Hyperhidrosis is a condition with a tremendous psychosocial and occupational impact for the patients affected. In axillary hyperhidrosis, the slightest emotional or mental activity leads to wet armpits, showing up as stains on clothes, which can be socially embarrassing. Furthermore, skin maceration and subsequent microbial infection lead to discomfort, and body odors can impede social contacts. Palmar hyperhidrosis leads to a slippery grip and to a cold, wet handshake. Certain occupations are impossible because of staining of paper or other materials handled. There also is an increased risk for developing delayed type hypersensitivity to nickel and other contact allergens. Patients spend large amounts of their time and energy hiding their condition in social contexts.

Several treatments have been offered to patients suffering from hyperhidrosis but they were either of limited effectiveness or had numerous side-effects. With the discovery of botulinum toxin A for the treatment of hyperhidrosis, a treatment is available which relieves the symptoms in a relatively simple and safe fashion, although only for a limited time.

Types and Diagnosis of Hyperhidrosis

Hyperhidrosis can be focal (axillary, palmar, plantar or forehead) or generalized. It can be classified according to the stimuli inducing the sweating response. These stimuli correlate with the sites of origin of the neuronal impulses for sweating—emotional, mental or sensory hyperhidrosis (cortical reflex), thermoregulatory sweating (hypothalamic), gustatory sweating (medullary), hyperhidrosis following spinal cord transection, injury or disease (spinal), and localized sweating (axon reflex).
The most frequent triggers of focal hyperhidrosis affecting axillae or palmoplantar areas are emotional (cortical) stimuli. Hyperhidrosis is usually idiopathic, resulting from a neurogenic overactivity of the sweat glands. Only rarely is it associated with psychiatric disorders such as social anxiety disorder. Generalized hyperhidrosis can be secondary to a number of causes such as diabetes, hyperthyroidism, chronic infections or malignancy. Emotional sweating is always diurnal whereas thermoregulatory sweating may be diurnal or nocturnal. A history of “night sweats” always points to secondary hyperhidrosis.

The sweat glands responsible for focal hyperhidrosis are eccrine glands innervated with anatomically sympathetic, but functionally cholinergic fibers. The neurotransmitter involved is therefore acetylcholine.

The diagnosis of primary focal hyperhidrosis can usually readily be made based upon the patient’s history of wet armpits and massive sweating of the palms and soles after emotional stress. Causes of secondary hyperhidrosis should be excluded by careful history and appropriate laboratory investigations. The areas affected can be visualized with Minor’s Iodine starch test (Fig. 1). The extent of hyperhidrosis can be quantified with gravimetric methods, but this is usually unnecessary, as the diagnosis is obvious and the decision to treat is based on the subjective perception of the suffering by the patient.

**Treatment**

There are various treatment modalities for hyperhidrosis. Medications for generalized hyperhidrosis, such as anticholinergics and antidepressants, are often disappointing because the dose necessary to inhibit sweating is high enough to cause substantial side effects (see Table 1).

A first line treatment for localized hyperhidrosis, both axillary and palmoplantar, is the local application of metal salts, usually aluminum chloride or zirconium salts, in an aqueous or ethanolic solution. These metal salts penetrate the acrosyringium of the sweat glands and form a plug, thereby reducing the amount of sweat. They are best applied in the evening, before a period of relative inactivity of the sweat glands. Applications are initially needed daily, followed by a maintenance therapy with once or twice weekly applications. The effect only lasts as long as the maintenance dose is applied, although the sweat glands may definitively involute after prolonged application.

Another form of treatment achieving a substantial reduction of sweating, particularly for palmoplantar hyperhidrosis, is tap water iontophoresis. The hands or feet are immersed in tap water and a low current is applied for approximately ten minutes. Treatments should initially be performed 3-5 times per week. For maintenance therapy, which can be performed 1-3 times per week, patients sometimes prefer to buy their own iontophoresis equipment.

For a more definitive cure, surgical treatments have to be considered. Local excision of axillary sweat glands can be performed in tumescence local anesthesia and usually shows good results. Thoracal sympathectomy reduces palmar hyperhidrosis effectively but carries the risk of compensatory sweating.

**Botulinum Toxin A**

Botulinum toxin (BTX) is a neurotoxin produced by the anaerobic bacterium clostridium botulinum. It inhibits the release of acetylcholine at the presynaptic nerve endings of the motor endplates. At the end of the 18th century, it was recognized as the cause of botulism, a frequently fatal form of food poisoning. Therapeutic use of the poison started in the 1960s, when ophthalmologists recognized that minute amounts of BTX could effectively paralyze eye muscles in patients with strabism and blepharospasm. Clinical use for other muscle disorders, such as cramped sphincters in anal fissures and urogenital dystonias followed quickly. In the early 1990s, after clinicians observed that patients treated with BTX for hemifacial spasms no longer sweated in the treated area, the idea arose to use the toxin to treat...
hyperhidrosis. In the meantime, BTX has become widely established for the treatment of hyperhidrosis and hyperfunctional facial lines.

Seven serotypes of BTX exist; of these, serotype A is the one most often used to treat hyperhidrosis. By preventing the exocytosis of acetylcholine, BTX-A exerts an inhibitory effect on the cholinergically innervated eccrine secretory cells and thus reduces sweat production. BTX-A is available in two commercial forms (BOTOX® [Allergan] in the USA and Europe and Dysport® [Ipsen] in Europe), whereby 1 unit of BOTOX® is about equal to 3-4 units of Dysport®. The affected area is first visualized with Iodine starch staining (Minor test). Then 50-200 units of BOTOX® are injected intradermally; the dose is divided into 10-15 aliquots injected at spatial intervals of approximately 2 cm, enough to cover the entire affected area. Injection in the axillae is usually well tolerated without anesthesia. Injections in palms and soles can be very painful and are therefore best performed under regional anesthesia (median and ulnar nerve block for palms, sural and posterior tibial nerve block for soles). Alternatively, the area can be rendered relatively pain free by prior application of anesthetic cream (EMLA, AstraZeneca) under occlusion, iontophoretic application of lidocaine, or cryospray.

The anhidrotic effect of BTX-A, which can be perceived after 2-4 days, is usually very satisfying. Several studies have reported it to be effective in more than 90% of patients, compared to response rates around 35% for placebo. This is true both for axillary10-12 and palmoplantar13,14 hyperhidrosis. Quality-of-life assessments showed a substantial reduction of the adverse impact of hyperhidrosis.15,16 Although apocrine sweat glands are innervated by adrenergic fibers, treatment with BTX-A showed marked improvement of unpleasant body odor (bromhidrosis).17 The mechanism of action for this effect may be a reduction of the moist environment favorable for bacterial growth, or the inhibition of cholinergic apocrine glands. In patients with dyshidrotic hand dermatitis, treatment of the palms with BTX-A may reduce the severity of the eczema, as hyperhidrosis is considered to be a precipitating factor in this condition.18

A drawback of the treatment with BTX-A when compared to surgical approaches is the limited duration of its effect. After one treatment, anhidrosis lasts between 3 and 17 months with a median duration of approximately 7 months. Higher doses of BTX-A seem to lead to a slightly longer duration of effect,19 outweighed by the higher costs and the higher risk of antibody formation. Repeat treatments can be performed at intervals guided by the patient’s requests and lead to sustained good results.10 For many patients this may be preferable to the ongoing treatments required by metal salts and tap water iontophoresis. However, a definitive

<table>
<thead>
<tr>
<th>Mode of application</th>
<th>Mechanism of action</th>
<th>Duration of effect</th>
<th>Major advantages</th>
<th>Major drawbacks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metal salts</td>
<td>Local application</td>
<td>Plugging of sweat glands</td>
<td>As long as applied</td>
<td>Easy application, few side effects</td>
</tr>
<tr>
<td>(aluminum chloride, zirconium)</td>
<td>under occlusion at bedtime</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tap water iontophoresis</td>
<td>Immersion of affected sites 3-5 times weekly for 10 minutes</td>
<td>Unknown</td>
<td>As long as applied</td>
<td>Few side effects</td>
</tr>
<tr>
<td>Botulinum toxin A</td>
<td>Intradermal injection</td>
<td>Inhibition of exocytosis of acetylcholine</td>
<td>Several (3-17) months</td>
<td>Very effective</td>
</tr>
<tr>
<td>Surgical procedures</td>
<td>Local excision of axillary sweat glands in tumescence anesthesia</td>
<td>Reduction of sweat glands</td>
<td>Lasting</td>
<td>Long term effectiveness</td>
</tr>
<tr>
<td>Thoracal sympathectomy</td>
<td>Denervation of sweat glands</td>
<td>Lasting</td>
<td>Long term effectiveness</td>
<td>Compensatory sweating, (rarely) complications</td>
</tr>
</tbody>
</table>

Table 1: Summary of available treatments for focal hyperhidrosis
cessation of the symptoms has not been observed even after multiple treatments, and histological examination of sweat glands shows no involution due to inactivity. A treatment algorithm for axillary and palmoplantar hyperhidrosis is proposed in Fig. 2.

Adverse effects of the treatment with BTX-A are minor and very rare. Hematomas at injection sites are usually of little concern. Injection into the palms can lead, by diffusion of the toxin, to a transient weakness of the small muscles in the hand. Subjectively increased sweating at non-treated sites has been reported. Especially when higher doses of BTX-A are used, antibody formation (leading to ineffectiveness of the treatment) can theoretically occur, but this has been observed only very rarely. Contraindications include pregnancy and lactation, and special precautions should be applied in patients with motor neuron disease, myasthenia gravis, Eaton-Lambert syndrome, patients on aminoglycoside antibiotics or with hypersensitivity to BTX-A or any ingredient in the formulation.

Conclusion

Intradermal application of Botulinum toxin A (BTX-A) has added a valuable and very effective option to the hitherto available treatments of focal hyperhidrosis. While the effect is only of limited duration and repetitive treatments are necessary, it has a very good safety profile. It can add significantly to patients’ quality of life, especially when other treatment options have proven ineffective.

Fig. 2: Treatment Algorithm for focal hyperhidrosis. Steps may be omitted based on availability and patient preferences.

References

ABSTRACT

Blepharoplasty of the upper and/or lower eyelids can restore a youthful appearance to the aging face. This is a minimally invasive procedure that can be accomplished with little bleeding and a small incision. Laser-assisted blepharoplasty was pioneered in 1980, with the technique simplified after the subsequent introduction of the pulsed carbon dioxide laser. Laser-assistance helps mitigate bleeding during blepharoplasty. In ideal circumstances, the laser can be used as a multipurpose device that simultaneously offers cutting, cautery and blunt dissection capabilities. However, there is little experimental evidence confirming the superiority of laser-assisted blepharoplasty over more traditional scalpel surgery. For some procedures cold-steel may be preferable, and some surgeons prefer to use a knife for initial incisions and then laser for its coagulative properties. Patient factors and physician skill should guide the selection of the ideal blepharoplasty technique.

KEY WORDS: blepharoplasty, facial aging, laser

Over the past two decades, western society has placed increasing demands on physicians to perform procedures with greater speed and efficiency and shortened recovery times. Perhaps no discipline has been more affected by these demands than aesthetic surgery. Once considered a luxury available only to the extremely wealthy and long considered a “taboo” topic, aesthetic surgery has become a part of mainstream Western culture. Fashion magazines, the internet, and television shows feature aesthetic surgery topics that are so current that they discuss the use of products not yet approved for use by the US FDA. Cosmetic surgery has consequently become a part of mainstream Western culture.

Some of the earliest changes of facial aging are reflected in the periocular region. These changes may include excess skin on the upper and/or lower eyelids (dermatochalasis), prominent upper or lower eyelid fat pads, and loosening of the lower eyelids due to laxity of the canthal tendons. It is thus not surprising that blepharoplasty is one of today’s most popular aesthetic surgical procedures.

To enhance efficiency, hasten a return to routine activities and reduce morbidity associated with a surgical procedure, efforts are typically made to minimize incision size, limit the amount of dissection, and shorten the operative time. Applying these concepts to blepharoplasty, the variable most amenable to change is duration of the operative procedure. Operative times may be shortened through operator skill and experience, and via use of a device to enhance intraoperative hemostasis.

Numerous devices permit soft tissue incisions to be made with little or no bleeding. Some examples include sapphire tips heated by an Nd:YAG laser, needle-tipped radiofrequency devices, fine-tipped monopolar cautery, CO₂ laser-heated ultra-sharp diamond knife, and free beam CO₂ laser. While hemostasis is important, when one is evaluating these devices the amount of thermal damage produced along the wound edges must also be considered, as excessive thermal effect will produce delayed wound healing, dehiscence, or even hypertrophic scarring.

Laser assisted blepharoplasty was first performed by Baker in 1980. He reported the results of his first 40 cases in 1984, concluding that this technique held promise.¹ Despite Baker's optimism, the prevailing opinion in the 1980s was that CO₂ lasers produced too much thermal damage to be useful in cutaneous, much less aesthetic, surgical procedures.²

Interest in laser-assisted blepharoplasty was renewed in the early 1990s with the introduction of a high-energy pulsed CO₂ laser. This device, known by the trade name UltraPulse® (Lumenis, Palo Alto, CA), produced a high frequency pulsed beam that made incisions with a smaller zone of thermal injury than was previously possible. This
laser cut soft tissue with a pulsed beam whose frequency and energy could be independently varied to achieve the ideal blend of cutting and coagulation. Even when operated in “continuous wave” mode, this laser produced a pulsed beam with a frequency of 1000-3000 Hz. The UltraPulse® also produced a small (0.2mm) diameter beam that made it more useful for working in the periorbital region. When used properly, surgery could be performed quickly, intraoperative hemostasis and visualization of delicate anatomic structures was dramatically improved, and the zone of thermal injury surrounding the laser incisions was only about 115µm. Consequently, when these wounds healed they were usually indistinguishable in appearance from cold steel wounds. Similar devices subsequently produced by other manufacturers (e.g., Unipulse®, Nidek Incorporated, Fremont, CA, 0.2mm spot, peak power = 40 W) yielded equally satisfactory results, leading to more widespread acceptance of laser incisional surgery as a viable technique in certain clinical settings. In an effort to further reduce the risk of complications, in 1998 Sciton (Palo Alto, CA) began adapting an Er:YAG laser to produce soft tissue incisions. Unfortunately the Er:YAG laser was unable to produce sufficient hemostasis to make it practical for use in soft tissue incisional surgery.

Clinical Perspective

Proponents of laser incisional surgery find that soft tissue surgery may be performed more efficiently and, in some cases, more effectively with lasers than with standard techniques. There are several reasons for this. First, when used properly, the laser handpiece acts as three instruments: a cutting tool, a cautery, and a blunt dissection device. The intraoperative transfer of instruments and therefore total operating time is thus decreased. Second, intraoperative efficiency is increased further by the near absolute hemostasis that is often achieved when working in areas such as the periorbital region where most blood vessels have an internal diameter of 0.5mm or less. For this reason, the CO₂ laser has found its greatest incisional applications in the periorbital region. Third, dissection with the CO₂ laser in the eyelids and periorbital region allows surgery to be performed on delicate vascular structures such as the levator palpebrae superioris and the superior tarsal (Müller’s) muscle with a lower risk of tissue distortion, functional impairment, or hematoma formation. Consequently, the use of lasers allows certain incisional procedures such as blepharoptosis repair or correction of eyelid retraction to be performed with greater precision.

One of the most important questions is whether using lasers to perform incisional procedures benefits the surgeon, the patient, both, or neither. The literature is decidedly unclear in attempts to answer this question. Anecdotal reports and small unmasked studies offer conflicting conclusions as to the benefit of lasers in blepharoplasty, the aesthetic procedure performed most often with lasers rather than traditional instrumentation. Some authors report that the CO₂ laser offers little advantage over the scalpel, while a recent survey comparing scalpel versus CO₂ laser blepharoplasty indicated that the benefits of using a laser included quicker recovery time to usual activities (6.3 vs. 9.1 days), and shorter operating times (four eyelid blepharoplasty times of 58 vs. 94 minutes). Biesman and colleagues have performed the only prospective, multicenter, double-blind study to address this issue. Ophthalmic plastic surgeons who were experienced in both laser-assisted and traditional technique (at least 100 cases of each over the preceding 2 years) performed blepharoplasty procedures on 50 patients using laser on one side and cold steel on the other. The side treated with laser was randomly selected and the patients were blinded to the surgeon's choice. Patients were examined 1, 2, and 4 weeks after surgery. Results were assessed by patient questionnaire and by evaluation of photographs by a skilled, masked observer. Two weeks after surgery there was no significant difference in the amount of swelling, discoloration, or wound appearance. The surgeons preferred performing surgery with the laser when possible due to the improved intraoperative hemostasis. This study did not evaluate surgical times.

Despite these findings, after years of experience performing periorbital surgery with an array of incisional devices including cold steel, radiofrequency, monopolar cautery, long-pulsed Er:YAG laser and CO₂ laser, I continue to prefer the CO₂ laser when performing certain incisional procedures, especially for most cases of upper eyelid blepharoplasty, upper eyelid ptosis repair, and lower eyelid transconjunctival blepharoplasty. I have even found
that the laser enables me to operate with a greater degree of safety on certain anticoagulated patients who require eyelid or orbital surgery but are unable to discontinue anticoagulation without significant risk of an untoward event.

I do not advocate the use of laser in all cases of periorbital surgery. Due to inconsistent results, I no longer use the laser to make the initial skin incision when performing upper blepharoplasty on patients with “tight” skin such as young patients, Asians, or patients with prominent epicanthal folds. I also prefer to make lower eyelid skin incisions with sharp instruments. However, once the initial incisions have been completed, I use the laser to complete the remainder of the dissection.

The CO₂ laser produces a zone of irreversible thermal injury (coagulative necrosis) along the wound edge, an observation that has been correlated with the well recognized delay in the rate of laser wound healing, postoperative wound dehiscence, and unacceptable scarring. As long as these tissue effects are recognized and understood, postoperative problems can be avoided. For example, laser incisions should be made parallel to relaxed skin tension lines. This will allow wounds to be closed with the least amount of tension, thus reducing the risk of unacceptable scarring. Similarly, cutaneous laser incisions should be placed in areas such as the head and neck that have a rich blood supply. When closing cutaneous laser wounds, I believe that absorbable suture materials should be avoided as the coagulative necrosis produced by the laser, in conjunction with the inflammation stimulated by the suture material can produce wounds with an unacceptable appearance. I prefer nylon or polypropylene suture, and leave the sutures in place approximately 7 days as opposed to the 3-4 days I leave sutures after cold steel blepharoplasty. This gives the laser wounds an opportunity to heal more completely prior to suture removal.

Conclusion
When used appropriately and judiciously, lasers can play an important role in periorbital incisional surgery.

References
### Update on Drugs

#### Class

<table>
<thead>
<tr>
<th>Name/Company</th>
<th>Approval Dates and Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antibacterial Agent</strong></td>
<td>PA mAb Abthrax™ Human Genome Sciences The US FDA approved a Fast Track Product designation in August 2003, for the prevention and treatment of anthrax infections. A Phase I placebo-controlled, dose-escalation clinical trial has been initiated in healthy adult volunteers to evaluate the safety, tolerability and pharmacokinetics of this product.</td>
</tr>
<tr>
<td><strong>Immunomodulatory Agent</strong></td>
<td>Thalidomide THALOMID® Pharmion/Celgene The Australian Drug Evaluation Committee recommended approval of this product in August 2003, for the treatment of patients with relapsed and refractory multiple myeloma, and for the treatment of cutaneous manifestations of erythema nodosum leprosum.</td>
</tr>
<tr>
<td><strong>Antiviral Agent</strong></td>
<td>Valacyclovir Caplets Valtrex® GlaxoSmithKline The US FDA approved a supplemental new drug application in August 2003, for this antiviral product for suppressive therapy in otherwise healthy adults with genital herpes in order to reduce the risk of heterosexual transmission of genital herpes.</td>
</tr>
<tr>
<td><strong>Antibacterial Agent</strong></td>
<td>Ertapenem Sodium Invanz® Merck Frosst Canada TPP Canada approved this new once-daily monotherapy antibiotic in September 2003, for the treatment of adults with moderate-to-severe infections, caused by a wide range of bacteria. These include skin and skin structure infections, intra-abdominal infections, and community acquired pneumonia.</td>
</tr>
<tr>
<td><strong>Antipsoriatic Agent</strong></td>
<td>Efalizumab Raptiva® Genentech/XOMA The US FDA Dermatologic and Ophthalmic Drug Advisory Committee unanimously recommended approval of this product in September 2003, for the treatment of moderate-to-severe plaque psoriasis in adults aged &gt;18 years.</td>
</tr>
<tr>
<td><strong>Oncologic Agent</strong></td>
<td>INGN 201 Advexin® Gene Therapy Introgen Therapeutics The US FDA granted Fast Track designation for this investigational cancer therapy in September 2003, for the treatment of squamous cell carcinoma of the head and neck. This product combines the p53 gene with an adenoviral delivery system designed to kill cancer cells and stop tumor growth without harming normal cells.</td>
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### Drug News

**Malignant Melanoma** According to a study published in the *Journal of Foot and Ankle Surgery*, malignant melanoma is increasing at a rate faster than any other cancer in the US, and the overall 5-year survival rate of patients with a primary tumor on the foot is significantly higher than for patients with primary melanomas elsewhere on the lower extremity (52% vs. 84% respectively). Melanoma can be more easily misdiagnosed than a melanoma located elsewhere, and the authors recommend that patients with moles on their feet should watch them carefully and have them removed if they change in color and shape.