Running title:

Squeeze bottle versus syringe nasal saline irrigation

TYPE OF ARTICLE: ORIGINAL CONTRIBUTION

Squeeze bottle versus syringe nasal saline irrigation for persistent allergic rhinitis - a randomized controlled trial

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SUMMARY

Background*:* Nasal irrigation is widely used as an adjunctive treatment for allergic rhinitis. There is little evidence regarding the efficacy of the devices used in this procedure. The objective of this study was to evaluate the efficacy of the squeeze bottle nasal saline irrigation in persistent allergic rhinitis patients compared with a syringe.

Methodology/Principal*:* We included patients between 18- and 60-years old presenting with persistent allergic rhinitis. All patients were instructed to perform nasal irrigation twice daily for four weeks. The patients were randomly assigned to use either the squeeze bottle nasal irrigation or a syringe for nasal irrigation. Symptoms score, physical examination results, satisfaction scores and adverse events were collected.

Results*:* There were 116 patients enrolled in the study, 58 of whom used the squeeze bottle nasal irrigation system and 58 of whom used a syringe. During a four-week follow-up, improvements in patients' nasal symptom scores for rhinitis symptoms were significantly greater in the group treated with the squeeze bottle (mean difference = 0.82, p-value = 0.020, 95% CI = 0.12 to 1.51). However, the physical examination score was no statistically significant difference (mean difference = 0.48, p = 0.205, 95% CI = -0.27 to 1.23). No adverse events were reported. The overall satisfaction scores for both devices were excellent.

Conclusions*:* This study supports the regular use of nasal irrigation with a positive-pressure device, particularly a squeeze bottle, as an effective adjunctive treatment for allergic rhinitis. It is effective for reducing allergic rhinitis symptoms and can be used by patients with good compliance and minimal side effects.

Trial registration: ClinicalTrials.gov/NCT02763241.

Key words: allergic rhinitis, irrigation, nasal irrigation

INTRODUCTION

Allergic rhinitis is a common disease in both adult and paediatric group. The symptoms are aggravated when the patients exposed to an allergen such as mite, fungus or cockroaches. Allergic rhinitis symptoms include rhinorrhea, nasal obstruction, nasal itching, and sneezing [1].

Allergic diseases can affect patient's quality of life, decrease the performance and productivity. In the European Union, people with allergies are estimated to have symptoms for an average of 51 working days per year [2]. Current ARIA guidelines recommended nasal saline irrigation as an adjunct therapy to nasal steroids and antihistamine [1].

Nasal saline irrigation is a procedure in which the nasal cavity is rinsed with saline solutions. Saline nasal irrigation can be performed with various devices such as a spray, pump, squeeze bottle, nebuliser, or neti pot. These are available over the counter and can be used as standalone or adjunct treatments [3].

The nasal irrigation can immediately help to unblock the nose by a direct mechanical flush of the secretion [4, 5]. There were some pieces of evidence that the nasal irrigation can also decrease the infective pathogens [6] and inflammatory mediator's load [7, 8] and improve the mucociliary function [9, 10].

According to the recent multicenter survey, large-volume high-pressure devices such as squeeze bottle was more effective than other kinds of device [11]. To our knowledge, there has been no randomized controlled study directly compared each type of nasal irrigation devices. This study was designed to determine if the use of the squeeze bottle nasal saline irrigation adjunct to standard therapy improves nasal symptom score, physical examination score and adverse events in patients with persistent allergic rhinitis compared with syringe irrigation.

MATERIALS AND METHODS

Study design and setting

We conducted a parallel-group, open-label, randomized controlled trial with an equal allocation ratio between January 28, 2016 and January 30, 2018. The patients were recruited from the Otorhinolaryngology Department at Khon Kaen University, Faculty of Medicine's Srinagarind Hospital in Thailand.

Participants

We included patients between 18 and 60 years old presenting with persistent

allergic rhinitis according to ARIA guidelines [1]. Allergic rhinitis was defined as rhinorrhea, nasal obstruction, nasal itching, and sneezing which are reversible either spontaneously or with treatment. Post-nasal drip mainly occurs either with profuse anterior rhinorrhea in allergic rhinitis or without significant anterior rhinorrhea in chronic rhinosinusitis.

Allergic rhinitis is subdivided into "intermittent" and "persistent" disease. Intermittent rhinitis means that the symptoms are present less than four days a week or for less than four consecutive weeks. Persistent rhinitis means that the symptoms are present more than four days a week and for more than four consecutive weeks.

We excluded patients with (a) acute or chronic rhinosinusitis according to EP3OS guideline [12], (b) acute nasopharyngitis (common cold), (c) a tendency to aspirate resulting from causes such as a cerebrovascular accident or craniofacial diseases, and (d) sinonasal, nasopharyngeal, and skull base tumors.

Interventions

We randomly assigned participants to use either the squeeze bottle nasal irrigation or a syringe for nasal irrigation. They were instructed to perform the nasal irrigation twice a day – once in the morning and once in the evening. Both groups were received standard treatment for persistent allergic rhinitis, i.e., intranasal corticosteroid (fluticasone furoate) and oral non-sedative antihistamine (loratadine) for one month.

Squeeze bottle nasal irrigation: This method includes one 250 ml positive pressure squeeze bottle and 60 powdered saline packets. The patient was instructed to dissolve one packet into 250 ml of clean water in the bottle. If possible, the patient was instructed to use sterile, distilled, filtered, or previously boiled water (cooled to lukewarm, room, or body temperature).

Syringe nasal irrigation: The patients were given a 20 ml syringe and 15 pre-mixed 1,000 ml saline solution bottles to be used for one month.

Randomisation

The randomisation list was computer-generated by a statistician based on the block randomisation method with randomly selected block sizes of 2, 4, 6 and 8. The allocation assignment was sealed in opaque, sequentially numbered envelopes.

Because of the nature of the interventions, it was not possible to conceal the

group allocation from the participants and health care providers.

Outcomes

Nasal symptom score

The 10-point visual analogue scale (VAS) was used as suggested by ARIA guidelines [(1)]. Ten indicates that the participant is not bothered at all and zero means that the participant is extremely bothered. Participants' recorded their scores on the VAS daily.

Physical examination score

The modified Lund-Kennedy score was used for nasal assessment. The score has three domains: discharge, inflammation, and polyp [(13)]. The scoring mechanism is as follows: 1) Polyp: 0 – absent; 1 – limited to the middle meatus; 2 – extending to the nasal cavity 2) Mucosa edema: 0 – absent; 1 – mild/moderate edema; 2 – polypoid degeneration 3) Secretion: 0 – absent; 1 – hyaline; 2- thick and/or mucopurulent.

Ease of use, learning curve, and satisfaction scores

A questionnaire was distributed to evaluate the ease of use, learning curve, and satisfaction scores of the nasal irrigation devices. The patients were asked to score each item on a 7-point Likert scale [(14, 15)]. A score of one meant 'strongly disagree' and seven meant 'strongly agree'.

Follow-up

Follow-ups were conducted at one month. The physical examination was assessed at baseline and after one month of continuous use of the nasal irrigation device. The side effects were recorded by the patients in the diary and by the physician at baseline and follow-up.

Ethical consideration

The research protocol was reviewed and approved by the Khon Kaen University Ethics Committee for Human Research (HE581519). Patients eligible for investigation were approached by a research assistant. The patients were given a detailed explanation of the research procedures and possible impacts of the study. Patients who agreed to participate gave written informed consent. This research was

performed in accordance with relevant guidelines/regulations.

Statistical Analysis

The sample size was calculated using the confidence level of 95 percent and power of 90 percent to detect 1 ± 2.5-point difference in VAS score and 10 percent for lost to follow-up. The total sample size of 116 was needed.

Statistical analyses were performed using the SPSS version 20 and Stata version 14. Data were described as either means (for the continuous variables) or frequencies and percentages (for the categorical variables). Significant differences between groups were determined using the Student t-test or the Mann-Whitney U test for continuous variables. The chi-square test or the Fisher-exact test were used to determine whether there was a significant difference between the expected frequencies and the observed frequencies. The repeated measure outcome, i.e., VAS score was analysed using the generalized estimating equation. For all tests, $p < 0.05$ was considered statistically significant.

The intention to treat approach was used for the analysis. All 116 patient's data were used and compared within the groups to which they were allocated. In case of lost to follow-up, the data up to the last follow-up date was used in the analysis [16].

RESULTS

There were 116 patients enrolled in the study, 58 of whom used the squeeze bottle nasal saline irrigation system and 58 of whom used a syringe for irrigation. The participant flow diagram was shown in figure 1.

There were 50 male and 66 female participants, and the average age was 45.29 ± 15.62 years. There was no statistically significant difference in terms of age, sex, severity at baseline, or underlying diseases between the two groups (Table 1).

We first used the independent sample t-test analysis to compare the mean nasal symptom score (range 0-10, higher is better) between two groups at a specific time point i.e. at baseline and day 30. The nasal symptom score at baseline for squeeze bottle and syringe were 3.97 and 3.79 points respectively (mean difference

(MD) 0.17; 95% CI -0.48 to 0.83; p = 0.604). The nasal symptom score at day 30 for squeeze bottle and syringe were 8.02 and 7.17 points respectively (MD 0.85; 95% CI 0.06 to 1.63; p = 0.0035), which was statistically significant (Table 2).

Then, as the patients used the allocated devices at home and recorded their nasal symptom score daily for 30 days. A repeated measure analysis, which accounted for all recorded nasal symptom scores using visual analogue scale (VAS) from day 1 to day 30 using a generalized estimating equation model, found the overall mean difference to be 0.82 points (p-value = 0.020, 95% CI = 0.12 to 1.51), which was statistically significant.

Figure 2 showed the mean VAS scores at each time point for both groups. The VAS scores were increased over time in both groups. The superiority of the squeeze bottle was clear cut at the early phase of treatment and became less prominent in the later phase.

The modified Lund-Kennedy score (lower is better) decreased after treatment in both groups. However, there was no statistically significant difference between groups (mean difference = 0.48, p = 0.205, 95% CI = -0.27 to 1.23).

No patients in this study reported the adverse events such as epistaxis, pain, headache, aspiration or retained fluid in sinuses. Based on the 7-point Likert scale questionnaire, both groups rated their devices as excellent (more than 6; higher is better) for ease of use, learning curve, and satisfaction scores.

DISCUSSION

Nasal irrigation is widely used as an adjunctive treatment for allergic rhinitis. A recent Cochrane's systematic review [17] found that saline irrigation may improve patient-reported disease severity compared with no saline at up to four weeks (SMD = -1.32, 95% CI = -1.84 to -0.81; 407 participants; six studies; low quality) and between four weeks and three months (SMD = -1.44, 95% CI = -2.39 to -0.48; 167 participants; five studies; low quality). Although the evidence was low quality, the SMD values at both time points were considered as indicating a large effect.

Until now, there have been no randomized controlled studies to compare nasal irrigation devices for treatment of allergic rhinitis. According to the recent multicentre survey, regular use of nasal irrigation, particularly with large-volume high-pressure devices such as squeeze bottle was an effective treatment for nasal disease. The subgroup analysis found that allergic rhinitis patients are likely to get more benefit

from large-volume high-pressure devices as indicated by better ease of use, learning curve, and satisfaction score [11].

To our knowledge, this is the first randomized controlled trial to show that a squeezable bottle exhibits greater symptom relief than a disposable syringe for allergic rhinitis patients. In this study, we found a statistically significant difference in nasal symptom score between the two groups, with a mean difference of 0.82 points (p-value = 0.020, 95% CI = 0.12 to 1.51). Furthermore, scores indicating satisfaction, ease of use and learning curve were excellent.

The superiority of the squeeze bottle was clear cut at the early phase of treatment and became less prominent in the later phase. This can be explained by the learning curve of the syringe users that in later stage could hold the syringe in the exact position that was snugly fit and prevented the saline leakage while the squeeze bottle users did not have this problem.

Although the analysis showed a statistical significance of the nasal symptom scores between two groups, it is questionable whether the mean difference of 0.82 points (95% CI = 0.12 to 1.51) was clinical significance or not?

Currently, there was no standard minimal clinically significant difference (MCSD) in VAS nasal symptom score. However, there were some studies of MCSD in VAS pain score. The 95% confidence interval of the MCSD in VAS pain score was ranged between 0.9 to 1.5 point [18, 19].

There was no statistically significant difference in physical signs (mean difference = 0.48, p = 0.205, 95% CI = -0.27 to 1.23). This may be due to the sensitivity of the physical examination tool was not high enough to detect the difference. The modified Lund-Kennedy score was originally designed to evaluate rhinosinusitis patients. Furthermore, in the Cochrane's systematic review of saline irrigation for allergic rhinitis [17], there was only one study from 14 studies that reported the physical examination results [20]. This problem suggested there was a needed for a validated physical examination tool for allergic rhinitis patients.

There were two forms of normal saline in this study. The squeeze bottle group used the dry saline powder in a packet to mix with clean water while the syringe group used premixed saline. This difference may not affect the nasal symptom or physical examination score but may affect the ease of use and satisfaction score of the patients. However, we did not find a statistically significant difference in ease of use and satisfaction score in this study.

From our patient's experience, squeeze bottles can more effectively release the correct volume of solution into the nasal cavity, as the tip of the bottle fits into each nostril resulting in minimal leaking of the irrigated solution. This more effectively clears mucus from the nasal cavity, thereby allowing the sinus ostium to open secretions to be drained from the sinus. The squeeze bottle is easier to hold, and the volume of the irrigated solution can be adjusted by controlling squeezing pressure. For syringe irrigation group, although there were no complaints and the learning curve was rated as excellent. From the evidence in Figure 2, we found that the patients needed about 3 weeks to effectively use the syringe to relief symptom.

CONCLUSIONS

This study supports the regular use of nasal irrigation with a positive-pressure device, particularly a squeezable bottle, as an effective adjunctive treatment for allergic rhinitis. It is effective for reducing allergic rhinitis symptoms and can be used by patients with good compliance and minimal side effects.

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AUTHORSHIP CONTRIBUTION

P.P. conceptualized, designed, and supervised the study, raised funding for the study, performed data analysis, interpreted results, and drafted the manuscript. P.K. and W.R. contributed to participant recruitment, follow-up, and data collection. All authors contributed to the interpretation and discussion of the results, and read and approved the final manuscript

CONFLICT OF INTEREST

The authors declare no conflict interests.

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309 **REFERENCES**

310 1. Bousquet J, Van Cauwenberge P, Khaltaev N, Aria Workshop G, World
311 Health O. Allergic rhinitis and its impact on asthma. The Journal of allergy and
312 clinical immunology. 2001;108(5 Suppl):S147-334.
313 2. Zuberbier T, Lotvall J, Simoens S, Subramanian SV, Church MK. Economic
314 burden of inadequate management of allergic diseases in the European Union: a
315 GA(2) LEN review. Allergy. 2014;69(10):1275-9.
316 3. Chong LY, Head K, Hopkins C, Philpott C, Glew S, Scadding G, et al. Saline
317 irrigation for chronic rhinosinusitis. The Cochrane database of systematic reviews.
318 2016;4:CD011995.
319 4. Karadag A. Nasal saline for acute sinusitis. Pediatrics. 2002;109(1):165.
320 5. Kurtaran H, Karadag A, Catal F, Avci Z. A reappraisal of nasal saline solution
321 use in chronic sinusitis. Chest. 2003;124(5):2036-7; author reply 7-8.
322 6. Piromchai P, Kasemsiri P, Laohasiriwong S, Thanaviratananich S. Chronic
323 rhinosinusitis and emerging treatment options. Int J Gen Med. 2013;6:453-64.
324 7. Ponikau JU, Sherris DA, Kephart GM, Kern EB, Congdon DJ, Adolphson CR,
325 et al. Striking deposition of toxic eosinophil major basic protein in mucus:
326 implications for chronic rhinosinusitis. The Journal of allergy and clinical
327 immunology. 2005;116(2):362-9.
328 8. Georgitis JW. Nasal hyperthermia and simple irrigation for perennial rhinitis.
329 Changes in inflammatory mediators. Chest. 1994;106(5):1487-92.
330 9. Boek WM, Graamans K, Natzijl H, van Rijk PP, Huizing EH. Nasal
331 mucociliary transport: new evidence for a key role of ciliary beat frequency. The
332 Laryngoscope. 2002;112(3):570-3.
333 10. Talbot AR, Herr TM, Parsons DS. Mucociliary clearance and buffered
334 hypertonic saline solution. The Laryngoscope. 1997;107(4):500-3.
335 11. Piromchai P, Puvatanond C, Kirtsreesakul V, Chaiyasate S, Thanaviratananich
336 S. Effectiveness of nasal irrigation devices: a Thai multicentre survey. PeerJ.
337 2019;7:e7000.
338 12. Fokkens W, Lund V, Mullol J. on behalf of the European Position Paper on
339 Rhinosinusitis and Nasal Polyps Group. EP3OS 2012: European position paper on
340 rhinosinusitis and nasal polyps 2012. Rhinology. 2012:1-136.
341 13. Psaltis AJ, Li G, Vaezeafshar R, Cho KS, Hwang PH. Modification of the
342 Lund-Kennedy endoscopic scoring system improves its reliability and correlation
343 with patient-reported outcome measures. The Laryngoscope. 2014;124(10):2216-23.

14. Garavello W, Somigliana E, Acaia B, Gaini L, Pignataro L, Gaini RM. Nasal lavage in pregnant women with seasonal allergic rhinitis: a randomized study. Int Arch Allergy Immunol. 2010;151(2):137-41.
15. Juniper EF, Howland WC, Roberts NB, Thompson AK, King DR. Measuring quality of life in children with rhinoconjunctivitis. The Journal of allergy and clinical immunology. 1998;101(2 Pt 1):163-70.
16. Hollis S, Campbell F. What is meant by intention to treat analysis? Survey of published randomised controlled trials. Bmj. 1999;319(7211):670-4.
17. Head K, Snidvongs K, Glew S, Scadding G, Schilder AG, Philpott C, et al. Saline irrigation for allergic rhinitis. The Cochrane database of systematic reviews. 2018;6:CD012597.
18. Kelly AM. The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. Emerg Med J. 2001;18(3):205-7.
19. Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. Ann Emerg Med. 2001;38(6):633-8.
20. Marchisio P, Varricchio A, Baggi E, Bianchini S, Capasso ME, Torretta S, et al. Hypertonic saline is more effective than normal saline in seasonal allergic rhinitis in children. Int J Immunopathol Pharmacol. 2012;25(3):721-30.

FIGURES

Figure 1. Participant flow diagram

Figure 2. VAS score between groups

TABLES

Table 1. Demographic Data

	Squeeze bottle	**Syringe**	**p-value**
Age	44.83 ± 15.47	45.76 ± 15.88	0.75[a]
Male (female)	22 (36)	28 (30)	0.26[b]
Underlying diseases (percent)			
- Diabetes mellitus	7	1	
- Hypertension	7	2	0.99[c]
- Thyroid diseases	1	1	0.38[c]
Nasal symptom score at baseline	3.97	3.79	0.60[a]
Physical examination score at baseline	2.84	2.66	0.68[a]

a- independent sample t-test; b - Chi-square test; c- Fisher's exact test

401 **Table 2.** Nasal symptom score at baseline and day 30

Nasal symptom score	**Squeeze bottle**	**Syringe**	**Mean difference**	**95% CI (p-value)**
Baseline (0-10)	3.97 ± 1.82	3.79 ± 1.76	0.17	-0.48 to 0.83 (p = 0.604)
Day 30 (0-10)	8.02 ± 1.91	7.17 ± 2.33	0.85	0.06 to 1.63 (p = 0.035)

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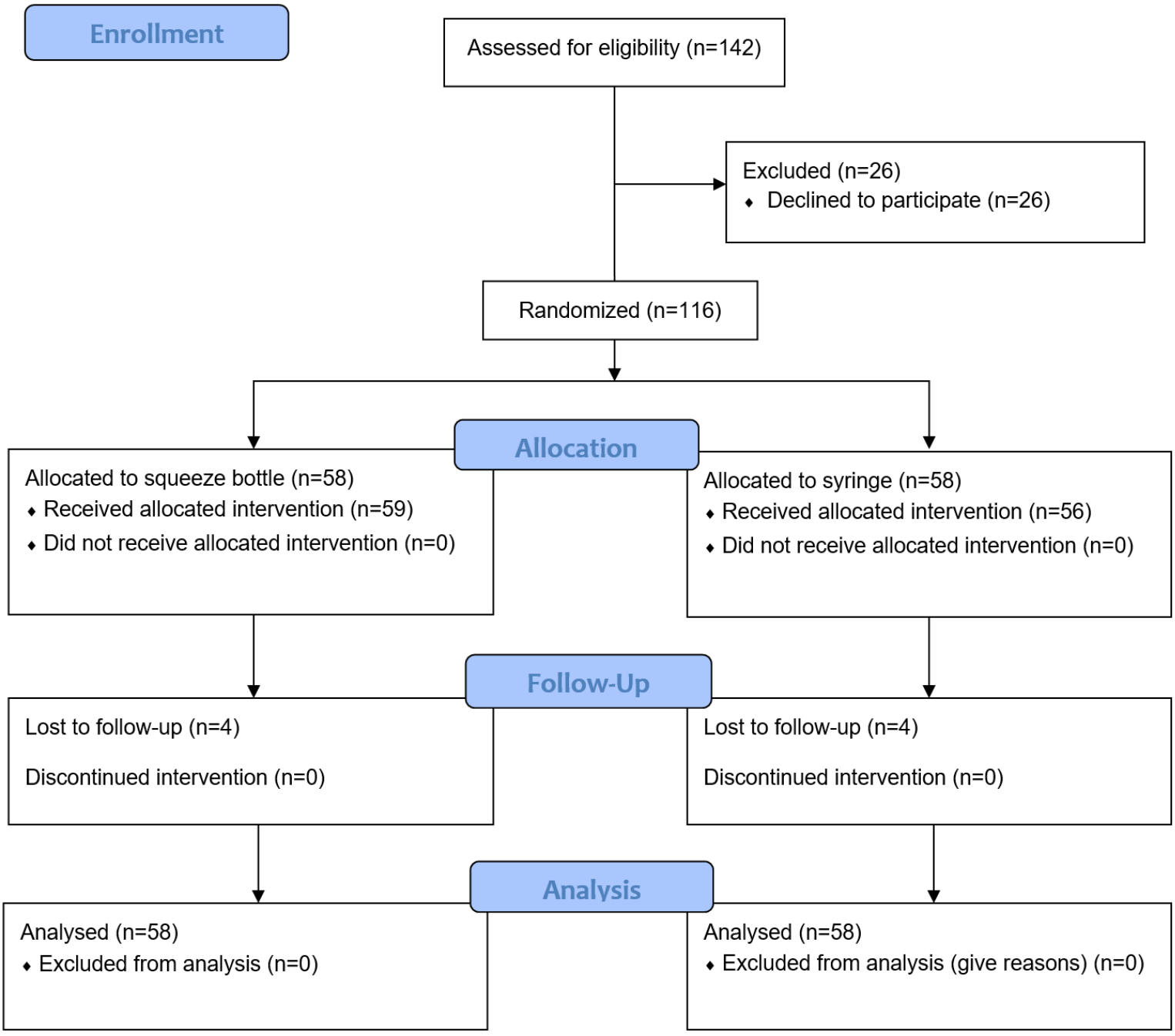
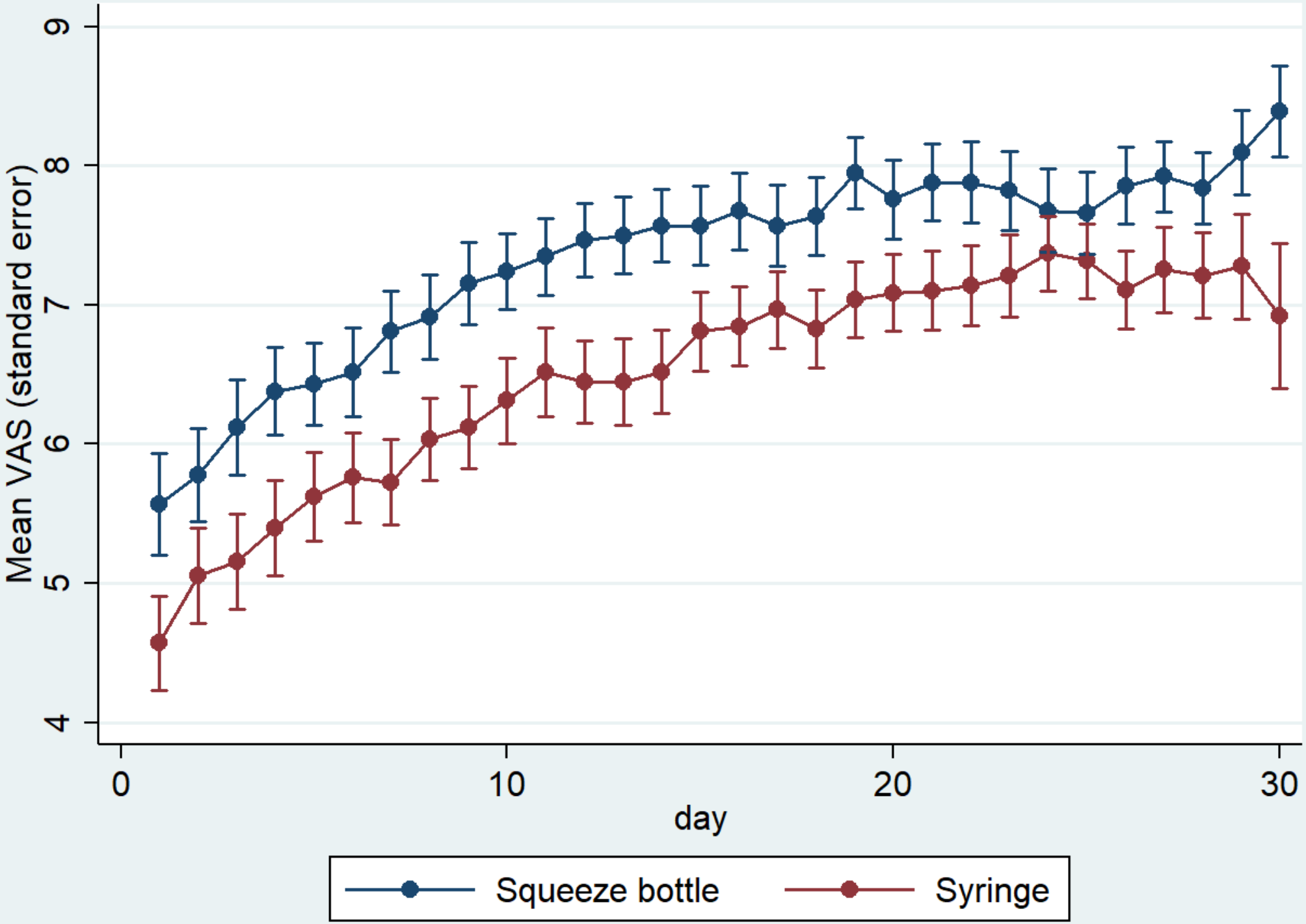

Enrollment
Assessed for eligibility (n=142)
Excluded (n=26)
Declined to participate (n=26)
Randomized (n=116)
Allocation
Allocated to squeeze bottle (n=58)
Received allocated intervention (n=59)
Did not receive allocated intervention (n=0)
Allocated to syringe (n=58)
Received allocated intervention (n=56)
Did not receive allocated intervention (n=0)
Follow-Up
Lost to follow-up (n=4)
Discontinued intervention (n=0)
Lost to follow-up (n=4)
Discontinued intervention (n=0)
Analysis
Analysed (n=58)
Excluded from analysis (n=0)
Analysed (n=58)
Excluded from analysis (give reasons) (n=0)


Mean VAS (standard error)
4
5
6
7
8
9
0
10
20
30
day
Squeeze bottle
Syringe