomach. It has been seen to contribute to the overall viscosity of the gastric contents as well.[18] The precipitate that has formed acts like a barrier that prevent reflux episodes.[19] This was also compared to having a 'cork' effect on the lower esophageal sphincter that minimizes and helps reduce reflux of gastric contents.[20]

OBJECTIVES

General Objective

This study aims to determine the efficacy and safety of Alginate-based formulations in the treatment of gastro-esophageal reflux among neonates and infants.

Specific Objectives

1. To determine the effect of Alginate-based formulations in reducing the frequency of GER in neonates and infants.
2. To determine the effect of Alginate-based formulations in reducing symptoms caused by GER such as cough, crying, irritability, anorexia/food refusal, and vomiting.
3. To determine the effect of Alginate-based formulations in reducing apnea as a complication of GER.
4. To determine the safety issues encountered in neonates and infants using alginate-based liquid formulations.

METHODS

Search Criteria

Type of Studies

This systematic review included all published randomized control trials, and experimental studies evaluating the efficacy of alginate-based formulations in decreasing gastro-esophageal reflux episodes in neonates and infants.

Types of Participants

The participants included in this study are neonates 0-28 days old and infants up to 1 year of age, whether preterm or term receiving both breastfeeding and formula-feeding who experience gastroesophageal reflux.

Types of Intervention

The studies in this systematic review involved alginate-based formulations, including sodium alginate or magnesium alginate, in preventing and reducing gastro-esophageal reflux episodes in neonates as the intervention in this study. Comparison used was placebo.

Types of Outcomes

Primary Outcomes

The primary outcome is the reduction in the gastroesophageal reflux episodes of neonates and infants with the use of alginate-based formulations.

Secondary Outcome

The efficacy in reducing symptoms of GER after administration of the alginate-based formulations compared with placebo, or standard of care. Safety issues related to the use of alginates was observed among the studies.

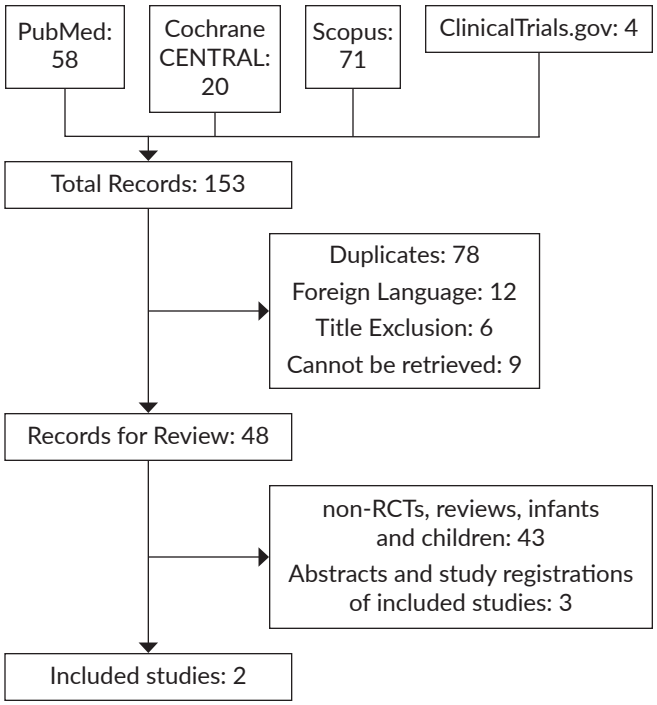

Figure 1. Study flow diagram for the electronic search using keywords "newborn," or "neonate," or "infant," or "baby," or "babies," and "gastroesophageal reflux," or "acid reflux."

Search Methods

Electronic Searches

An electronic search which includes MEDLINE via Pubmed, Herdin Plus, Cochrane Central Register of Controlled Trials, SCOPUS, and Clinical Trials Registry was done. Related citations of articles were done to search for other possible studies. Keywords included "gastroesophageal reflux," "acid reflux," "neonates," "newborn," "infants," "baby," "babies," and "alginate." Herdin Plus revealed no or zero searches. The search was updated until September 11, 2021.

Data Collection and Analysis

Selection of Studies

Two independent authors reviewed and assessed the eligibility of full text articles of the randomized control trials (RCTs). A total of two RCTs were included in this study.

Data Extraction and Management

Each study and data were compared to check for possible errors. The following data such as name, authors, the respective year of publication, study setting, and period, type of study design, population and sample size, interventions, outcomes, and outcome measurement method were included. The disagreements were resolved with the third party to settle the differences. Whenever possible the Review Manager (RevMan) version 5.4 software was attempted.

Assessment of Risk of Bias in Included Studies

The methodological quality of the chosen articles was assessed independently by the authors. As per the Cochrane Handbook for Systematic Reviews of Intervention, these were followed:

Sequence generation

The methods used for sequence generation were done to assess for possible selection bias by comparing systematic differences. These methods were as follows:

- Low risk – application of randomization such as computer-generated methods
- High risk – use of non-random process
- Unclear – insufficient information

Allocation Concealment

The allocation concealment methods were used to conceal the allocation sequence and were assessed for possible selection bias. These will be assessed as follows:

- Low risk – telephone randomization or numbered-sealed envelopes
- High risk – Unsealed or non-opaque envelopes
- Unclear – insufficient information

Blinding

The methods used for blinding the study personnel from knowledge of intervention received by the participants were assessed for possible performance and detection bias. The methods were assessed as follows:

- Low risk, high risk, or unclear for personnel; or
- Low risk, high risk, or unclear for outcome assessors

Incomplete Outcome Data

The completeness of data was assessed for completeness for each study used. These include the reporting of dropouts, comparison of numbers for every stage in the analysis, and whether the missing data were spread throughout groups and outcomes. These were assessed to be:

- Low risk – No missing data or reasons were stated
- High risk – Missing data are likely to be related to outcomes or not balanced across groups
- Unclear – insufficient reporting of exclusions

Selective Reporting Bias

The studies were assessed as the following:

- Low risk – the prespecified and expected outcomes were mentioned and reported
- High risk – the prespecified and expected outcomes were not completely reported
- Unclear – Incomplete information were given

Other Sources of Bias

The studies were evaluated for other possible sources of bias. They will be categorized as such:

- Low risk – no other possible sources of bias
- High risk - there is a high risk of bias
- Unclear – insufficient reporting done

Measure of Treatment Effect and Assessment of Heterogeneity

Dichotomous outcomes were reflected as summary risk ratio between the study and control groups with 95% confidence intervals. Heterogeneity in the reported results across and between studies were evaluated using Cochran's Q and I^2 statistics. The null hypothesis, that the studies are homogenous were rejected if the P value for heterogeneity was <0.10 or I^2 was >50 %. The fixed-effects model was utilized if heterogeneity was low (P > 0.10, I^2<50 %). On the other hand, the random-effects model was used to pool studies if heterogeneity exceeded an I^2 of 50%.

Data Synthesis

Statistical analysis was performed using Review Manager (RevMan) version 5.4 software whenever applicable.

Sensitivity Analysis

No sensitivity analysis was performed to evaluate the effect of the individual studies in the pooled result in this systematic review.

RESULTS

Characteristics of the Studies

The results of the search detailed earlier in Figure 1 showed a final list of remaining two studies that fit the inclusion criteria needed to be eligible in this systematic review. The characteristics of the two randomized controlled trials were described in detail in Table 1.

Participants

Combining the two studies eligible for review in studies evaluating the effect of alginate-based liquid formulations in gastroesophageal reflux, a total of 165 patients aged 1-10 months with a mean of five months in the study by Ummarino et al.[21] were included while 90 patients aged 0-12 months were considered in the trial by Miller et al.[22] Both studies satisfied the inclusion criteria where subjects should belong to the neonate or infant group. The former included infants who are formula-fed and whose symptoms are considered that of gastroesophageal reflux while the latter had both breastfed and formula-fed subjects who presented with regurgitation as well.

Intervention

The participants in the included studies received alginate-based liquid formulations as part of the intervention with the intention to treat. In the study by Ummarino et al., the intervention group was given magnesium alginate aluminum-free formulation plus simethicone at a dose of 2.5 mL thrice a day for infants weighing less than 5 kilograms

Table 1. Description of Included Studies

Study ID	Country	Population	Intervention	Comparison	Outcomes
Ummarino 2015	Italy	Full-term, formula-fed infants aged 1 to 12 months, with symptoms suggestive of GER (score ≥7 in i-GERQ) and with infant regurgitation defined according to the Rome III criteria	In addition to reassurance and lifestyle changes, **magnesium alginate aluminum-free formulation plus simethicone** at a dose of 2.5 mL 3 times per day for infants weighing <5 kg or 5 mL 3 times per day for those weighing >5 kg, to be given 10 minutes after feeding.	Reassurance and lifestyle changes only	Measures: Infant Gastroesophageal Reflux Questionnaire, Adverse effects reported in a daily diary Time frame = 4 and 8 weeks
Miller 1999	United Kingdom	Infants aged between 0 and 12 months with symptoms consistent with GER — persistent, unmanageable vomiting/ regurgitation or vomiting/ regurgitation at least twice daily for the two days prior to the start of the study	**Sodium alginate / magnesium alginate**, available as a sachet, containing the active ingredients; sodium alginate (225 mg) and magnesium alginate (87.5 mg) in a total of 0.65 g, administered with food, dependent on the infant's weight and feeding method (2 sachets if weight ≥4.54 kg, otherwise 1 sachet).	Placebo	Measures: Severity and frequency of symptoms (vomiting/ regurgitation), feeding patterns, compliance, unwanted symptoms, and concomitant medications recorded in a diary Time frame = 7 and 14 days

Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
Miller 1999	Sodium alginate / magnesium alginate	Placebo	Severity and frequency of GER symptoms; Adverse events	1	!	+	+	+	–	–
Ummarino 2015	Aluminum-free magnesium alginate plus simethicone	Reassurances and lifestyle changes	i-GERQ symptom scores; Adverse events	1	!	!	+	!	+	!

Figure 2. Risk of bias graph for included studies.

D1 – Randomisation process; D2 – Deviations from the intended interventions; D3 – Missing outcome data; D4 – Measurement of the outcome; D5 – Selection of the reported result.

+ *Low risk* ! *Some concerns* + *High risk*

or at an adjusted dose of 5 mL thrice a day for more than 5 kilos timed 10 minutes after feeding. The strength of the formulation was not specified although the active ingredients include magnesium alginate, simethicone, fructose, xanthan gum, honey, and sodium bicarbonate, among others. On the other hand, in the study by Miller et al., sodium alginate in the form of a sachet containing the two active ingredients of sodium alginate 225 mg and magnesium alginate 87.5 mg in a total of 0.65 g was used. This was also adjusted based on the weight of the child - wherein those weighing less than 4.54 kilograms, a sachet containing the two active ingredients were given while two sachets were provided for those weighing more than 4.54 kilograms.

In Ummarino et al.'s study, the formula that was used was milk-based and nonhydrolyzed. On the other hand, Miller's study included patients whose feeding included solid foods, milk formula, and breastfeeding. No other description of the milk-based formula was given that might include ingredients against reflux.

Control

The control groups in the two studies differ in that Ummarino et al. employed reassurance and lifestyle changes for the control group while Miller et al. used placebo as a control group.

Outcomes

The included population's response to the intervention were measured using forms such as a validated questionnaire for Ummarino et al. – the Infant Gastroesophageal Reflux Questionnaire, while a diary to record symptom changes was used by Miller et al. Both studies recorded adverse events throughout the implementation of the trial.

Period of Measurement

Ummarino et al. conducted the clinical trial over a span of two months compared to that of Miller et.al whose intervention was employed over a 2-week period.

Risk of Bias in the Included Studies

The studies evaluated showed concerns in the selection bias while only one of two studies showed a high risk of bias in the selection of the reported result as shown in Figure 2. Combined, a high risk of bias is present. A more detailed breakdown of the evaluation of bias is shown in Figure 3.

Effects of the Interventions

Primary Outcome

Reduction of Symptoms of Gastroesophageal Reflux

A meta-analysis could not be done for this outcome as the time frame employed by authors Ummarino et al., and Miller et al., differ vastly in that the former utilized 4-8 weeks in the trial while the latter conducted the experiment over two weeks. A quantitative analysis would provide a marked disparity and unreliable result. A qualitative analysis was deemed more appropriate.

The study by Ummarino et al. showed that in group A of their study – where the infants received magnesium alginate with simethicone, there was a significant reduction of the symptoms of GER (P<0.005) compared to that of group C who only received reassurances and lifestyle changes alone. Twelve of the 25 patients (48%) treated with this combination became free of symptoms compared to the four of the 25 patients (16%), who had thickened formulation after a month of treatment. Moreover, it has been shown more effective after a 4-week treatment with the same intervention compared to reassurance alone (P<0.0001).

In Miller et al., where the intervention is sodium alginate with magnesium alginate, it has been found that the decrease

Domain	Signaling question	Response Ummarino 2015	Response Miller 1999
Bias arising from the randomization process	1.1 Was the allocation sequence random?	Y	PY
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	NI	NI
	1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	PN	N
	Risk of bias judgement	**Some concerns**	**Some concerns**
Bias due to deviations from intended interventions	2.1. Were participants aware of their assigned intervention during the trial?	NI	NI
	2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	PN	PY
	2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?	N	NI
	2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?	NA	NA
	2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?	NA	NA
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	PY	Y
	2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyze participants in the group to which they were randomized?	NA	NA
	Risk of bias judgement	**Low**	**Some concerns**
Bias due to missing outcome data	3.1 Were data for this outcome available for all, or nearly all, participants randomized?	PY	PY
	3.2 If N/PN/NI to 3.1: Is there evidence that result was not biased by missing outcome data?	NA	NA
	3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?	NA	NA
	3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?	NA	NA
	Risk of bias judgement	**Low**	**Low**
Bias in measurement of the outcome	4.1 Was the method of measuring the outcome inappropriate?	N	PN
	4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?	PN	N
	4.3 Were outcome assessors aware of the intervention received by study participants?	PN	PY
	4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?	NA	PY
	4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?	NA	PN
	Risk of bias judgement	**Low**	**Some concerns**
Bias in selection of the reported result	5.1 Were the data that produced this result analyzed in accordance with a pre-specified analysis plan that was finalized before unblinded outcome data were available for analysis?	PN	PY
	5.2 ... multiple eligible outcome measurements (e.g., scales, definitions, time points) within the outcome domain?	N	PN
	5.3 ... multiple eligible analyses of the data?	N	PN
	Risk of bias judgement	**Some concerns**	**Low**
Overall bias	**Risk of bias judgement**	**Some concerns**	**Some concerns**

Figure 3. Detailed Risk Bias Assessment

in the vomiting and regurgitation episodes was statistically significant compared to those with placebo alone (P=0.009). The median value of 8.5 episodes of vomiting at baseline for the control group decreased down to 3.0 at the end with the intervention group compared to the placebo group where the baseline episode of 7.0 was decreased to 5.0. As the assessment of efficacy of administration also depends on the judgement of both the investigator and parent/guardian, it was noted that global evaluation of the investigator was statistically more significant compared to placebo (p=0.008). The patients on alginates were considered 'very good' (36%) than those receiving placebo (15%). The same goes for the parents whose evaluation favors the use of alginates compared to placebo (p=0.002). The guardians of those on alginates assessed their children to have 'much better' symptoms (48%) than those belonging to the placebo group (24%).

Secondary Outcome

Reduction of Complications of Gastroesophageal Reflux

A meta-analysis cannot be made for this outcome as both studies have not looked into reduction of complications of Gastroesophageal reflux including that of apnea. Other journal articles have investigated this, however, observational, or case-control ones.

Safety Issues Encountered

A qualitative analysis was deemed more appropriate as well. In the study by Ummarino et al., only one patient complained of constipation with the use of magnesium alginate with simethicone. No other untoward incidents were noted anymore.

In the study by Miller et al., fifty seven percent (51/90 patients) had at least one adverse event noted. This pertains to both groups combined where 26 patients on alginate reported at least one adverse event while 25 patients on placebo also recorded as such. The listed ones include diarrhea, emesis, teething syndrome, constipation, and colic. However, there was no noted statistically significant difference in the incidence of the adverse event between treatment groups (p > 0.1).

DISCUSSION

Summary of Results

This systematic review summarizes the available evidence on the use of alginate-based liquid formulations for use in neonates and infants. A total of 165 subjects from 0-12 months of age showed that there is a significance in the use of the intervention compared to that of placebo alone. The symptoms of gastroesophageal reflux as manifested by vomiting and irritability have been shown to decrease in the infants included. Ummarino et al. demonstrated that there was statistically significant effect in reducing regurgitation and vomiting compared to reassurance alone but not against thickened formula. Miller's study showed that decreasing the absolute number of vomiting and regurgitation was statistically significant, but the severity only showed a trend to favor alginate use. Alginate-based formulations have been generally safe to use, and no severe hospitalizations have been attributed to it.

Overall Completeness and Applicability of Evidence

Only two randomized control trials have been included in this systematic review. None of these have tackled the secondary outcome on the lessening of the associated complications such as apnea. Ummarino et al.'s study attempted to look at the effect of magnesium alginate. However, simethicone was also included as an ingredient in the formulation used in the study. The effects of the former, hence, cannot be isolated as simethicone might have contributed to the lessening of symptoms of reflux. The studies included show promising and favorable results, but with only 165 total subjects, it was hard to make recommendations. No study has focused on neonates (aged 0-28 days) as well, making it difficult to apply to this age group.

Quality of the Evidence

The scarcity of available clinical trials and the differences between some of its method make the available evidence of a very low certainty. The GRADE approach was used in this study (Figure 4). The very low-quality evidence from two

Certainty assessment							Impact	Certainty	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Frequency and severity of GER symptoms									
2	randomized controlled trial	very serious[a]	not serious	serious[b]	not serious	none	The studies suggest that alginate use decreases vomiting and regurgitation episodes.	⨁◯◯◯ VERY LOW	
Adverse events									
2	randomized controlled trial	very serious[a]	not serious	serious[b]	not serious	none	There are no significant adverse events caused by alginate use and safety profile is similar to placebo.	⨁◯◯◯ VERY LOW	

Explanations: [a]One study was at high risk of bias; [b]One study included simethicone in the intervention group

Figure 4. GRADE Certainty of Evidence Assessment

randomized control trials shows that alginates probably result in a slight reduction in the frequency and severity, and GER symptoms. The true effect, however, might be substantially lower than what is reported. A high risk of bias for the studies suggest that the results should be taken with caution. In a pharmacological intervention deemed generally safe to use, it might still seem to be a viable treatment option. More studies including this population of neonates and infants would be needed to make a more applicable recommendation.

Agreements and Disagreements with other Studies and Reviews

There have been other systematic reviews on the use of pharmacological interventions done in children – but none known to the authors on the use of alginate-based formulations alone. There are currently no new randomized control trials applied in the clinical trials registry. A meta-analysis could not be executed with the available data currently.

CONCLUSION

Implication for Practice

Gastroesophageal reflux remains one of the most common complaints encountered by parents in their infants. There is insufficient evidence to recommend the use of these alginate-based formulations based on the available evidence, but the studies suggest a generally safe profile and may still be worth a trial of use. Comparing its mechanism of action to other medications used for GER, alginate-based formulations have not been known to alter the gastric physiology, hence making it a viable option to explore.

Implication for Research

With the current available evidence, more randomized control trials using alginate-based formulations are encouraged to be pursued. Compared to proton-pump inhibitors, and histamine 2 antagonists, the use of alginates carry a relatively safe profile making it a possible area of research even in the local setting. With the advent of the arrival of more products in the country, randomized control trials can be suggested. Apart from neonates and infants, a separate study looking into children as subjects can also be conducted.

Statement of Authorship

TJJA made the primary investigation of the topic; wrote the introduction as well as the Review of Related Literature; one of two primary evaluators of articles. EAC contributed in writing the results and discussion; helped in conceptualizing the whole article; one of two primary evaluators of the articles. MEVU contributed in the conceptualization of the work; became the third party in deciding the use of articles; revised the manuscript, and approved the initial, interim, and final versions of the manuscript.

Author Disclosure

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REFERENCES

1. Campanozzi A, Boccia G, Pensabene L, Panetta F, Marseglia A, Strisciuglio P, et al. Prevalence and natural history of gastroesophageal reflux: pediatric prospective survey. Pediatrics. 2009 Mar;123(3): 779-83. doi: 10.1542/peds.2007-3569.
2. Nelson SP, Chen EH, Syniar GM, Christoffel KK. Prevalence of symptoms of gastroesophageal reflux during infancy: a pediatric practice-based survey. Arch Pediatr Adolesc Med. 1997 Jun;151(6): 569-72. doi:10.1001/archpedi.1997.02170430035007.
3. Dranove JE. Focus on diagnosis: new technologies for the diagnosis of gastroesophageal reflux disease. Pediatr Rev. 2008 Sep;29(9): 317-20. doi: 10.1542/pir.29-9-317
4. Jeffery HE, Page M. Developmental maturation of gastro-oesophageal reflux in preterm infants. Acta Paediatr. 1995 Mar;84(3):245-50. doi: 10.1111/j.1651-2227.1995.tb13623.x.
5. Vandenplas Y, Salvatore S, Hauser B. The diagnosis and management of gastro-oesophageal reflux in infants. Early Hum Dev. 2005 Dec; 81(12):1011-24. doi: 10.1016/j.earlhumdev.2005.10.011
6. Rosen, R, Vandenplas Y, Singendonk M, Cabana M, DiLorenzo C, Gottrand F, et.al. Pediatric Gastroesophageal Reflux Clinical Practice Guidelines: Joint Recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr. 2018 Mar; 66(3):516-54. doi: 10.1097/MPG.0000000000001889.
7. Lightdale JR, Gremse DA, Heitlinger; Section on Gastroenterology, Hepatology, and Nutrition. Gastroesophageal reflux: management guidance for the pediatrician. Pediatrics. 2013 May;131(5):e1684-95. doi: 10.1542/peds.2013-0421.
8. Osatakul S, Sriplung H, Puetpaiboon A, Junjana C, Chamnongpakdi S. Prevalence and natural course of gastroesophageal reflux symptoms: a 1-year cohort study in Thai infants. J Pediatr Gastroenterol Nutr. 2002 Jan;34(1):63-7. doi: 10.1097/00005176-200201000-00015.
9. Miyazawa R, Tomomasa T, Kaneko H, Tachibana A, Ogawa T, Morikawa A. Prevalence of gastro-esophageal reflux-related symptoms in Japanese infants. Pediatr Int. 2002 Oct;44(5):513-6. doi: 10.1046/j.1442-200x.2002.01609.x.
10. Hegar B, Satari DHI, Sjarif DR, Vandenplas Y. Regurgitation and gastroesophageal reflux disease in six to nine months old Indonesian infants. Pediatr Gastroenterol Hepatol Nutr. 2013 Dec;16(4): 240-7. doi: 10.5223/pghn.2013.16.4.240.
11. Menon AP, Schefft GL, Thach BT. Apnea associated with regurgitation in infants. J Pediatr. 1985 Apr;106(4):625-9. doi: 10.1016/s0022-3476(85)80091-3.
12. Perkett EA, Vaughan RL. Evidence for a laryngeal chemoreflex in some human preterm infants. Acta Paediatr Scand. 1982 Nov; 71(6): 969-72. doi: 10.1111/j.16512227.1982.tb09558.x.
13. Wu DN, Tanifuji Y, Kobayashi H, Yamauchi K, Kato C, Suzuki K, et al. Effects of esophageal acid perfusion on airway hyperresponsiveness in patients with bronchial asthma. Chest. 2000 Dec;118(6):1553-6. doi: 10.1378/chest.118.6.1553.
14. Baldassare ME, Di Mauro A, Pignatelli MC, Fanelli M, Salvatore S, Di Nardo G, etal. Magnesium alginate in gastro-esophageal reflux: a randomized multicenter cross-over study in infants. Int J Environ Res Public Health. 2019 Dec;17(1):83. doi: 10.3390/ijerph17010083.
15. Thomson M. Disorders of the oesophagus and stomach in infants. Baillieres Clin Gastroenterol. 1997 Sep;11(3):547-71. doi: 10.1016/s0950-3528(97)90031-2.

16. Jadcherla SR. Upstream effect of esophageal distention: effect on airway. Curr Gastroenterol Rep. 2006 Jun;8(3):190-4. doi: 10.1007/s11894-006-0074-9.
17. Del Buono R, Wenzl TG, Ball G, Keady S, Thomson M. Effect of Gaviscon Infant on gastro-oesophageal reflux in infants assessed by combined intraluminal impedance/pH. Arch Dis Child. 2005 May;90(5):460–3. doi: 10.1136/adc.2002.024463
18. Mandel KG, Daggy BP, Brodie DA, Jacoby HI. Review article: alginate-raft formulations in the treatment of heartburn and acid reflux. Aliment Pharmacol Ther. 2000 Jun;14(6):669-90. doi: 10.1046/j.1365-2036.2000.00759.x.
19. Lambert JR, Korman MG, Nicholson L, Chan JG. In-vivo anti-reflux and raft properties of alginates. Aliment Pharmacol Ther. 1990 Dec;4(6):615-22. doi: 10.1111/j.1365-2036.1990.tb00509.x.
20. Zentilin P, Dulbecco P, Savarino E, Parodi A, Iiritano E, Bilardi C, et al. An evaluation of the antireflux properties of sodium alginate by means of combined multichannel intraluminal impedance and pH-metry. Aliment Pharmacol Ther. 2005 Jan;21(1):29–34. doi: 10.1111/j.1365-2036.2004.02298.x
21. Ummarino D, Miele E, Martinelli M, Scarpato E, Crocetto F, Sciorio E, et al. Effect of magnesium alginate plus simethicone on gastroesophageal reflux in infants. J Pediatr Gastroenterol Nutr. 2015 Feb;60(2):230-5. doi: 10.1097/MPG.0000000000000521.
22. Miller S. Comparison of the efficacy and safety of a new aluminum-free paediatric alginate preparation and placebo in infants with recurrent gastro-oesophageal reflux. Curr Med Res Opin. 1999;15(3):160-8. doi: 10.1185/03007999909114087.