An Update on the Role of Topical Metronidazole in Rosacea

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ABSTRACT

Topical metronidazole (Noritate® 1% Cream, Dermik; MetroCream™ 0.75% Cream, MetroLotion® 0.75% Lotion, Metrogel® 0.75% and 1% Topical Gel, Galderma) has been used for the treatment of rosacea for over 30 years. Several placebo-controlled trials have demonstrated its effectiveness in the treatment of moderate-to-severe rosacea. It is also effective in preventing relapses of disease and is well tolerated by most patients. A growing number of formulations are available.

Key Words: rosacea, metronidazole, antibiotic, anti-inflammatory

Rosacea is one of the most common conditions seen by dermatologists. Its etiology and pathogenesis are unknown despite its high prevalence. Topical metronidazole, which was first reported to be effective in the treatment of rosacea in 1983, remains a cornerstone of therapy. Although the use of metronidazole in the treatment of rosacea has been reviewed previously, continued research has prompted this updated review.

Mechanism of Action

The mechanism of action of metronidazole in the treatment of rosacea is unclear. The efficacy of this broad spectrum antibiotic has been attributed to its antimicrobial and anti-inflammatory effects. In vitro studies have shown that metronidazole interferes with neutrophil release of reactive oxygen species that cause tissue injury at sites of inflammation. This antioxidant activity may be the basis of its anti-inflammatory effect in rosacea.

Pharmacokinetics

Metronidazole is poorly absorbed after topical application, with either undetectable or trace serum concentrations reported after topical use. Based on pharmacokinetic data on the original 0.75% gel formulation, it was originally thought that the optimal application frequency should be twice daily. More recent research has shown that metronidazole is degraded into active metabolites that may prolong the clinical efficacy of the parent drug.

Placebo-Controlled Trials

Metronidazole has been shown to be effective for the treatment of moderate-to-severe rosacea in a number of placebo-controlled trials (Table 1). In a recent trial comparing metronidazole 1% gel, 1% cream, and gel vehicle applied once daily for 10 weeks, the efficacy of the 1% gel was at least that of the 1% cream and superior to the gel vehicle.
**Comparative Trials With Other Rosacea Treatments**

A number of studies have compared topical metronidazole with other treatment options for rosacea. These are summarized in Table 2.

Regardless of the formulation, studies have shown a significant reduction of papulopustular lesions and erythema scores compared with placebo. Although most studies have not shown improvement of telangiectasias, Tan, et al. reported a significant reduction in the telangiectasia score in patients with moderate-to-severe rosacea using metronidazole 1% cream with sunscreen SPF 15 (Rosasol®, Steifel Canada) for 12 weeks.12 In their review of randomized controlled trials of patients with moderate-to-severe rosacea in the Cochrane Database of Systemic Reviews, van Zuuren, et al. concluded that topical metronidazole is more effective than placebo, but that the quality of studies evaluating rosacea treatments was generally poor, and that good randomized controlled trials that include quality of life assessments are needed.14

**Comparative Trials Between Different Formulations of Metronidazole**

Metronidazole is currently available in a variety of formulations, and comparative studies have shown equal efficacy. In a study comparing commercially available products, significant differences were observed in terms of efficacy and adverse effects. Here is a summary of the studies:

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Study Design</th>
<th>Frequency and Duration</th>
<th>Number of Patients</th>
<th>Percent Reduction in Lesion Count vs. Placebo**</th>
<th>Significant Reduction in Erythema</th>
<th>Adverse Effects</th>
<th>Onset of Efficacy (Weeks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metronidazole 0.75% gel</td>
<td>R, SF, DB</td>
<td>b.i.d. 9 wks</td>
<td>47</td>
<td>51 vs. 4</td>
<td>Yes</td>
<td>None</td>
<td>3</td>
</tr>
<tr>
<td>Aronson, et al.5</td>
<td></td>
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<tr>
<td>Metronidazole 0.75% gel</td>
<td>R, SF, DB</td>
<td>b.i.d. 9 wks</td>
<td>40</td>
<td>65 vs. 15</td>
<td>Yes</td>
<td>None</td>
<td>3</td>
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<tr>
<td>Bleicher, et al.7</td>
<td></td>
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<tr>
<td>Metronidazole 1% gel</td>
<td>R, PG, SB, 1% gel vs. 1% cream vs. gel vehicle</td>
<td>q.d. 10 wks</td>
<td>&gt;1200 total</td>
<td>67 (1% gel) vs. 58 (1% cream) vs. 46 (gel vehicle)</td>
<td>3% (1% gel), 4% (1% cream and gel vehicle)</td>
<td></td>
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<tr>
<td>Beutner, et al.8</td>
<td></td>
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<tr>
<td>Metronidazole 0.75% cream</td>
<td>R, PG, DB</td>
<td>b.i.d. 12 wks</td>
<td>143 total</td>
<td>62.5 vs. 43</td>
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<td></td>
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<tr>
<td>Drake, et al.9</td>
<td></td>
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<tr>
<td>Metronidazole 1% cream</td>
<td>R, PG, DB</td>
<td>q.d. 10 wks</td>
<td>89</td>
<td>53 vs. 17</td>
<td>Yes</td>
<td>2% had adverse skin effects</td>
<td>2-4</td>
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<tr>
<td>Breneman, et al.10</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Metronidazole 1% cream</td>
<td>R, PG, DB</td>
<td>q.d. vs. b.i.d. vs. P, 10 wks</td>
<td>277 total</td>
<td>58 vs. 30 (q.d.), 58 vs. 40 (b.i.d.)</td>
<td>Significant only for q.d. application</td>
<td>3 application site reactions</td>
<td>4</td>
</tr>
<tr>
<td>Jorizzo, et al.11</td>
<td></td>
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<tr>
<td>Metronidazole 1% cream with Sunscreen</td>
<td>R, PG, DB</td>
<td>b.i.d. 12 wks</td>
<td>61</td>
<td>65 vs. 25</td>
<td>Yes</td>
<td>Mild application site reactions</td>
<td>4</td>
</tr>
<tr>
<td>Tan, et al.12</td>
<td></td>
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</tr>
<tr>
<td>Metronidazole 0.75% lotion</td>
<td>R, PG, DB</td>
<td>b.i.d. 12 wks</td>
<td>65</td>
<td>57 vs. 27</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Breneman, et al.13</td>
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*Table 1: Placebo-controlled trials of metronidazole for rosacea*

R=randomized, SF=split-face, PG=parallel group, DB=double-blind, SB=single-blind, P=Placebo

* table includes studies using commercially available products

** all changes in lesion count were significant compared with placebo
available formulations of both metronidazole 0.75% and 1% cream, applied once daily for 12 weeks for the treatment of moderate-to-severe rosacea, both were equally effective.  

Remission and Relapse

In a study of patients who achieved remission of rosacea with the use of systemic tetracycline, two thirds relapsed within 6 months of treatment cessation. 

Nielsen reported that metronidazole 1% cream applied daily or every other day is at least as effective in preventing relapses as tetracycline 250mg taken twice daily. In a more recent study, metronidazole 0.75% gel applied twice daily maintained remission compared with vehicle after successful treatment with a combination of metronidazole gel and oral tetracycline.

Adverse Effects

Metronidazole is generally well tolerated, with adverse events reported in less than 5% of patients. Local reactions include dryness, redness, pruritus, aggravation of acne or rosacea, burning, and stinging. True allergic contact dermatitis is rare.

Conclusion

Topical metronidazole remains a cornerstone in the treatment of rosacea. Several placebo-controlled trials have confirmed its ability to reduce both inflammatory lesions and erythema. Daily dosing has been shown to be effective in numerous clinical trials. As well, metronidazole is effective in preventing relapses of rosacea.

References


20. Torok HM, Webster G, Dunlap FE, Egan N, Jarratt M, Stewart D. Combination sodium sulfacetamide 10% and sulfur 5% cream with sunscreens versus metronidazole 0.75% cream for rosacea. Cutis 75(6):357-63 (2005 Jun).


The nose is one of the most challenging anatomic facial areas for the reconstructive surgeon to achieve an optimal, esthetic, and functional result. When large skin areas are missing on the nose and those areas extend to cartilage, the forehead flap provides ample skin, which matches the missing skin in both texture and thickness. Although this flap is relatively simple in concept, we have found that following certain principles will result in an optimal cosmetic and functional outcome. We will describe our most commonly used forehead flap technique.

History
Reconstruction of the nose using distant pedicle flaps has been done for centuries, even before local or general anesthesia existed. Initially in the West (meaning Europe) the favored method was the Tagliacozzi flap described around 1600 in Italy. This flap raised a pedicle on the inner arm, which was used to reconstruct the nose. It became known as the Italian flap. In contradistinction, the Indian flap was popularized in the early 19th century by the English, who learned it during their occupation of India. This latter method used the mid-forehead for nasal reconstruction and the donor forehead wound was allowed to heal by second intention. The modern forehead flap is a refinement of the Indian flap and was popularized in the US by Kanzanjian.

Patient Assessment
As for any surgical procedure, the patient’s medical status should be assessed preoperatively. Most importantly for the forehead flap procedure, the patient’s likelihood of bleeding should be determined and a history of excessive bleeding with previous surgical procedures should be noted. If the patient is anticoagulated, some thought needs to be given to how to minimize bleeding during and after the procedure. Usually we have the patient discontinue aspirin 10 days prior to a forehead flap procedure. Coumadin can be continued, but the patient’s international normalized ratio (INR) should be within therapeutic range.

Another important preoperative issue to determine is whether the patient is a current smoker and how much the patient smokes. If the patient is a heavy smoker (two or more packs per day), he or she should be encouraged to stop smoking or at least cut down to less than one pack per day following the procedure. Also, the surgeon may wish to create a wide pedicle for the forehead flap to ensure adequate blood flow in a patient who is a heavy smoker.

The donor area of a forehead flap is the central forehead. If the patient has a “low forehead” (meaning there is a relatively short vertical distance between the anterior hairline and the eyebrows), there is less available donor hairless skin than in a patient with a high balking forehead. If the patient’s forehead is very low, a forehead flap may not be the optimal procedure to repair a nasal defect.

The physician should discuss with the patient the extent of a forehead flap procedure and the fact that it will require at least two surgical procedures, which will not be completed for at least 4-8 weeks. Some patients may prefer a simpler procedure for wound closure (e.g., skin graft) even though the ultimate cosmetic result may be less than optimal.

ABSTRACT
The forehead flap is a useful technique to reconstruct deep and large nasal defects. It can safely be performed under local anesthesia in an outpatient setting. Advantages of this flap include the fact that it provides an excellent color and texture match to the missing nasal skin. Disadvantages include the fact that it is at least a two-stage procedure and that often patients require “touch up” surgeries to provide the best possible cosmetic outcome.

Key Words: forehead flap, nasal defects
Wound Assessment

Every nasal wound is different and every nose is different. In planning reconstruction of a nose defect, one needs to be cognizant of these two parameters (e.g., Figure 1). If the defect extends from the nose onto the cheek, perhaps the cheek defect is best repaired before planning the forehead flap. If the defect extends full thickness through the ala, a greater flap length from the forehead needs to be obtained than that necessary if a full thickness defect does not exist. Sometimes it may be preferable to consider enlarging a nasal defect to include a whole esthetic unit prior to flap design. Such enlargement will help camouflage the subsequent forehead flap, because one skin type instead of two will cover one esthetic unit.

Technique

Making the Template

We cut a Telfa® pad to create precisely the pattern of the wound shape. This Telfa® template is then rotated 180° and placed on the midforehead just inferior to the hairline. The outer perimeter of the template is traced on the forehead skin using gentian violet (Figure 2). In addition we mark, with gentian violet, the lateral vertical borders of the flap pedicle, which extends from the marked template to just above the eyebrows. Generally, the pedicle width is roughly the distance between the medial eyebrows.

Estimating Flap Length

We use a piece of gauze to estimate the pedicle flap length necessary, so that upon rotation, the distal flap end will reach the more distal nasal defect. We place one end of the gauze, which is stretched to the flap length, in the glabella just above the eyebrows and the other end on the midforehead near the hairline at the superior side of the previously marked donor site (Figure 3). While keeping the gauze on the glabella set as a pivot point, we rotate the superior end of the gauze over the forehead 180° to the distal end of the nasal recipient wound. If the stretched gauze length is insufficient for wound closure after rotation, one may need to laterally angulate the superior forehead donor site to provide adequate flap length. If so, the Telfa® template of the wound is used to mark a new donor site, which is then, in turn, checked again using stretched gauze to confirm adequate pedicle flap length.
Cutting the Flap

The flap is cut along the previously marked lines down to the underlying fascia (Figure 4). It is unnecessary to incise all the way to the periosteum. As one extends the pedicle incision inferiorly to just above the eyebrow area, the incision is carried superficially just beneath the dermis at first. Then, using tenotomy scissors, the subcutaneous tissue underneath the superficial incision is carefully separated so as not to transect the supratrochlear arteries. The flap and the donor site wound edges are then undermined, bleeding is stopped using biterminal electrocoagulation, and the flap is rotated 180°.

Suturing the Flap

The donor portion of the flap end is thinned, if necessary, to conform to the depth of the recipient wound. If underlying aponeurosis from the superior forehead is present, it is best to trim it off; if left, the aponeurosis will prevent vascularization of the flap from the wound below. This vascularization might be critical for flap survival. The recipient nasal wound edges are undermined and verticalized by trimming excess subcutaneous tissue. The first stitch placed is a buried 4-0 Vicryl® (polyglactic 910) suture from the most proximal portion of the nasal wound to the underside of the flap. This suture anchors the flap in its proper position. A few more buried anchoring sutures may be necessary to further anchor the flap to different nasal contours. The flap wound edges are then apposed to the recipient wound edges using 5-0 Vicryl® and 5-0 Prolene® (polypropylene) sutures. The donor site wound edges are also sutured closed in a vertical direction down the center of the forehead (Figure 5). Care must be taken at this point to ensure that all bleeding vessels are electrocoagulated in the exposed flap pedicle.

Dressing

Sutured wounds on the nose and forehead are dressed with antibiotic ointment, Telfa®, gauze, and tape. Three additional special aspects of forehead flap dressing include:

1) Vaseline® gauze is placed on the open pedicle to maintain its moisture.
2) Gauze is opened and fluffed, then placed along the sides of the nose and taped into place.
3) A nasal packing is inserted into one or both nostrils if necessary.

The fluffed gauze is used to catch any bleeding that may occur during the first 24 hours after the procedure. The nasal packing is created by cutting a finger from a surgeon’s glove. The cut glove finger is stuffed with fluffed gauze, greased on the outside with ointment and inserted into the nasal vestibule. Nasal packing is generally used if the forehead flap abuts onto a significant portion of the nasal ala. The nasal packing stays in place for 1 week. We usually have the patient change the dressing over the sutures daily except the Vaseline® gauze on the open pedicle. The nasal packing is removed after the flap procedure, usually occurs after 1 week on the nose and 2 weeks on the forehead. The open wound at the pedicle stays in place for 1 week. We usually change the Vaseline® gauze every 2-3 days in the office until all the sutures are removed.
base is kept moist with antibiotic ointment until it heals by second intention. When healed, the pedicle edges curl together. This is referred to as “self-tubing.”

**Insetting**

The open flap pedicle stays in place for 4-6 weeks after the initial forehead flap (Figure 6). Although some surgeons advocate insetting the pedicle as early as 14 days after the initial procedure, a longer time gives the distal flap end adequate time for full vascularization and allows for aggressive flap shaping should this procedure be necessary at the time of insetting.

The flap pedicle is transected horizontally at its midpoint. The lower end of healed donor site scar between the eyebrows is incised vertically. The incision is carried further inferiorly and vertically along the healed scar in the proximal pedicle. The scar is a result of the pedicle healing by second intention. This whole incision creates a triangular wound at the base of the proximal pedicle and allows the distance between the eyebrows to return to normal. The proximal portion of the pedicle is rotated superiorly and trimmed to fit the newly created triangular recipient area. After bleeding is stopped with biteminal electrocoagulation, a 5-0 Vicryl® buried anchoring suture is placed in the center of the small rotation flap and its wound edges opposed to the recipient wound edges by 5-0 Vicryl® and 5-0 Prolene® sutures. After the proximal pedicle has been inset into the glabella, the distal part of the pedicle is then inset into the nose. The distal pedicle flap is lifted up and a rectangular recipient wound is created in the underlying nose. Part of the newly created recipient wound connects underneath the superior portion of the distal pedicle to the original wound into which the pedicle was originally placed. The pedicle is then trimmed and thinned to fit the newly created recipient wound. Additional thinning of the distal part of the pedicle flap overlying the original recipient wound may be necessary and can be done at this stage assuming an adequate blood supply. As with the proximal part of the pedicle in the glabella, the distal part of the pedicle is stitched into place with 5-0 Vicryl® and 5-0 Prolene® after bleeding has been stopped (Figure 7).

**Touch-up Procedures**

Once the insetting site is healed, most forehead flaps can be improved by minor procedures. The most common touch-up procedures we do include flap thinning, and scar line excision with resuturing. For removal of telangiectasias, the vascular laser (e.g., pulsed dye laser) works very well (Figure 8).

**Controversies**

**Median vs. Paramedian Forehead Flaps**

Although the paramedian forehead flap is currently in vogue, we prefer the median forehead flap, which is described in this article. In the paramedian forehead flap, the pedicle is cut vertically and superiorly just above the medial side of one eyebrow. In our opinion, the median forehead flap results in a much less noticeable donor site scar on the forehead than that resulting from the paramedian forehead flap. In addition, increased vascular supply is created by the broader median forehead flap base, although the central forehead has a rich blood supply.

**Whole vs. Partial Esthetic Unit**

If the recipient wound only involves a portion of a whole aesthetic unit, should the recipient wound be enlarged to include the whole aesthetic unit? Although
a replaced whole aesthetic unit generally looks better than a partially replaced aesthetic unit, replacing a whole aesthetic unit may involve more extensive surgery to close the donor site than if a smaller recipient site wound exists. For some patients, because of their age and medical condition, it might be preferable to opt for less surgery.

To Replace or Not to Replace Missing Cartilage
Although some physicians advocate replacing the missing nasal cartilage underneath a forehead flap, in general, we find this procedure to be unnecessary. The forehead flap generally provides adequate tissue bulk to round out nasal contours and to recreate a missing ala. However, if contour is an issue after the forehead flap, cartilage can always be added later.

Conclusion
Forehead flaps can create an excellent cosmetic result when used to repair certain nasal wounds. Adherence to principles of patient selection, wound selection, and technique can ensure a successful outcome.

References
### Drug News

#### Updated Labeling

The US FDA, in January 2006, approved updated labeling for two eczema drugs, pimecrolimus (Elidel®, Novartis), and tacrolimus (Protopic®, Astellas Pharma). The new labeling will include a boxed warning about a possible risk of cancer, informing healthcare professionals that the long-term safety of these drugs has not been established, though studies are underway and there is a recognized benefit associated with these drugs when used appropriately. The new labeling also clarifies that these drugs are recommended for use as second-line treatments. Use of these drugs in children <2 years of age is not recommended. A Medication Guide has been published that provides consumer-friendly information to patients about how to use the drugs safely. Pharmacists are required to provide the Medication Guide to patients when dispensing the drug.

#### Dear Doctor Letter

In January 2006, HPB Canada sent out a Dear Healthcare Professional letter concerning hepatitis B virus relapse in all TNF blocking agents, including etanercept (Enbrel®, Amgen Canada/Wyeth Pharmaceuticals), adalimumab (Humira®, Abbott) and infliximab (Remicade®, Centocor). These effects are very rare (<1 adverse event/10,000 treated patients) and are not unique to the anti-TNF-α products, having been reported for other immunosuppressive agents as well. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before beginning therapy with any anti-TNF-α product. Those patients identified as carriers of HBV should be monitored for signs and symptoms of HBV relapse throughout their therapy and for several months following termination of therapy.

#### Dear Doctor Letter

In October 2005, Biogen Idec sent out a Dear Doctor letter to inform healthcare providers of new safety information for AMEVIVE® (alefacept), which is now contraindicated for patients with HIV disease. This decision is based on the pathophysiology of HIV and the fact that AMEVIVE® reduces CD4+ T lymphocyte counts. Such a reduction could accelerate disease progression or increase complications of disease in these patients.

#### Cleansing Agents

In a study by Retroscreen Virology, a subsidiary of University of London’s Queen Mary School of Medicine, Skinvisible’s patent-pending Chlorhexidine Hand Sanitizer demonstrated a >99% kill on the “bird flu virus” (H5N1) within seconds of contact. *In vitro* studies demonstrate a sustained release of the active ingredient over a 6 hour period. The results were presented at the Retroscreen Virology Conference, “Bird Flu: The First Pandemic of the 21st Century” in January 2006.