Accepted Article

Antacid monotherapy is more effective in relieving epigastric pain than in combination with lidocaine. A randomized double-blind clinical trial

Antacid alone is best for epigastric pain

Jaimee Warren[1 2] MBBS, Blake Cooper[1 2] MBBS, Anton Jermakoff [1 2] MBBS, Jonathan C Knott[1 2 3] PhD

1 Emergency Department, Royal Melbourne Hospital, Melbourne, Australia

2 Melbourne Medical School, University of Melbourne, Parkville, Australia

3 Centre for Integrated Critical Care, University of Melbourne, Parkville, Australia

E-mail: jaimee.warren@unimelb.edu.au, blake.cooper@unimelb.edu.au, anton.jermakoff@unimelb.edu.au, jonathan.knott@mh.org.au

Presented at the Australasian College for Emergency Medicine Scientific Meeting, Hobart Australia, November 2019

All authors were involved in the design of, and recruitment to, the study. JW drafted the manuscript, supervised by JK. JK undertook the analysis of the data. The study was unfunded.

The study was pre-registered at the Australian New Zealand Clinical Trials Registry (ACTRN12619000928112)

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/ACEM.14069

This article is protected by copyright. All rights reserved

Corresponding author: Jonathan Knott

We would like to thank the doctors and nurses in the Royal Melbourne Hospital for incorporating the study protocol into their medical management of patients, Hayley Zarth for her expertise and protocol implementation as an ED pharmacist, and to Maggie Bock and Celine Yap for their logistical support of the study design.

Word Count: 1486

All authors have no conflict of interest and receive no financial benefits from this study

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

DR. JONATHAN C KNOTT (Orcid ID : 0000-0003-1503-0440)

Article type : Research Letter

This was a double-blind, randomized clinical trial comparing three different solutions for the treatment of adults with epigastric pain or dyspepsia presenting to the emergency department (ED). It was conducted in the Royal Melbourne Hospital, a tertiary, adult-only, inner-city center in Melbourne with 75,000 annual ED visits. Data were collected over three months, from June to August 2019, between 0800 and 2300, seven days a week.

Epigastric pain and dyspepsia in EDs around the world are typically treated with an antacid, either alone or combined with other medications. Such medications include viscous lidocaine, an antihistamine, a proton pump inhibitor, or an anticholinergic [1, 2].

The aim of this study was to compare antacid monotherapy, antacid/lidocaine 2% solution, and antacid/lidocaine 2% viscous gel in reducing pain at 30 minutes. The primary outcome was change in pain scores 30 minutes after treatment. Thirty minutes was chosen to match previous studies, and it was expected to be sufficient time for the analgesia to take effect [3, 4]. The pre-determined minimum clinically important difference was a 13 mm decrease on a 100 mm visual analogue scale (VAS) from baseline [5].

Secondary outcomes were medication palatability (taste, bitterness, texture, and overall acceptability) using a VAS, and change in pain score 60 minutes post-administration.

Patients prescribed an antacid/lidocaine mixture by the treating emergency doctor were approached for enrolment. To replicate clinical practice, no standardized

This article is protected by copyright. All rights reserved

Accepted Article

criteria for inclusion was used; rather, the study relied on the treating doctor's clinical discretion and their documented prescription of an antacid/lidocaine mixture. Patients were excluded if they were unable to consent or were under 18 years of age.

The study was approved by the Melbourne Health Human Research and Ethics Committee and pre-registered at the Australian New Zealand Clinical Trials Registry (ACTRN12619000928112).

Randomization was conducted in a ratio of 1:1:1 in blocks of six, using a random-number table. Opaque envelopes were prepared by a research assistant not involved in recruitment. The envelopes were provided in sequence to the attending nurse and contained instructions to give one of three medication mixtures.

Solutions were not made to look identical, because a secondary outcome of this study was palatability. An attempt to make the solutions of equivalent color, appearance or viscosity would potentially interfere with these assessments. The volume given was identical, investigators and patients remained blinded to the solution they received, but not the nursing staff who prepared and administered the mixtures.

Nurses paged investigators immediately after an antacid/lidocaine mixture was prescribed and before it was administered. Investigators were expected to present to the bedside in under five minutes to begin enrolment, to minimize delays to analgesia administration.

- Arm 1 (Viscous): received 10 mL oral lidocaine 2% viscous gel plus 10 mL antacid (traditional antacid/lidocaine mixture)
- Arm 2 (Solution): received 10 mL lidocaine 2% solution plus 10 mL antacid
- Arm 3 (Antacid): received 20 mL antacid alone

Lidocaine 2% viscous gel is manufactured in Australia by Perrigo® and consists of lidocaine hydrochloride in a 2.13% weight to volume gel for oral use. Lidocaine 2% solution is manufactured by Pfizer® as 2% lidocaine hydrochloride for injection. The antacid, Gastrogel®, is manufactured by Aspen Pharma®. Each 10 mL contains dried aluminum hydroxide gel equivalent to 500 mg, Magnesium trisilicate 240 mg and magnesium hydroxide 240 mg.

This article is protected by copyright. All rights reserved

Accepted Article

All data were collected electronically in REDCap®. Baseline data included date, age, gender, pain at time zero, brief past medical history, current medications, and medications taken prior to ED presentation. Pain was recorded along an electronic VAS from 0 mm to 100 mm, 0 mm being no pain and 100 mm being maximal pain. The patient self-selected their pain score. Immediately after the first pain score was obtained, medication was administered. After 30 minutes, the pain was scored again, with the patient unable to view their previous score. A similar VAS was used to obtain scores for taste, bitterness, texture, and overall acceptability at 30 minutes, with 0 mm being unacceptable and 100 mm being acceptable. At 60 minutes, a final pain score was obtained. Data regarding effects experienced, ED medications given, and ED discharge diagnosis were recorded once the final VAS was obtained.

Analysis was undertaken on an intention-to-treat. Proportions were tested for significance using the chi-square test. Continuous variables were assumed to be non-parametric and tested using the Kruskal-Wallis test. Stata® software was used for all analyses. The null hypothesis was that there would be no difference in pain scores at 30 minutes comparing the addition of either lidocaine viscous, or lidocaine solution, to an antacid. Assuming a standard deviation of 15 mm and the equivalence limit of 13 mm (power 80% and alpha is 0.05), 20 patients needed to be recruited into each arm. Allowing for potential differences in patient allocation and heterogeneous recruitment, the target was increased from 60 to 80 patients.

Lidocaine viscous was accessed 219 times in the ED during the recruitment period, 120 patients (55%) were approached for recruitment, 94 were enrolled, and five were excluded as pain scores were not obtained. Eighty-nine (95%) enrolled patients completed the protocol.

Table 1 outlines patient characteristics and findings. There were no statistically significant baseline differences between the treatment groups. Importantly, all three groups started with a similar pain score. In terms of the primary outcome, Solution and Antacid provided clinically important (>13 mm) analgesia at 30 minutes, Viscous did not. Though the traditional mixture of antacid/viscous lidocaine was least effective and antacid monotherapy demonstrated the greatest degree in pain relief, none of the differences between treatments were statistically significant.

This article is protected by copyright. All rights reserved

Accepted Article

Regarding secondary outcomes, at 60 minutes, all treatment groups experienced additional pain relief. The change in median pain scores was clinically significant (>13 mm) for all three arms. Participants found antacid monotherapy to be the most palatable solution, with statistically significant differences in taste, bitterness, and overall acceptability.

The most prominent adverse effect was oral numbness, experienced by treatment groups containing lidocaine, Viscous (n=6, 20%) and Solution (n=8, 26%). Patients in the Viscous arm reported dizziness and tiredness (n=2, 7%), patients in the Solution arm reported cough, nausea, and dizziness (n=4, 13%). One patient in the Antacid arm reported a dry mouth (n=1, 4%).

The overall finding of this study was the beneficial effect of antacid monotherapy in multiple ways. In addition to no statistical difference in pain relief at 30 and 60 minutes, antacid monotherapy was favored in terms of palatability and acceptability, and there were fewer side effects.

Previous studies of acute dyspepsia management in the ED have been of varying methodological quality with mixed results. In a 1990 single-blind study comparing 30 mL of antacid with or without 15 mL of viscous lidocaine [3], Welling et al found the addition of lidocaine significantly increased pain relief (decreased pain score by 40 mm compared to 9 mm with antacid monotherapy). That antacid monotherapy did not produce clinically significant pain relief contrasted with prior studies that demonstrated just that [6, 7]. Another randomized single-blind study comparing antacid plus either benzocaine solution or viscous lidocaine found no difference between the two arms, but there was no antacid monotherapy arm [8]. A larger, more rigorous double-blind randomized clinical trial in 2003 enrolled 113 patients and compared 30 mL of antacid monotherapy, antacid with 10 mL of an anticholinergic, and antacid with anticholinergic and 10 mL of 2% viscous lidocaine. Similar to our study, Berman et al found all treatments were clinically effective and there was no difference in pain relief between the three arms [4]. Their conclusion was to recommend antacid monotherapy.

In addition to being a single center study, this clinical trial had several limitations. Enrolment was determined prospectively by the prescribing of an antacid mixture by ED medical staff, rather than based upon a final diagnosis of acute

This article is protected by copyright. All rights reserved

dyspepsia. A final diagnosis of cardiac pathology was made in 14% of enrolled patients; these were spread evenly across the three arms. This subgroup tended to have an increase in pain scores over time and would dilute the efficacy of the antacid mixtures.

The amount of antacid used in the monotherapy arm was 20 mL, compared to 10 mL in the other arms. This was to ensure liquid volumes were equivalent and keep patients and physicians blinded. No studies could be found on dosage response curve for antacids. However 10-20 mL of the study antacid is within therapeutic guidelines for treatment of dyspepsia [9]. A future study might consider using a minimum of 20 mL antacid in each arm.

Nursing staff dispensing the medication were unblinded. However, nursing staff did not collect study data and researchers remained blinded to which medication had been given.

In conclusion, 20 mL dose of antacid alone is no different in analgesic efficacy than a 20 mL mixture of antacid and lidocaine (viscous or solution). Antacid monotherapy was more palatable and acceptable to patients. A change in practice is therefore recommended to cease adding lidocaine to antacid for management of dyspepsia and epigastric pain in the ED.

Accepted Article

This article is protected by copyright. All rights reserved

Accepted Article

References

1. Peter J Kahrilas, M. *Medical management of gastroesophageal reflux disease in adults*. 2018. Available from: https://www.uptodate.com/contents/medical-management-of-gastroesophageal-reflux-disease-in-adults. Last accessed May 4, 2019.

2. Talley, N.J. and N. Vakil, *Guidelines for the management of dyspepsia.* Am J Gastroenterol, 2005. **100**(10): p. 2324-37.

3. Welling, L.R. and W.A. Watson, *The emergency department treatment of dyspepsia with antacids and oral lidocaine.* Ann Emerg Med, 1990. **19**(7): p. 785-8.

4. Berman, D.A., R.S. Porter, and M. Graber, *The GI Cocktail is no more effective than plain liquid antacid: a randomized, double blind clinical trial.* J Emerg Med, 2003. **25**(3): p. 239-244.

5. Gallagher, E.J., et al., *Reliability and validity of a visual analog scale for acute abdominal pain in the ED.* Am J Emerg Med, 2002. **20**(4): p. 287-290.

6. Weberg, R. and A. Berstad, *Symptomatic effect of a low-dose antacid regimen in reflux oesophagitis.* Scand J Gastroenterol, 1989. **24**(4): p. 401-6.

7. Graham, D.Y. and D.J. Patterson, *Double-blind comparison of liquid antacid and placebo in the treatment of symptomatic reflux esophagitis.* Dig Dis Sci, 1983. **28**(6): p. 559-63.

8. Vilke, G.M., et al., *Prospective randomized study of viscous lidocaine versus benzocaine in a GI cocktail for dyspepsia.* J Emerg Med, 2004. **27**(1): p. 7-9.

9. *Gastro-oesophageal reflux*. 2019. Available from: https://tgldcdp.tg.org.au/index. Last accessed June 4, 2019.

This article is protected by copyright. All rights reserved

Table 1. Population characteristics and findings (N = 89)

	Viscous	Solution	Antacid	p-value
Participants, n (%)	30 (34)	31 (35)	28 (31)	
Gender – Female, n (%)	21 (70)	21 (68)	15 (54)	
Age, median (IQR)	43 (32-70)	38 (28-61)	42 (32-72)	
Past Medical History, n (%)				
• Acid-related (gastroesophageal reflux disease/peptic ulcer disease/gastritis)	7 (23)	8 (26)	4 (14)	
• Other gastrointestinal*	4 (13)	2 (6)	6 (21)	
• Other#	17 (57)	16 (52)	15 (54)	
Previous Antacid / Proton Pump Inhibitor Use, n (%)	8 (27)	9 (29)	6 (21)	
Medication Count, median (IQR)	2 (0-4)	1 (0-3)	1 (0-3)	
Pre-hospital medication, n (%)				
• Antacid/Proton Pump Inhibitor	6 (20)	3 (10)	4 (14)	
• Other Analgesia^	9 (30)	10 (32)	8 (29)	
• Other~	7 (23)	6 (19)	8 (29)	
Emergency medication, n (%)				
• Proton Pump Inhibitor	9 (30)	11 (35)	12 (43)	
• Other Analgesia^	19 (63)	13 (42)	13 (46)	
• Other~	11 (37)	7 (23)	12 (43)	
Discharge Diagnosis, n (%)				
• Gastrointestinal	22 (73)	27 (87)	22 (79)	
• Cardiac	5 (17)	2 (7)	3 (11)	
• Otherμ	3 (10)	2 (6)	3 (10)	
Initial VAS Pain Score (mm), median (IQR)	64 (36-81)	65 (31-78)	69 (57-80)	
Change in pain score (mm), t=30 minutes median (IQR)	9 (3-26)	17 (7-27)	20 (7-36)	0.30
Change in pain score (mm), t=60 minutes median (IQR)	21 (3-31)	26 (9-41)	32 (13-42)	0.18
Taste VAS score (mm), median (IQR)	37 (12-62)	29 (15-50)	76 (34-88)	<0.01
Bitterness VAS score (mm), median (IQR)	42 (24-82)	38 (12-55)	82 (66-94)	<0.01
Texture VAS score (mm), median (IQR)	36 (27-78)	52 (32-80)	64 (27-87)	0.26
Overall acceptability VAS score (mm), median (IQR)	50 (32-79)	57 (50-73)	75 (50-89)	0.01

*** other non-acid related gastrointestinal disorders**

 # other past medical history unrelated to the gastrointestinal system

^ other analgesia included acetaminophen, ibuprofen, fentanyl and morphine

~ other medications included glyceryl trinitrate, hyoscine butyl bromide and ondansetron

μ other discharge diagnoses included psychiatric, kidney stones, prostatitis, T12 fracture, vertigo

IQR = interquartile range, VAS = visual analogue scale

This article is protected by copyright. All rights reserved