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Is Topical High-Volume Budesonide Sinus Irrigation Safe?

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BACKGROUND

Chronic rhinosinusitis (CRS) is an inflammatory disease affecting the nasal cavity and paranasal sinus mucosa. Corticosteroids are commonly used for CRS medical management in various formulations, including oral steroids and nasal sprays. In recent years, concentrated budesonide respules added to high-volume saline irrigations have also been adopted in the treatment of CRS patients. The dosing of budesonide used in these concentrated irrigations ranges from 0.25 mg to 2 mg per 240 mL saline irrigation, compared to 64 μg to 400 μg per spray in budesonide nasal spray formulations. However, very little high-volume budesonide irrigation is retained in the sinuses. The concern for increased systemic steroid absorption and associated side effects remains an active area of investigation. Given the increasing adoption of this off-label usage and the higher doses of budesonide used, it is important to examine the safety profile of topical high-volume budesonide irrigation.

LITERATURE REVIEW

Although steroids can be associated with an array of side effects, existing studies of the safety profile of high-volume budesonide irrigation have focused on effects on the hypothalamic-pituitary-adrenal (HPA) axis and/or intraocular pressure (IOP).

Prior studies have demonstrated that short-term use of budesonide irrigation does not significantly affect the HPA axis or IOP. In a 2010 prospective study of adult CRS patients with recurrent polyposis, Welch et al. monitored serum cortisol and 24-hour urinary cortisol before and after 6 weeks' use of topical budesonide 0.5 mg/2 mL respule per 240 mL saline twice daily. The 10 patients who completed the study had previously undergone endoscopic sinus surgery (ESS) and had not taken any oral corticosteroids in the 3 months before the study. Average cortisol levels did not decrease after treatment, with average serum cortisol levels of 9.8 ± 5.4 μg/dL at baseline and 12.8 ± 3.5 μg/dL post-treatment. Similarly, urinary cortisol levels did not decrease after treatment.[1]

In a 2008 retrospective study of patients with CRS with nasal polyposis (CRSwNP), Bhalla et al. evaluated pre- and post-treatment cortisol levels in 18 patients, 16 of whom had previously undergone ESS, who received at least 8 weeks of treatment (ranging from 8 to 23 weeks) with budesonide 0.5 mg per 120 mL irrigations twice daily. They found no evidence of HPA axis suppression after therapy. The subgroup of patients who had continued budesonide irrigations for longer than 8 weeks also completed the more sensitive adrenocorticotropic hormone (ACTH) stimulation test; no patients' results suggested HPA axis suppression.[2]

In 2013, Seiberling et al. investigated the effect of budesonide irrigations on IOP for two groups of CRSwNP patients. The first group of 10 patients had already received at least 1 month of treatment (average duration of 6.3 months, ranging from 1 to 22 months) with budesonide 0.25 mg per 240 mL irrigation twice daily. The second group of eight patients had not yet begun budesonide irrigations at the time of study enrollment. In the first group, IOP was normal bilaterally ($\leq$21 mm Hg) at the time of enrollment in nine patients and elevated in one eye of one patient (22 mm Hg). In the second group, IOPs were measured before and after at least 4 weeks (average duration 5.89 weeks) of the same budesonide irrigation regimen. No patient in the second group had an elevated IOP at either time point, and none had a statistically significant change in IOP.[3]

Recently, two studies examined patients using high-volume budesonide rinses for longer treatment periods. Smith et al. performed a 2016 cross-sectional cohort study of 35 post-ESS CRS patients (69% with nasal polyposis) using budesonide 1 mg per 240 mL irrigations twice daily for at least 12 months (mean duration of 38 months, ranging from 15 to 96 months). Eighteen of these patients were also taking inhaled corticosteroids concurrently. Average cortisol levels for the cohort (431.2 nmol/L) were within normal limits. Additional ACTH stimulation testing was performed in the 19 patients with cortisol levels below 500 nmol/L and did not demonstrate results indicative of

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HPA axis suppression. The authors concluded that long-term budesonide irrigation does not cause detectable HPA axis suppression.[4]

In 2016, Soudry et al. studied 48 post-ESS CRS patients who had been treated with long-term (6 to 66 months, mean 22 months) budesonide 0.5 mg per 240 mL once or twice daily irrigations. Thirty-two of the 48 patients were also using other topical steroid formulations (i.e., nasal sprays, pulmonary inhalers, ophthalmic drops). The IOP was tested in 46 patients and was normal in all patients tested. All 48 patients completed the ACTH stimulation test, and 11 patients had abnormally low stimulated cortisol levels. However, these patients did not report symptoms associated with HPA axis suppression. Four of these patients repeated the test after discontinuing budesonide irrigation for 30 days, and stimulated cortisol levels then increased in three of these patients. The remainder of these patients continued budesonide therapy under the supervision of an endocrinologist with no reported complications. Of note, the simultaneous use of two additional topical steroid formulations (nasal sprays and pulmonary inhalers together) was associated with lower stimulated cortisol levels.[5]

BEST PRACTICE

The use of topical high-volume budesonide irrigation does not appear to have a significant effect on IOP and carries a low risk of HPA axis suppression when used long term. Patients who experience HPA axis suppression may be asymptomatic, but may benefit from the supervision of an endocrinologist. Simultaneous use of multiple additional topical steroid formulations appears to be a risk factor for HPA axis suppression. Larger prospective studies are needed to determine the effect of long-term topical high-volume budesonide irrigation on the HPA axis. Furthermore, additional studies in CRS patients without nasal polyposis would be worthwhile, as the majority of patients studied in the above articles had CRSwNP. Lastly, risk factors for HPA axis suppression, such as concomitant use of other steroid formulations, should be further explored.

LEVEL OF EVIDENCE

The studies reviewed above were either prospective or retrospective cohort studies lacking control groups and represent level 4 evidence.

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