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Review Article

Use of intranasal corticosteroids in sinonasal infection and after surgery

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Abstract

The use of intranasal steroids by otolaryngologists in the treatment of patients with infective rhinosinusitis and after endonasal surgery, particularly endoscopic sinus surgery, is unlicensed, as stated in the *British National Formulary* and in the manufacturers' leaflets supplied with nasal steroid medications. However, despite this, nasal steroids continue to be prescribed in these circumstances. Debate continues as to the exact role of intranasal steroids in sinonasal infection and after sinonasal surgery and whether their use in these circumstances should still be unlicensed.

This article reviews the current medical literature regarding this topic and aims to clarify whether intranasal steroid usage in these circumstances should be recommended.

Key words: Rhinitis; Sinusitis; Topical Drug Administration; Endoscopy; Steroid

Introduction

While intranasal steroids are used extensively in ENT practice, their use in rhinosinusitis and after sinonasal surgery is unlicensed, although they are routinely prescribed in these situations. The *British National Formulary* states that they should be avoided in untreated nasal infection and after sinonasal surgery.[1] This advice is reiterated in the information leaflets supplied with intranasal steroids.

We undertook a literature search of the Medline (1950 onwards) and Pubmed (1950 onwards) databases, using the following medical subject heading terms: nasal steroids, rhinosinusitis, nasal surgery, and sinus wound healing. We then reviewed the evidence for the efficacy of intranasal steroids in rhinosinusitis and after sinonasal surgery. We also reviewed any evidence that they might be contraindicated in these situations.

Intranasal steroids

Mechanism of action and pharmacology

Corticosteroids are effective in reducing inflammation by altering protein synthesis. The steroid molecule enters the cytoplasm by passive diffusion, and then attaches to the glucocorticoid receptor, forming a steroid–receptor complex. This complex undergoes a conformational change and enters the nucleus of the cell, where it binds reversibly to specific sites on deoxyribonucleic acid. This binding results in either induction or suppression of the gene transcription product. It is these proteins that are responsible for the effects seen in an inflammatory cascade. These gene products tend to be pro-inflammatory cytokines as well as pro-inflammatory enzymes.

Corticosteroids are produced endogenously and are regulated by negative feedback through the hypothalamo-pituitary-adrenal axis. This axis may be disrupted by systemic steroid administration, in which case steroid side effects may be observed or an Addisonian adrenal crisis precipitated.

The degree to which intranasal steroids are systemically available depends on their absorption profile. The characteristics of intranasal steroids that determine their absorption into the systemic circulation are related to their topical potency, lipid solubility and systemic bioavailability.[2]

Topical potency is assessed by the MacKenzie assay. This assay measures topical vasoconstriction through skin-blanching responses, and also measures the inhibitory action of intranasal steroids on cluster of differentiation four (CD4) glycoprotein cell derived cytokine production. These tests show that the newer generation of intranasal steroids (fluticasone and mometasone) are more potent than the older generation (beclomethasone, budesonide and betamethasone).[2]

The more lipophilic the substance, the faster its uptake by the nasal mucosa, the greater its retention within the tissue and the more enhanced its glucocorticoid receptor binding. All these functions tend to

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be enhanced in the new generation intranasal steroids.[2]

Intranasal steroids are absorbed locally, but most of the dose is swallowed and absorbed across the gut mucosa (Figure 1). Systemic absorption from the nasal mucosa is not subject to the first-pass metabolism which acts on the swallowed portion. Hence, systemic bioavailability is primarily determined by the different degrees of first-pass hepatic metabolism of the swallowed portion of intranasal steroids. Studies have shown that systemic bioavailability is greater with the old generation intranasal steroids, compared with the new generation.[2]

Safety profile

The safety profile of intranasal steroids can be split into their systemic and local adverse effects. The systemic adverse effects are related to the effect on the hypothalamo-pituitary-adrenal axis, as well as the effect on metabolism and ocular function.[2]

Steroids and hypothalamo-pituitary-adrenal axis

The absorbed steroid inhibits the secretion of corticotrophic hormone from the thalamus and so subsequently inhibits the secretion of adrenocorticotrophic hormone from the pituitary gland. As a result of the decreased secretion of these products, secretion of corticosteroids from the adrenal cortex is altered. Thus, the adrenal cortex's normal response to stress and metabolic demands is affected, resulting in adrenal insufficiency syndrome. There are several biochemical tests which are used to measure cortisol levels and hence basal hypothalamo-pituitary-adrenal axis activity, and stimulation tests to assess adrenal reserve function. These tests have been used in various studies to investigate the effect of intranasal steroids on the hypothalamo-pituitary-adrenal axis. Most of the literature indicates that therapeutic doses of intranasal steroids have little or no effect on hypothalamo-pituitary-adrenal axis activity.[2] These studies also showed that once-daily administration of intranasal steroids produces less of an effect on the hypothalamo-pituitary-adrenal axis[2] compared with twice-daily regimes.

There are reported cases of adrenal insufficiency after treatment with intranasal steroids. However, these involved patients treated with older preparations of intranasal steroids, such as dexamethasone nose drops, who tended to be over-compliant with these treatments.[2]

Steroids and metabolism

It is well known that steroid use is associated with suppression of growth and bone metabolism. An

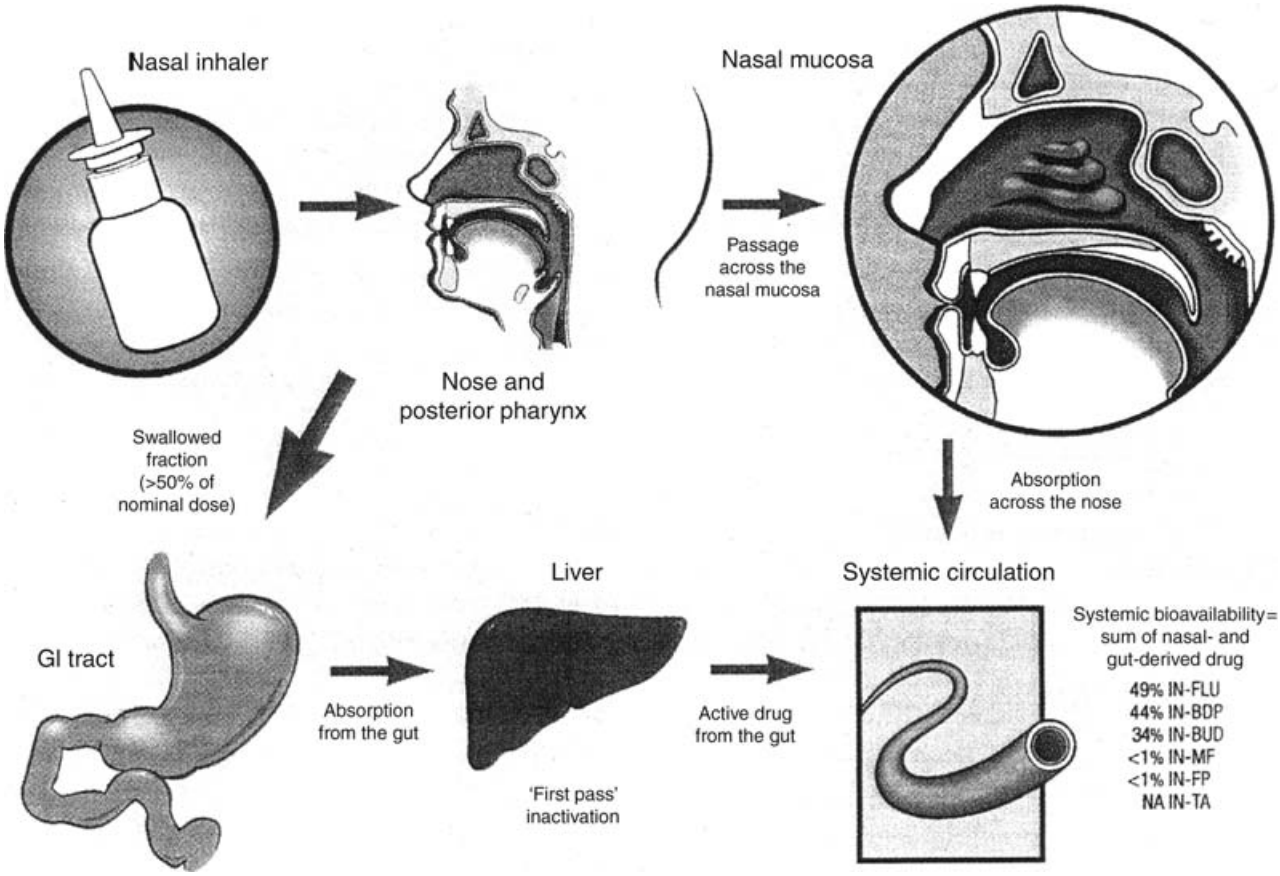

FIG. 1

The fate of intranasal steroids.[3] Reprinted with permission. GI = gastrointestinal; IN = Intranasal; FLU = Flunisolide; BDP = Beclomethasone Dipropionate; BUD = Budesonide; MF = Momentasone Furoate; FP = Flucticasone Propionate; NA = not available; TA = Triamcinolone Acclonide

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increased steroid burden has the potential to impair normal growth by suppressing the release of growth hormone, the activity of insulin-like growth factor one, the expression of growth hormone receptors and the production of collagen. However, studies have shown no effect on growth and final adult height in children treated solely with intranasal steroids.[2]

Steroids and calcium metabolism

Steroids affect bone metabolism by altering both calcium homeostasis and adrenal sex hormone production. Steroids alter osteoblastic and osteoclastic activity, resulting in increased resorption and decreased deposition of bone calcium, subsequently leading to osteoporosis. Steroids also alter sex hormone release, which can affect bone metabolism and so bone mass. Studies have shown that intranasal steroids have no significant effect on bone metabolism.[2]

While long-term oral steroid treatment is associated with ocular changes such as glaucoma and cataracts, intranasal steroids produce no such side effects.[2]

Local adverse effects

There have been reports of local adverse effects of intranasal steroids, involving mucosal atrophy manifesting as epistaxis, dryness and burning discomfort. However, there have been no biopsy confirmed studies of this. There have also been some case reports of septal perforation. Studies have shown that mucosal atrophy does not occur with the newer generation of intranasal steroids currently in use.[2]

Rhinosinusitis

Rhinosinusitis is a clinical diagnosis based largely on a patient's symptom complex. This symptom complex can be divided into major and minor symptoms (see Table I). The diagnosis of rhinosinusitis can be made if the patient's symptom complex contains two major symptoms or one major and two minor symptoms, according to the diagnostic guidelines for rhinosinusitis published in 1997 by the American Academy of Otolaryngology – Head and Neck Surgery.[4] Rhinosinusitis can then be classified chronologically according to the frequency and duration of symptomatic episodes.[5]

TABLE I

DIAGNOSTIC FACTORS FOR RHINOSINUSITIS

Major symptoms
Facial pain or pressure*
Nasal obstruction or blockage
Nasal discharge, purulence or discoloured postnasal drainage
Hyposmia or anosmia
Purulence in nasal cavity on examination
Fever (acute only)†
Minor symptoms
Headache
Fever (all non-acute)
Halitosis
Fatigue
Dental pain
Cough
Ear pain, pressure or fullness

*Facial pain or pressure alone does not constitute a suggestive history for rhinosinusitis in the absence of another major nasal symptom or sign.
†Fever in acute rhinosinusitis alone does not constitute a suggestive history for acute rhinosinusitis in the absence of another major nasal symptom or sign.

Rhinosinusitis comprises a variety of disorders involving inflammatory oedema of the nasal and sinus mucosa, obstruction of the sinus ostia, and impaired mucociliary activity. This may involve a number of causes (bacterial, viral, fungal, allergic, non-allergic, inflammatory, pharmacological, neural, genetic or hormonal).[4]

Bacterial rhinosinusitis occurs when there is retention of mucous secretions in the paranasal sinuses, and these then become infected by opportunistic bacteria present in the nose. Normally, micro-organisms and foreign particles become trapped in the mucociliary apparatus and are propelled out of the paranasal sinuses by the cilia of the nasal and sinus mucosa through the sinus ostia into the nose, into the nasopharynx, and are then swallowed and digested. Hence, the pathogenesis of rhinosinusitis involves an interaction between multiple factors relating to the retention of these infected mucous secretions. These factors could include: anatomical abnormalities of normal sinus drainage; oedema and obstruction of the sinus ostia; abnormalities of the normal mucociliary system; and overproduction of nasal secretions.[6,7]

It has become clear, however, that anatomical variations such as concha bullosa or septal deflections do not result in an increased incidence of rhinosinusitis.

The interaction of these factors can be seen when acute rhinosinusitis occurs after a viral upper respiratory tract infection. The acute viral rhinitis results in oedematous obstruction of the osteomeatal complex and the subsequent retention of mucous secretions. It also results in impaired sinus gas exchange and a negative sinus pressure, favouring aspiration of bacteria from the nose and a hypoxic environment. These infected mucous secretions inhibit normal ciliary function, further impairing the drainage of mucous secretions from the sinuses. They also result in increasing mucosal oedema around the sinus ostia, thus creating a vicious cycle of swelling, pressure and reduced ciliary action.[6]

Once the diagnosis of rhinosinusitis is made, medical treatment is instituted, comprising primary treatment with analgesics and antibiotics. Adjunctive therapies could include topical or oral decongestants, topical or oral corticosteroids, steam inhalation, and saline douches. Topical or oral decongestants are used to improve nasal obstruction symptoms, increase the size of the maxillary ostium and so help facilitate drainage of the infected mucous secretions. Topical or oral corticosteroids work in a similar way, predominately by reducing nasal mucosal inflammation and reducing nasal secretions, thereby increasing drainage of the infected mucous secretions from the sinuses and preventing the overproduction of nasal secretions. Steam and saline help

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to reduce the viscosity of the mucous secretions, thereby aiding their drainage from the sinuses. Mucolytic agents have also been used. There are no solid indications for the use of these adjunctive therapies, but usually at least one is employed. Anecdotally, topical corticosteroids tend to be the commonest adjunctive therapy chosen by otolaryngologists.[5,6–8]

Should medical therapy fail, a computed tomography (CT) scan of the paranasal sinuses is indicated. This may show partial or complete opacification of the paranasal sinuses and individual air cells, indicating disease and infection, as well as delineating their anatomy and that of the osteomeatal complex. A positive CT scan and limited or no success with medical therapy leaves surgery as the only available option to help improve the patient's symptoms. Sinus surgery is now performed endoscopically, following the advent of the fibre-optic scope.[5,6,8]

Very rarely, rhinosinusitis is complicated by: periorbital cellulitis; intracranial extension of the infection with a subdural, epidural or intracerebral abscess; cavernous sinus thrombosis; or osteomyelitis. These complications are now very rare as a result of the introduction of antibiotics. There is no evidence that the use of intranasal steroids increases their incidence.[5,9–18]

Use of intranasal steroids in rhinosinusitis

There have been several type one evidence trials of the use of intranasal steroids in rhinosinusitis which showed a statistically significant benefit both in acute and chronic rhinosinusitis.[9–19] Intranasal steroids were found to improve the chances of resolution, shorten the episode and reduce the need for surgery.[9–19]

Despite this evidence, intranasal steroids remain unlicensed for use in these circumstances, as their use may result in a theoretical increase in the incidence of adverse effects. It is possible that, in the presence of rhinosinusitis, there is increased local absorption of steroids from the inflamed nasal mucosa due to its increased blood perfusion. It is also possible that intranasal steroids may exert an immunosuppressive effect, allowing organisms to grow unchecked, with a theoretical risk of increased infective complications, as discussed above.

Nayak *et al.* reported a multicentre, double-blind, randomised, controlled trial in which patients with CT-confirmed rhinosinusitis were given oral antibiotics and adjuvant therapy in the form of placebo, 200 μg mometasone furoate nasal spray or 400 μg mometasone furoate nasal spray. These authors also performed hypothalamo-pituitary-adrenal testing, in the form of pre- and post-cosyntrophin stimulation cortisol concentrations, in a subset of these patients. These tests showed no clinically relevant decreases in mean basal or stimulated plasma cortisol levels in any treatment group. There were also no statistically significant differences in pre- and post-stimulation cortisol values between the groups. This means that both dosages of mometasone furoate nasal spray were well tolerated; the plasma cortisol response to cosyntrophin stimulation indicated that there was no suppressive effect on the hypothalamo-pituitary-adrenal axis. These findings are consistent with data from clinical trials dealing with mometasone furoate nasal spray use in the treatment of allergic rhinitis, which showed lack of both hypothalamo-pituitary-adrenal axis suppression and childhood growth suppression. Nayak and colleagues' trial dealt with a large number of cases (864 to be exact), although the number in which the hypothalamo-pituitary-adrenal axis was assessed was not reported.[17]

Lund *et al.* and Parikh *et al.* have both stated that there is no increase in the incidence of infection in patients treated with topical corticosteroids.[13,18] However, only the former report was of a large enough power to carry any conviction;[13] the power of the latter report was small.[18]

Meltzer *et al.* also showed this in an indirect fashion.[19] This paper reported a large, placebo-controlled, double-blinded, randomised, controlled trial that set out to assess the efficacy of mometasone furoate nasal spray monotherapy, compared with combination therapy with oral amoxicillin and placebo nasal spray, in the treatment of acute, untreated rhinosinusitis. A statistically significant difference was found between the two treatments, with mometasone furoate nasal spray performing better than the combination therapy in terms of symptom scores and resolution period, without any predisposition to bacterial infection and recurrence or exacerbation of rhinosinusitis. Only minor adverse effects were seen in this trial, and there was no statistically significant difference between the mometasone furoate spray and placebo spray groups.

The theoretical possibility of a change in sinus flora following topical steroid use was investigated directly in a paper by Nadel *et al.*[20] This study used endoscopically guided sinus cultures to assess if there were any differences between patients receiving and not receiving topical steroids. The authors found no significant differences between patients who did and did not use intranasal steroids. This study was also of a sufficient power to state this observation with conviction. However, the authors did not deal with the possibility of a time-related change in the sinus flora in patients receiving topical nasal steroids.

Norlander and colleagues' animal-based study of systemic steroids in induced sinusitis, using rabbit models, indicated (to a degree) how topical nasal steroids may be of benefit in rhinosinusitis.[21] This study showed that the administration of corticosteroids could reduce morbidity if host inflammation, rather than the harmful products of an infectious agent, was the primary reason for tissue damage. In rhinosinusitis, the inflammation and oedema of the nasal mucosa and collections of sinus secretions lead to progression of the disease; hence, corticosteroids would be of benefit.

The minor local adverse effects of intranasal steroids described earlier are mentioned in several

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papers. However, the incidences of these minor side effects are not increased when compared with intranasal steroid use in cases of allergic rhinitis, or when compared with the use of a placebo.[17,19]

There are also a few case reports regarding complications of intranasal steroids used in rhinosinusitis, in terms of adverse systemic effects. Such events, however, are rare and mainly involve the use of older generation intranasal steroids (which tend to have a higher bioavailability than the newer compounds) and overcompliance by patients.

Endoscopic sinus surgery

Endoscopic sinus surgery (ESS) is considered the final option available in the treatment of chronic rhinosinusitis. This treatment option is only considered when institution of maximal medical therapy has been unsuccessful in resolving the patient's infection. Sinus surgery is also used in treating nasal polyposis that cannot be controlled medically.[22]

In the post-operative stage of sinus surgery, clinicians often use nasal irrigations (e.g. saline) to aid wound healing by helping to wash away crusts and clots. Frequent post-operative cleaning of any undue granulation tissue, crusts and clots, in the outpatient clinic, has been said to aid proper wound healing and prevent adhesion formation. However, this is not now commonly performed by most clinicians, in view of the lack of evidence of benefit from such a time-consuming task. Many clinicians do, however, prescribe intranasal steroids for post-operative sinus surgery patients, as well as antibiotics.

The main aim in using intranasal steroids is to minimise post-operative oedema and ostial obstruction and to prevent excessive granulation tissue and scar tissue (*vide infra*).[22]

Use of intranasal steroids after sinonasal surgery

The beneficial effect of steroids post-operatively has been demonstrated in a number of animal studies.[21,23] These studies have helped to define the four overlapping phases of wound healing in the paranasal sinuses.

The first phase, during days one to 10, is characterised by blood crusts covering the whole wound. There is no change in the residual mucosa underneath these crusts for the first two to three days. Subsequently, however, there is granulation tissue formation and oedematous swelling, which becomes more marked during the second phase of wound healing. The second phase of wound healing, known as the phase of obstructive lymphoedema, occurs up to day 30. The oedematous swelling of the residual mucosa eventually regresses spontaneously and the wound enters the third phase, the phase of mesenchymal growth. This occurs for up to three months and involves mucosal reorganisation below the regenerated epithelial covering. Finally, the wound enters the fourth phase of healing, the phase of scarification. This occurs three months after surgery and is usually the time at which the reorganisation of tissue in the area of surgery has nearly finished. Notably, however, subepithelial mucosal changes have been demonstrated to occur for more than six months after sinus surgery.[21,23–26]

Nowadays, mucosa-sparing techniques are used to minimise the above sequence.

Infection, with additional destruction of the mucosa, or excessive granulation has been shown to slow down the epithelialisation stage of the third phase of sinus wound healing.[25] Based on these observations, the post-operative use of steroids after sinus surgery has been recommended in order to decrease post-operative granulations, oedema and swelling.

Systemic and local steroid applications in animal sinus surgery models have been shown to aid in the acceleration of wound healing by reducing the mucosal oedema seen in the second phase of wound healing, reducing the formation of granulation tissue and accelerating the late phases of epithelial wound closure.[23–26]

Given the benefits mentioned above, steroid usage in the post-operative management of sinus surgery patients is likely to improve and maintain the operative result obtained.

In the small number of prospective, randomised, controlled trials that have been conducted, systemic and local steroid use has been proven to be both subjectively and objectively beneficial in the post-operative care of ESS patients and in the prevention of recurrent nasal polyps.[27] None of these trials have reported any significant increase in complications as the result of steroid usage.

Long term post-operative use of intranasal steroids is helpful in preventing recurrent polyposis.[14] It is not associated with any increased risk of complications.

Mostafa alone found an increased risk of post-operative infection with intranasal steroid use.[28] Subsequently, however, this finding was refuted by Bross-Soriano *et al.*, Rowe-Jones and Mackay, and Rowe-Jones *et al.*[29–31]

Mostafa conducted a randomised, controlled trial of the post-operative use of beclomethasone and fluticasone nasal spray in endoscopic polypectomy cases after healing of the nasal cavities was completed in roughly four to six weeks.[28] A statistically significant increase was found in the incidence of post-operative infection in the surgical cavities of patients treated with fluticasone nasal spray, but not of those treated with beclomethasone spray. Mostafa attributed the increase in post-operative infection in the fluticasone group to the increased potency of this compound compared with beclomethasone.

Bross-Soriano *et al.* sought to confirm this possible increase in post-operative infection with intranasal steroid use in cases of endoscopic polypectomy.[29] They compared saline lavage alone with fluticasone nasal spray and saline lavage, and with beclomethasone nasal spray and saline lavage. However, the post-operative stage at which these treatments were instituted was not stated. This trial involved more patients than did Mostafa's. It showed that the use

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of beclomethasone or fluticasone nasal sprays was not associated with any increase in the prevalence of post-operative infection.[28,29]

Rowe-Jones and Mackay, and Rowe-Jones *et al.* compared placebo with fluticasone nasal spray in post-operative patients undergoing ESS and endoscopic polypectomy. The trial involved the institution of intranasal steroids six weeks after surgery and had a long, five-year follow-up period. These authors found no significant increase in post-operative infection amongst sinus surgery patients using fluticasone nasal spray.[30,31]

These studies showed that post-operative intranasal steroid use in ESS cases was not associated with an increase in post-operative infection, contrary to previous opinion. However, intranasal steroids were possibly used at the wrong stage of the wound healing process; in such circumstances, the maximum benefit of intranasal steroid use is likely to be in the second phase of nasal and sinus wound healing, roughly 10 days after surgery. Such earlier institution of post-operative intranasal steroid therapy may still result in an increase in the incidence of post-operative infection.

The possible systemic side effects arising from intranasal steroid use in these circumstances have yet to be investigated. However, there are no case reports in the literature of any adverse systemic effects of intranasal steroids use in post-operative ESS cases.

Conclusion

This literature review suggests that the use of intranasal steroids in sinonasal infection and following sinonasal surgery is justified, despite being currently an unlicensed usage. While further clinical studies are needed to answer the points mentioned above, a case can be made for licensing the use of intranasal steroids in cases of sinonasal infection and following sinonasal surgery. Such studies should address the possible time-related change in the sinus flora with intranasal steroid usage in rhinosinusitis, and the possible adverse effects of intranasal steroid usage at its most beneficial point after ESS, roughly seven to 10 days after the procedure.

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