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Viscous Topical is More Effective than Nebulized Steroid Therapy for Patients with Eosinophilic Esophagitis

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Abstract

We performed a randomized trial to compare nebulized and viscous topical steroid treatments for eosinophilic esophagitis (EoE). Subjects with incident EoE (n=25) received budesonide 1 mg twice daily—either nebulized and then swallowed (NEB) or as an oral viscous slurry (OVB)—for 8 weeks. Baseline eosinophil counts for the NEB and OVB groups were 101 and 83 (P=.62). Post-treatment counts were 89 and 11 (P=.02). The mucosal medication contact time, measured by scintigraphy, was higher for the OVB group than the NEB group (P<.005) and was inversely correlated with eosinophil count (R= −0.67; P=.001). OVB was more effective than NEB in reducing numbers of esophageal eosinophils in patients with EoE. OVB provided a significantly

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Dellon: project conception/design; data acquisition/analysis/interpretation; drafting of the article; critical revision
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higher level of esophageal exposure to the therapeutic agent, which correlated with lower eosinophil counts.

Keywords

Clinical trial; Corticosteroid; esophagus; inflammation

Corticosteroids are a mainstay of therapy for eosinophilic esophagitis (EoE).[1, 2] Rather than using them systemically, they are typically administered as a "topical" preparation; inhaled or nebulized formulations are swallowed to coat the esophagus.[1, 2] This approach was first described in retrospective studies of fluticasone and budesonide.[3–11] More recently, randomized controlled trials (RCT) have confirmed these agents decrease esophageal eosinophilia.[12–1415, 1617–19] However, there are few data comparing the efficacy modes of steroids delivery for treatment of EoE, and the esophageal distribution and duration of contact of swallowed topical steroids is not well described.

We conducted an RCT (see Methods, Supplemental Document 1) to compare two methods of topical steroid delivery in EoE. Subjects with incident EoE received budesonide 1 mg twice daily for 8 weeks either nebulized and then swallowed (NEB), or in oral viscous slurry (OVB). Our primary outcomes were eosinophil counts and dysphagia, as measured by Mayo Dysphagia Questionnaire-30 Day (MDQ). We also used nuclear scintigraphy to assess the effect of mucosal medication contact time on eosinophil counts. The median area under the esophageal emptying curve (AUC) was used to estimate esophageal mucosal contact time of the medication. We hypothesized that the steroid delivery method that resulted in the most prolonged mucosal medication contact would result in the best clinical and histological response.

Of the 34 patients screened, 25 met inclusion criteria, and 22 completed the protocol (Supplemental Figure 1). The mean age of the study subjects was 35 years, 60% were male, 88% were Caucasian; all had dysphagia. The baseline characteristics of the two groups were similar (Supplemental Table 1).

After treatment, eosinophil counts markedly improved in the OVB group but not the NEB group (Table 1). At baseline, maximum eosinophil counts for NEB and OVB were 101 and 83 eos/hpf (p=0.62). Post-treatment, the maximum counts were 89 for NEB and 11 for OVB (p=0.02; Supplemental Figure 2). There were similar trends for the histologic cut-point analysis (Table 1). In contrast to the eosinophil counts, dysphagia symptom scores improved in both groups (Table 1; Supplemental Figure 2), and this improvement persisted after excluding patients who received esophageal dilation at baseline. Additionally, improvement in dysphagia did not correlate with endoscopic or histologic improvement (data not shown).

On nuclear scintigraphy, the AUC was higher for OVB than for NEB, suggesting higher mucosal contact time with OVB (Table 1; Figure 1; Supplemental video). Higher mucosal contact time correlated with the decrease in eosinophil count regardless of treatment type (R=−0.67; p=0.001). Similar results were noted when the proximal, middle, and distal esophagus were analyzed individually (Table 1). The AUCs also inversely correlated with the percent change in eosinophil count at each level, with R=−0.44 (p=0.05), R=−0.49 (p=0.05), and R=−0.55 (p=0.009) for the proximal, mid, and distal esophagus. Patients with a complete histologic response tended to have higher mucosal contact times, regardless of treatment type (Table 1).

Budesonide was well-tolerated. Three patients (14%) had asymptomatic candidal esophagitis on post-treatment endoscopy (Table 1). One patient in NEB withdrew due to

epistaxis. No other local side effects were reported, and no other serious/non-serious adverse events occurred. No patients had adrenal insufficiency by cortisol stimulation testing. No budesonide was detected in the serum after 8 weeks of therapy. No endoscopic complications occurred.

This RCT is the first study comparing two methods of topical steroid delivery for treatment of EoE and the first examining the use of oral viscous budesonide in adults. It also assessed mucosal medication contact time in relation to eosinophil counts, using methodology not previously employed in EoE. We found that OVB was more effective that NEB for decreasing esophageal eosinophil counts, and that increased medication exposure, regardless of the budesonide formulation, was likely the most important determinant of response. The topical, rather than systemic, activity of the medication was further supported by normal post-treatment cortisol stimulation testing and negative serum budesonide levels in all subjects.

Swallowed formulations of topical steroids are popular for the treatment of adults with EoE in the U.S. The use of a viscous solution of budesonide in EoE was first reported by Aceves and colleagues.[10, 11] Placebo-controlled RCTs subsequently confirmed the utility of OVB in children,[17, 19] and those response rates are similar to the results from the OVB group in the present study. RCT data supporting the use of nebulized/swallowed budesonide in adolescents/adults comes from Straumann and colleagues.[18, 20] However, we did not observe the same response in our NEB group. Methodologic differences (length of treatment course; nebulization time) could explain this inconsistency. There have been no prior RCTs comparing different topical steroid agents, and only one case report has addressed this topic.[21] It makes intuitive sense that a swallowed formulation, such as OVB, would be easier to administer than a medication from a metered-dose inhaler or a nebulizer. Though the ideal medication delivery system does not yet exist, several are currently under development,[19, 22] and possibilities could include gels, powders, or dissolving tablets.

The symptom response in our study, with dysphagia improving in both groups, also warrants mention. Poor correlation between symptoms and histologic/endoscopic findings has been frequently reported.[19, 23–27] One reason for this is that no symptom score, including the MDQ, has been validated in EoE.[1] In addition, in our study there were more dilations at baseline in the NEB group than in the OVB group. While this could explain improved symptoms despite ongoing inflammation in the NEB group, an analysis excluding those dilated at baseline did not alter the results. Whether to allow baseline dilation will be an important consideration in future EoE studies that use symptoms as primary outcomes.

This study has limitations. Though the study was open label, potential bias was minimized since both arms knew they were receiving an active agent. While there was no placebo group, the placebo response for both OVB and NEB has been well-described and is low.[17–19] The sample size was small, but the study was adequately powered for the primary outcomes, and the effect size estimates for the power calculations proved to be accurate. Finally, the study was performed at a single center, so generalizability to other populations is unclear. However, the patients included this study fit the typical characteristics of EoE patients reported from other centers.

Several strengths of our study design deserve mention. The randomized controlled trial design is robust, and the histologic assessment was comprehensive. The mechanistic assessment with nuclear scintigraphy corroborated the main results and introduced new quantitative methodology to this area which may guide future drug development. Finally, the safety evaluation confirmed that both forms of budesonide do not cause adrenal insufficiency after 8 weeks.

In conclusion, this randomized, prospective, open-label, clinical trial showed that orally-administered viscous budesonide was more effective than nebulized/swallowed budesonide for improving esophageal eosinophil counts and endoscopic findings in adults with a new diagnosis of EoE. OVB also yielded significantly higher esophageal medication exposure which correlated with lower eosinophil counts regardless of treatment type, implying that the effect of budesonide is local rather than systemic. Therefore, novel delivery systems to optimize mucosal contact time for topical steroids are needed in EoE.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Abbreviations

AUC	area under the curve
EGD	esophagogastroduodenoscopy
EoE	eosinophilic esophagitis
eos/hpf	eosinophils per high-power field
MDQ	Mayo Dysphagia Quesionnaire – 30 day
NEB	nebulized/swallowed budesonide
OVB	oral viscous/swallowed budesonide
PPI	proton-pump inhibitor

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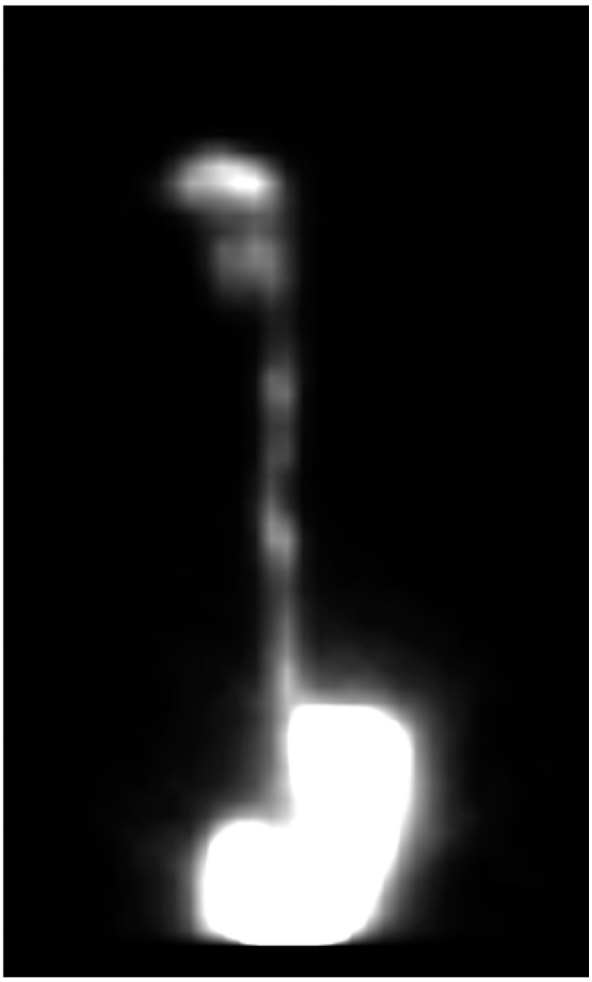
1A

Patient 1:

Patient 2:



1B

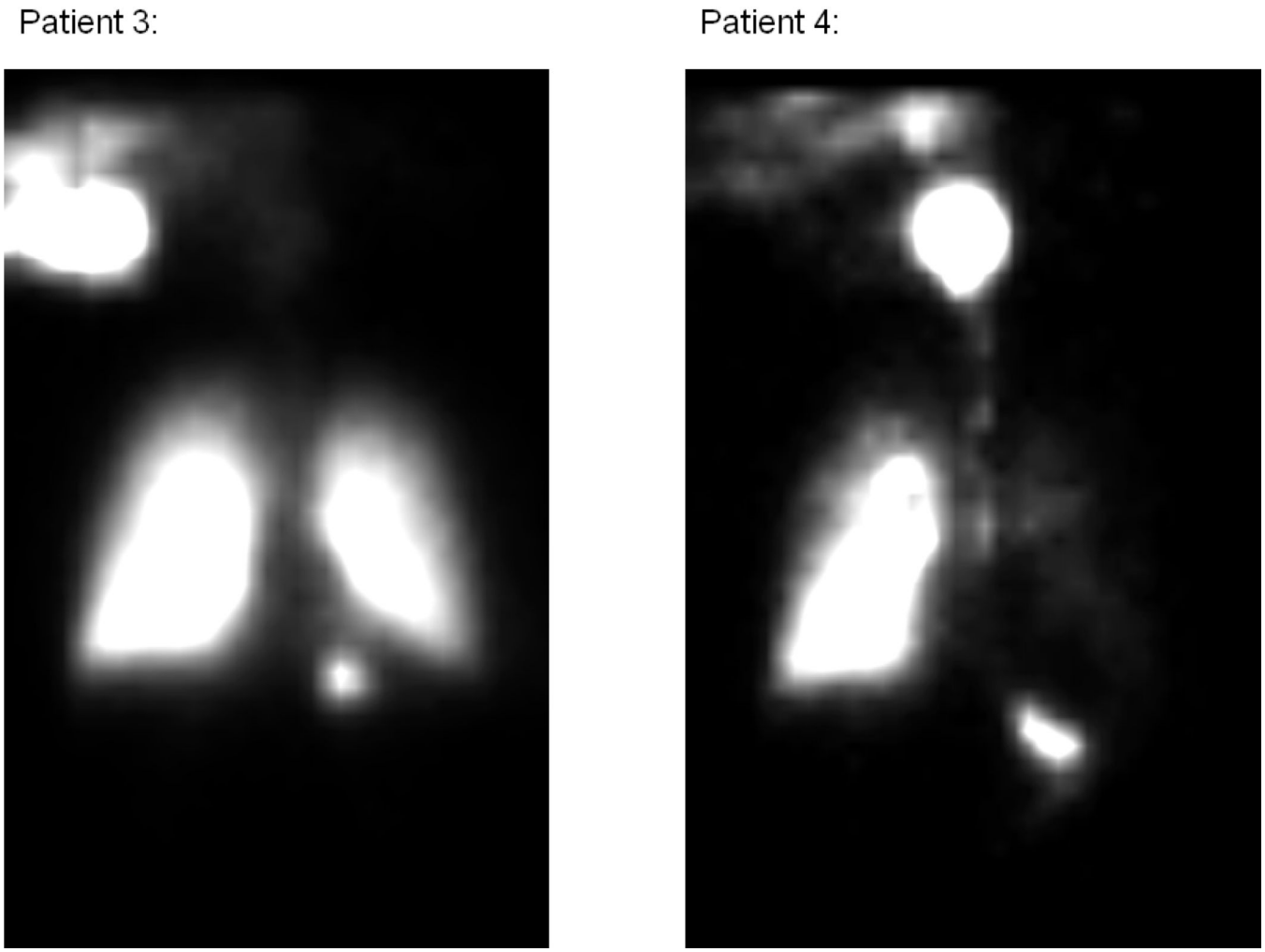


Figure 1.

Illustrative examples of nuclear scintigraphy esophageal emptying scans for the OVB (panel A) and NEB (panel B) groups. These images represent the total distribution of ^{99m}Tc-DTPA tracer throughout the imaging period. Note that for OVB, the medication deposit only in the oropharynx, esophagus and stomach, while for NEB there is also medication deposition in the lungs. In addition, there is qualitatively more deposition in the esophagus and stomach of OVB compared with NEB.

Table 1

Study outcomes

	NEB (n = 11)	OVB (n = 11)	p value
Primary outcomes			
Overall eosinophil counts (eos/hpf ± SD)			
Baseline maximum eosinophil count	101 ± 85	83 ± 89	0.62
Baseline mean eosinophil count	23 ± 20	20 ± 24	0.80
Post-treatment max eosinophil count *	89 ± 94	11 ± 23	0.02
Post-treatment mean eosinophil count *	31 ± 37	3 ± 7	0.02
Maximum eosinophil counts by level (eos/hpf)			
Baseline proximal esophagus	79 ± 73	54 ± 74	0.43
Post-treatment proximal esophagus †	57 ± 78	5 ± 17	0.04
Baseline mid esophagus	41 ± 47	59 ± 98	0.62
Post-treatment mid esophagus ‡	55 ± 57	8 ± 22	0.02
Baseline distal esophagus	54 ± 66	53 ± 49	0.96
Post-treatment distal esophagus #	69 ± 81	11 ± 23	0.03
Symptoms (mean score ± SD)			
Baseline MDQ score	34 ± 21	25 ± 18	0.30
Post-treatment MDQ score **	10 ± 12	16 ± 17	0.31
Secondary outcomes			
Mucosal medication contact time (median)			
Overall esophageal area under the curve	19200	48900	0.005
Proximal esophageal AUC	7300	14400	0.14
Mid esophageal AUC	2800	7800	0.01
Distal esophageal AUC	3800	18100	0.001
AUC with a complete histologic response	61000	65000	0.76
AUC without a complete response ††	19200	34000	0.06
Histologic response (n, %)			
Complete (< 1 eos/hpf)	3 (27)	7 (64)	0.09
Near-complete (< 7 eos/hpf)	4 (36)	8 (73)	0.09
Partial (< 15 eos/hpf)	5 (45)	8 (73)	0.19
Any response (< baseline eos/hpf)	6 (55)	10 (91)	0.06
Post-treatment EGD findings (n, % with finding)			
Rings	10 (91)	4 (36)	0.008
Narrowing	6 (55)	2 (18)	0.08
Stricture	3 (27)	2 (18)	0.61
Linear furrows	6 (55)	4 (36)	0.39
White plaques/exudates	3 (27)	3 (27)	1.0
Pallor/decreased vascularity	2 (18)	0	0.14
Crêpe-paper mucosa	0	0	--
Erosive esophagitis	0	0	--

	NEB (n = 11)	OVB (n = 11)	p value
Dilation performed	4 (26)	3 (27)	0.65/1.0
EGD improved (n, % global assessment)	5 (45)	10 (91)	0.02
Safety outcomes			
Candidal esophagitis (n, %)	1 (9)	2 (18)	0.53
Baseline adrenal insufficiency (n, %)	0	0	--
Post-treatment adrenal insufficiency (n, %)	0	0	--
Post-treatment serum budesonide detected (n, %)	0	0	--
Esophageal perforation (n, %)	0	0	--

* For max eosinophil count comparing baseline to post-treatment, p=0.79 for NEB and p=0.03 for OVB; For mean eosinophil count comparing baseline to post-treatment, p=0.71 for NEB and p=0.03 for OVB

† Comparing baseline to post-treatment for the proximal esophagus, p=0.53 for NEB and p=0.03 for OVB

‡ Comparing baseline to post-treatment for the mid esophagus, p=0.39 for NEB and p=0.01 for OVB

Comparing baseline to post-treatment for the distal esophagus, p=0.42 for NEB and p=0.03 for OVB

** For MDQ score comparing baseline to post-treatment, p=0.002 for NEB and p=0.04 for OVB

†† Comparing those with a complete histologic response to those without a complete histologic response, p=0.43 for NEB and p=0.01 for OVB.