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Indice

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Scripta Manent s.n.c. Via Bassini, 41 - 20133 Milano
Tel. 0270608091/0270608060 - Fax 0270606917
E-mail: scriman@tin.it
Abbonamento annuale (3 numeri) Euro 50,00
Pagamento: conto corrente postale n. 20350682
intestato a: Edizioni Scripta Manent s.n.c.
via Bassini 41- 20133 Milano
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SCRIPTA MANENT EDIZIONI

Early versus delayed escharectomy and skin grafting of the deeply burned hands.

Mohamed R. El-Hadidy, Ahmed M. Bahaa El-Din, Almoddather M. El-Hadidy, Amr Mohamed El-Hussiny Khater

Plastic and Reconstructive Surgery Unit, Mansoura University Hospital, Egypt

Summary

Early versus delayed escharectomy and skin grafting of the deeply burned hands.

Fifty-two patients were admitted to the Burn Unit of Mansoura University Hospital with burn injuries involving one or both hands. 22 patients required skin grafts to one or both hands resulting in 32 operated hands. Burns diagnosed on admission as full-thickness were generally treated by excision and grafting in 3 to 5 days post burn. Split-skin graft was harvested from a non-burned area, applied on the wound bed, and secured with staples. Surgery was delayed beyond 14th day if the diagnosis full-thickness depth of the burn was uncertain, to allow time for the wound to demarcate or when the general condition of the patient can not enable him to withstand the surgery. We applied the same post operative topic treatment and rehabilitation protocol in all patients. Fourteen patients of the 22 patients examined (63.6%) were treated early while 8 (36.4%) were cured conservatively and underwent surgery after the second week. Only 2 of the early treated cases (14%) needed late secondary correction for severe scars whereas 3 (37%), late treated patients, needed secondary surgery. The total amount of readmitted patients was therefore 5/22 (22, 7%). We confirm the importance of performing early surgery of deep burns of the hands, whenever possible, in order to achieve best results .

Key words: *Escharectomy; Skin grafting; Deeply burned hands.*

INTRODUCTION

Hands participate in everyday human's activities and they are the most vulnerable parts of a human body[1]. Hands are often injured trying to cover other parts of a body from the fire or other destructive factors. As different authors stated the hand and digit injuries compromise 30-75% of industrial injuries[2]. Hand burns compromise 6% of all hand injuries. Human loses up to 54% of function when he loses his hand function[3].
Treatment of the burned hand is a complex surgical challenge. Hands are frequently affected by serious and deep lesions, more often located on the dorsum[4]. Due to the functional, social and relational role of the hands, a rapid satisfactory functional recovery and a good aesthetic outcome are crucial for patients affected by deep burn lesions[5].
Traditional surgical approaches are early esharectomy and skin grafting within the first days after burn, or as an alternative an initial topical treatment followed by late eshare excision and skin grafting. The surgical strategy was dedicated by patient's general conditions and overall extent of burn[6].
In spite of all precautions, a high number of patients require one or more secondary surgical corrections after few months for impairing and unaesthetic scars[7].
Therefore, burn treatment surgical protocols should be optimized and constantly updated in order to reduce patient suffering, surgeon's work and public costs connected to re-admission[6].
For this purpose, we retrospectively reviewed the patients with deep burn of the hands treated at the Burn Unit in Mansoura University Hospital over 2 years, by assessing functional and aesthetic outcomes in relation to surgical timing and evaluating how many of them required secondary surgical revision.

PATIENTS AND METHODS

From January 2004 to July 2006, 52 patients were admitted to the Burn Center of

Table 1
Age and sex distribution among patients with burned hands

	<20 years	20-40 years	>60 years	Total
Male	6	17	7	30
Female	3	14	5	22
Total	9 (17, 3%)	31 (59, 6%)	12 (23, 1%)	52

Table 2
Average of TBSA in early and late surgically treated patients

	No. of Patients	Average TBSA	Average TBSA3
Early surgery	14(63.6%)	22%	9%
Late surgery	8(36.4%)	37%	22%

Mansoura University Hospital with burn injuries involving one or both hands. 22 patients required skin grafts to one or both hands resulting in 32 operated hands (Table 1, 2).
Patients who sustained a thermal injury of the hand were treated as follow: on admission, the depth and surface area of the burned hand were determined (HSA), as well as the depth and extent of the total body surface area burn (TBSA). Circumferential deep burns of the hand or digits were treated by escharotomy. Silver sulfadiazine cream was applied as a local antimicrobial treatment and dressings were changed daily. The hands were nursed in splints in a functional position and physical therapy was started as soon as possible.
Burns diagnosed on admission as full-thickness were generally treated by excision and grafting in 3 to 5 days post burn preserving, when possible, the superficial venous system and the paratenon. Removal of the eschar was performed by either tangential or facial excision. Split-skin graft was harvested from a non-burned area, applied on the wound bed, and secured with staples. Surgery was delayed beyond 14th day if the diagnosis full-thickness depth of the burn was uncertain, to allow time for the wound to demarcate or when the general condition of the patient can not enable him to withstand the surgery.

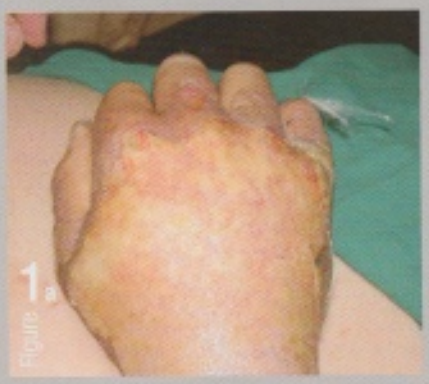
Parameters recorded for each patient included age on admission, TBSA burn, full thickness TBSA burn (TBSA3), total burned hand surface area (HSA), full thickness HSA burn (HSA3), postburn day of operation, survival of the grafted skin (graft take, estimated 5±7 days postsurgery) and the need for reconstructive surgery after a postoperative follow up period of 6 months.
Intensive pre- and post-operative rehabilitation was set up in all cases. At night, the wrist and the finger joints were splinted in the anti claw functional position. Physical therapy, including active and passive exercises and occupational therapy, were performed under physiotherapist supervision and occupational scheme. Compression gloves were used at 15th postoperative day and were applied for 6 months. During admission, psychological support was offered to all patients.

RESULTS

The results are presented in Table 3. Fourteen patients of the 22 patients examined (63.6%) were treated early while 8 (36.4%) were cured conservatively and underwent surgery after the second week. Only 2 of the early treated cases (14%) needed late secondary correction for severe scars whereas 3 (37%), late treated patients, needed secondary surgery. The total amount of readmitted patients was therefore 5/22 (22, 7%). Table 4 shows the type of secondary deformities, Table 5 the surgery performed.

DISCUSSION

In this series of 22 patients with deep burns of the hand, we operated 14 of them during the first 3 to 5 days after the admission while 8 of them were operated after two weeks. Our policy in the management of burned hands has always been oriented towards early surgical treatment.
Our results, according with the literature, confirm that the best functional and aesthetic results are obtained with early surgery.
The fact we valued functional and aesthetic results by clinically assessing joints and hand anatomic areas and furthermore considered the patient's need for functional and aesthetic improvement.
After the admission of these cases, identification of the depth of burn injury is essential. The estimation can be very difficult[4]. As a matter of fact, while the identification of full thickness lesions is normally easy, the judg-



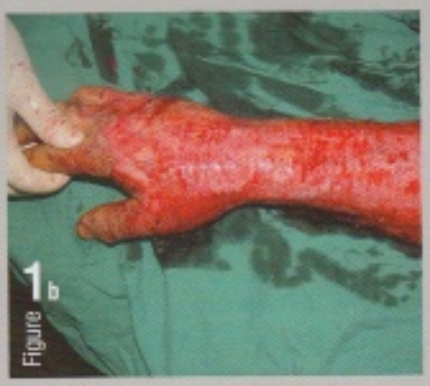


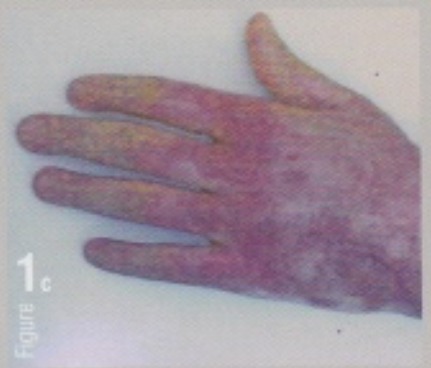
Figure 1
A male patient aged 40 years sustain deep burns of the face both upper limbs and both feet with an average TBSA is 25%.

Figure 1a
shows preoperative view of burned right hand.

Figure 1b
intraoperative view after tangential excision of burn wound preserving viable structures.

Figure 1c
shows 1 week postoperative view.

Figure 1d
shows 6 months postoperative view.



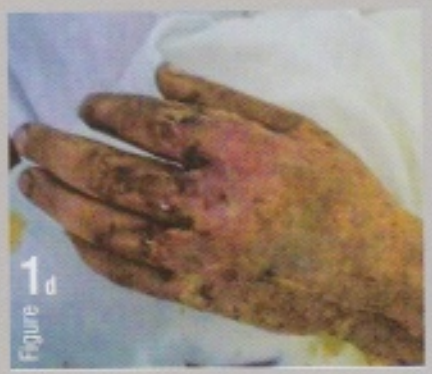


Table 3
Patient's distribution according to time of surgery and secondary procedures

		No need for 2ry revision surgery	Secondary surgery	Total
Early treatment	No. of patients	12	2 (14%)	14 (63, 6%)
	No. of burned hands	14	5	19
Late treatment	No. of patients	5	3 (37%)	8 (36, 4%)
	No. of burned hands	7	6	13
Total	No. of patients	17	5 (22%)	22
	No. of burned hands	21	11	32

Table 4
Postoperative unfavorable outcomes

Complication	Number of patients
Keloid	4
Syndactyly	2
Flexion deformity	2
Boutonniere deformity	1
Joint stiffness	2

Table 5
The types of secondary procedures performed

Main secondary procedures	Number of patients
Z-plasty	4
Steroid infiltration	4
Scar excision + skin grafting	2
Arthrodesis	1

ment between superficial and deep dermal burns, in the first days after injury, demands more experience since the depth's evolution is often unpredictable[6].

Although bedside clinical evaluation remains the most widespread method for depth diagnosis, it is accurate only about two thirds of the time.

Thermography, though less frequently employed, is about 90% accurate.

Indocyanine green (ICG) video angiography is unique in that it offers a dynamic portrait of vessel patency that fluctuates in real time.

Laser Doppler imaging (LDI) provides a static rather than dynamic perfusion map, but it retains other advantages over ICG video angiography. It is not only less invasive and faster but also more accurate, with validity as high as 99%[7].

However, the timing of surgery is less clear. Optimally, if the condition of the patient allows, excision and grafting of the upper limb burn wound needs to begin as soon as the depth of the wound is clear, usually by the 2nd or 3rd day postburn.

Wounds that are permitted to heal by secondary intention and take greater than two weeks to heal have a far greater incidence of abnormal (hypertrophic and keloid) scar formation. In some cases (hot metal, hot tar) where the deep partial thickness or full thickness nature of the injury is obvious, surgery may be undertaken immediately[8].

Supporters of early debridement and skin grafting believe the benefits are also associated with a shorter, less costly hospital admission[9].

If initial management is to monitor the burn wound, vigorous hand therapy must continue during the observational phase. With debridement within 72 hours where possible and a systematic team approach, 90% of patients with deep partial thickness or full thickness burns achieved normal post-injury function[10].

The use of dermal substitutes (i.e. engineered skin) can be a valid choice when delayed surgery is an unavoidable choice.

Some Authors advocate the use of alloderm and ultrathin split thickness skin graft for coverage of deep and partial thickness burn wounds. With AlloDerm, only ultra-thin epithelial autografts are required from the patient. The clinical observations of "take" were confirmed with histological evaluation of the biopsies, which exhibited fibroblast cells infiltration, neovascularization and neoepithelization without evidence of rejection[11].

In some series, 90% of patients with burns involving bone, joint or extensor mechanism were eventually able to perform activities of independent daily living. It is proposed that surgery within 2 weeks is associated with superior function and fewer reconstructive procedures[12].

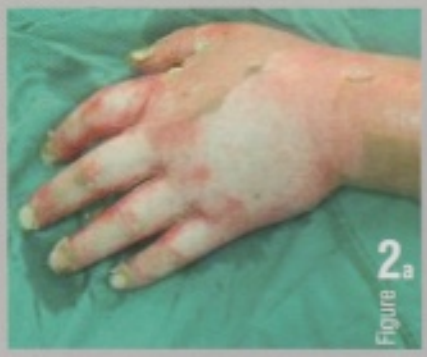
Excision of deep partial thickness areas may be hazardous to promote survival if the total burn area is so large that any spontaneous healing should be allowed even with scarring. Some surgeons consider preservation of all residual, viable dermal elements is of critical importance for late surgery following eschar separation. Provided intensive hand therapy is administered, functional results at one year have been shown to be similar to series where early excision is done[13].

Long term follow-up and re-operation rate for reconstructive problems is also an important consideration in determining an optimum time to operate. A ten-year follow-up study of deep hand burns found burns taking greater than 21 days to heal had a 100% need for subsequent reconstructive surgery. In contrast only 26% of patients initially operated on between 5 and 10 days required later reconstruction[14].

The burn wound should be excised by the technique of tangential excision with preservation of the maximum amount of viable tissue[15].

In deep partial thickness burns, the skin graft should be laid on the intact vascular deep dermis once adequate hemostasis has been achieved. Full thickness burns are treated with debridement of nonviable tissue preserving the maximum amount of dorsal veins and paratenon wherever possible. In such burns tangential excision may not be practical and sharp dissection can be used. In the arm and forearm, fascial excision may be indicated if the underlying fat is non-viable or blood loss is a limiting factor. Excision of either type can be done with or without the use of a tourniquet depending on the choice of the surgeon and position of the burn[16].

When presented with a severely burned hand with necrotic digits, it may be preferably to allow auto-amputation of the affected parts rather than early surgical removal.



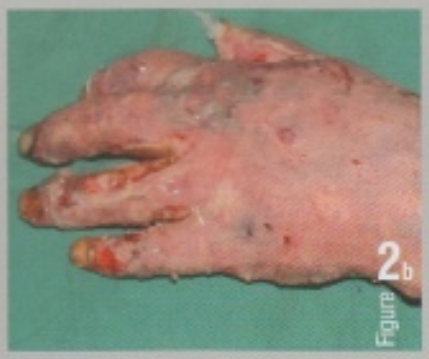
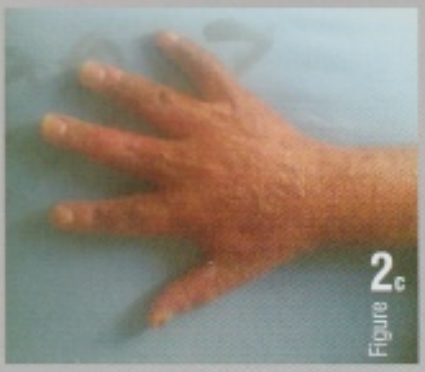


Figure 2
A female patient aged 24 years sustain deep burns of the face and both upper limbs with an average TBSA is 20%.

Figure 2a
shows preoperative view of burned right hand.

Figure 2b
postoperative view after 1 week.

Figure 2c and 2d
shows 6 months postoperative view.



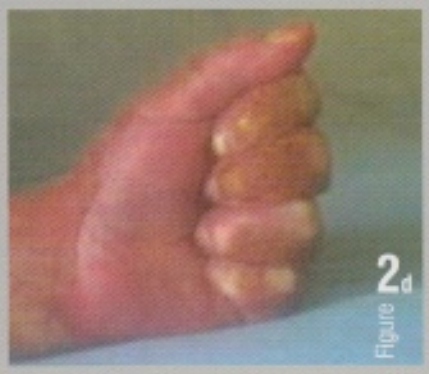
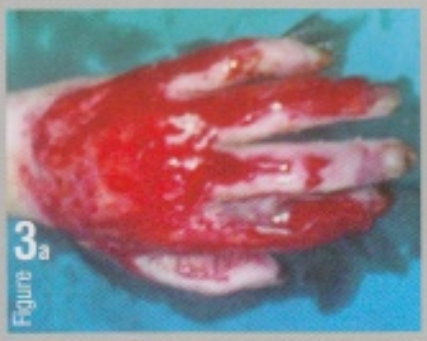
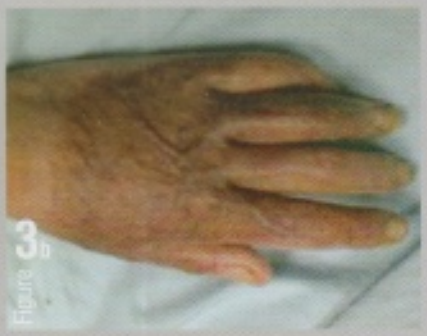


Figure 3
A female patient aged 4 years sustain deep burns of the face, both upper limbs and trunk with an average TBSA is 20%.

Figure 3a
shows intraoperative view of burned right hand.

Figure 3b
postoperative view after 1 month.





Mummified fingertips are usually not a source of sepsis and conservative treatment here may save tissue without endangering the patient or the limb[9].

Regardless of the type of skin graft used or method of post-operative care, the hand is splinted in the position of protection until the graft has stabilized. Active mobilization is then commenced, usually after a period of 4 to 6 days[10].

Burns of the palm requiring surgical intervention are relatively uncommon, because the skin of the palm is quite thick and relatively protected. Conservative treatment is therefore generally preferred, allowing eschar separation for 2 to 4 weeks. If excision must be undertaken, it should be by sharp dissection with preservation of all vital and viable tissue. A relatively thick split skin graft can be used to close the wound with the palm splinted with the hand outstretched with all joints in extension[10].

When the palmar aspect of the hand is involved, it is preferable to use FTSG where the burn is excised in the same manner and the most common source of the graft is the inguinal crease. The use of tissue expender to make a larger surface area of graft is also possible[10].

Some surgeons have described dermabrasion of the full thickness skin graft to remove the epidermis and then coverage of the wound with a thin split thickness skin graft from the foot. Healing from the sole graft may be optimal[18].

The major complain of FTSG to the palm is the tendency of the graft to become hyperpigmented. This may be an issue for people with darker skin. The hyperpigmentation issue has led some surgeons to advocate the use of skin from the sole of the foot where a thin STSG is taken from the thigh then harvest a FTSG from the sole. The STSG is placed back on the sole and the FTSG is placed on the palm[17].

CONCLUSION

Deep burns of the hand are treated by surgical excision of the burn eschar and wound coverage with split thickness skin grafts.
Early surgical excision and skin grafts is considered to patients with burns confined to the hands or when the total burn surface area is less than 25%. Late intervention is advocated when the priority is to maintain survival as when the total burn surface area is more than 25% or in critically ill patients.
Early wound excision and grafting has good aesthetic and functional results with minimal complications.
The patient rarely needs a secondary corrective surgery. It should be emphasized that the patient should start physiotherapy as early as possible to get good functional results.

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Local anesthetics. A review.

Deni F[1], Turi S[1], Cavallini M[2]

[1] Department of Anesthesia and Intensive Care, Università Vita-Salute San Raffaele, Milan, Italy.
[2] Institute of Plastic Surgery, University of Milan, Italy

Summary

Local anesthetics. A review.

The use and the importance of local anesthetics in plastic surgery are widely accepted. These drugs allow to reduce the sympathetic response during surgery, improve the comfort of the patients in the intra-operative period and reduce the post-operative pain.
However the use of local anesthetics can be associated to the development of serious side-effects and adverse reactions.
The aim of this article was to present the main characteristics of the most used local anaesthetics, their maximal allowable dosage and the most important adverse reactions associated to their use.
An evaluation of the literature, as well as clinical experience in the administration of local anesthetics provide the basis for this review.

Key words: *Local anesthetics; Lidocaine; Mepivacaine; Bupivacaine; Ropivacaine; Levobupivacaine.*

INTRODUCTION

American Society of Aesthetic Plastic Surgery statistics show that outpatient cosmetic procedures increased from 3 to 11 million (1997-2007), an increase of 457%, and $13 billion was spent[1].
Exponential growth, complexity of cases and patients, and media attention to high-profile untoward events are accompanied with concerns for patient safety and development of safer practices. Improved safety and efficacy in aesthetic surgery include sedation and local anesthesia. A coordinated team approach for patient management is essential.
Anesthetic techniques should be adapted to the needs of each patient, considering his safety and comfort as the most important considerations. Anesthesia for plastic surgery has progressed from simple injection of local anesthetics to sophisticated sedation and general endotracheal techniques[2].

LOCAL ANESTHETICS

The traditional anesthesia technique for plastic surgery has been local anesthesia supplemented by sedation. This technique requires a combination of skillful local administration, selection of appropriate sedation drugs in proper doses, and a cooperative patient[3].
The modern agents and techniques permit the patient to recover quickly, with minimum postoperative sequelae, and provide obvious comfort during the operative procedure.
An accurate knowledge of the properties, the possible side effects and the way of administration of local anesthetics is mandatory (Table 1).
Neural transmission involves the propagation of an electrical stimulus along the nerve fiber[4]. This propagation is possible because of a differential electrolyte concentration between the intracellular fluid [high potassium (K) and low sodium (Na)] and extracellular fluid (low K and high Na), which establishes an ionic gradient that is maintained by a Na K adenosine triphosphatase (ATPase) pump.
Studies have shown that local anesthetics inhibit depolarization of the nerve by interfering with the influx of Na ions[5].
Local anesthetics are thought to stabilize the membrane at resting potential, increase the threshold for electrical excitation, and reduce the propagation of an excitatory impulse, thereby blocking nerve conduction.

Table 1

Local anesthetic	Maximum allowable dosage (mg)	Hours of anesthesia
Lidocaine	300	1-3
Mepivacaine	500 (7 mg/kg)	1-4
Bupivacaine	150	2-8
Ropivacaine	250	2-8
Levobupivacaine	150	2-12

In order for local anesthetics to be effective they must be able to diffuse across the nerve cell membrane (necessitating lipophilic properties) and then convert to cationic form for better protein binding activity (hydrophilic characteristics). The more lipid soluble agents are able to diffuse easily across the cell membrane, which equates with higher potency, since lower concentrations of anesthetic are needed to produce the desired result. On the other hand, greater protein binding is associated with increased duration of action[5].

There are several methods for inducing local anesthesia: topical anesthesia, infiltrative anesthesia, field blocks, peripheral nerve blocks, and tumescent anesthesia.

Local anesthetics are classified as either ester or amide compounds.

Lidocaine was the first amino amidic agent used in the clinical practice. It presents a very rapid onset and its half life is about 1-3 hours, increased by the association with epinephrine. The maximum allowable dose dosage of this drug is of 300 mg (3 mg/kg)[6].

Mepivacaine has a pharmacological profile very similar to the one of lidocaine. This drug is characterized by a very fast onset although the nervous block is more prolonged than with lidocaine (its half life is about 1-4 hours, increasable by the combined use of epinephrine). It is not recommended to administer more than 500 milligrams (7mg/kg) for each patient.[6].

The first long acting local anesthetic widely used in clinical practice for its rapid onset combined with a long duration was **bupivacaine**.

It is used for local infiltration, for peripheral nerve block and for epidural and spinal anesthesia. Its onset is rapid and its half life is about 2-8 hours for local infiltration and 4-12 hours for peripheral nerve blocks.

All these useful properties explain the wide utilisation of bupivacaine in the treatment of peri-operative and post-operative chronic pain (by local infiltration or in high abdominal surgery by a continuous epidural perfusion).

The maximum allowable dose dosage is of 150 milligrams. Despite all these interesting properties, the accidental intravenous injection of bupivacaine has been associated to sudden cardiac arrest[7].

A prospective, double-blinded, randomized trial was performed to investigate the efficacy of pocket irrigation with bupivacaine and ketorolac in reducing pain, narcotic use, and methocarbamol use following subpectoral breast augmentation[8].

Patients who received pocket irrigation had significantly lower *Visual Analog Pain Scores* in the early postoperative period (1 and 6 hours postoperatively). These findings suggest that intraoperative administration of analgesics into the implant pocket may thus facilitate an early postoperative recovery.

Two new long acting local anesthetics seem to present a safer pharmacological profile, above of all for prolonged continuous infusion.

Ropivacaine is a long-acting amide local anesthetic released for clinical use in 1996[9,10]. Similar to bupivacaine, ropivacaine is equally effective for subcutaneous infiltration, epidural and peripheral nerve block for surgery, obstetric and post-operative analgesia.

Ropivacaine differs from most other amide-type local anesthetics in that it is marketed as a pure S-enantiomer, instead of as a racemate. This feature improves the safety of ropivacaine, and, indeed, studies have shown ropivacaine to have less cardiovascular and central nervous system toxicity than bupivacaine. Ropivacaine is nearly identical to bupivacaine in onset, quality and duration of sensory block, but it produces less motor block (half life about 2-6 hours for infiltration, 5-8 hours for peripheral nerve block, the maximum allowable dose dosage 250 milligrams).

Levobupivacaine is an enantiomer of the long-acting local anesthetic bupivacaine, which, as we stated previously, although currently the most widely used agent in surgery and obstetrics, is associated with potentially fatal cardiotoxicity[11,12].

Levobupivacaine 75 to 122 mg was less arrhythmogenic than the same dose range of bupivacaine in healthy volunteers. Its effects on the corrected QT interval were significantly weaker than those of bupivacaine, and it tended to have a weaker effect on QRS duration.

Levobupivacaine is as well tolerated as bupivacaine. Its onset and half life are very smiliar to the ones of bupivacaine (also if the duration of sensory block was significantly longer with levobupivacaine 0.75% than with levobupivacaine 0.5% or bupivacaine 0.5% or 0.75% in one study) and for this agent the maximum allowable dose dosage for each patient is of 150 milligrams.

A prospective double-blind study was conducted to compare the analgesic properties of levobupivacaine and ropivacaine in a bilaterally symmetrical mastopexy model[13].

In this recent study, each of the 18 patients undergoing bilateral mastopexy under conscious sedation received preoperative infiltration with levobupivacaine in 1 breast and equal volume of ropivacaine in the other.

Both anesthetics provided satisfactory analgesia for at least 10 hours, but constantly low pain scores were recorded for levobupivacaine for 10 hours postoperatively, whereas for ropivacaine only for 6 hours.

It is concluded that levobupivacaine is more effective for local infiltrative analgesia in mastopexy than ropivacaine, providing longer-lasting postoperative analgesia.

However, several clinical studies have evaluated the toxicology and clinical profiles of the three most important long acting local anesthetics; theoretically and experimentally, some differences can be seen, but the reflections of these characteristics into clinical practice have not been evident.

Evaluating randomised, controlled trials that have compared these three local anesthetics, it is possible to support the evidence that both levobupivacaine and ropivacaine have a clinical profile similar to that of racemic bupivacaine, and that the minimal differences observed between the three agents are mainly related to the slightly different anesthetic potency, with racemic bupivacaine>levobupivacaine>ropivacaine[14,15].

The most common adverse drug reactions to local anesthetics are neurological (seizures) and cardiac (conduction disorders, cardiac arrests)[16,17].

The possible side effects are very often associated to an accidental intra vascular injection and to a toxic dosage of the drug.

Neurological disorders include usually headache, dizziness, circumoral numbness and tingling of tongue, metallic taste, diplopia, blurred vision, tinnitus, slurred speech, muscle twitching, shivering, seizure, respiratory arrest.

Cardiovascular effects are instead usually detectable when plasmatic concentrations are very elevated and the neurological symptoms are easy to be observed.

Local anesthetics act directly on heart and on the vascular tone. They are associated to a vasodilatation and a negative inotropic effect dose related. In particular bupivacaine alters the action of calcium channels modifying the mitochondrial metabolism and causing, at high plasmatic concentrations, malignant arrhythmias, as ventricular fibrillation, refractory to medical therapy[18].

A local toxicity is also described. Generally it is possible to observe a traumatic and ischemic damage if an accidental intra-nervous injection is performed. Allergic reactions are very rare with the modern local anesthetics[19].

Esters are associated with a higher incidence of allergic reactions, due to a p-aminobenzoic acid (PABA) metabolite. Amide agents do not undergo such metabolism. However, preservative compounds (methylparaben) used in the preparation of amide-type agents are metabolized to PABA. Patients who are allergic to ester local anesthetics should be treat-

ed with a preservative-free amide local anesthetic. If the patient is not allergic to ester local anesthetics, these agents may be used in amide-sensitive patients. In the rare instance that hypersensitivity to both ester and amide local anesthetics occurs, or if skin testing cannot be performed, than alternative therapies including diphenhydramine, opioids, general analgesia, or hypnosis can be used.

A true immunologic reaction to a local anesthetic is rare. Intradermal skin testing of local anesthetic compounds, methylparaben, and metabisulfite should be performed in patients when a thorough history does not rule out a possible allergic reaction to local anesthetics and future local anesthesia is necessary.

Signs and symptoms of the various adverse reactions associated with local anesthetics are quite distinctive, permitting rapid diagnosis and treatment. Serious reactions are extremely infrequent and, when treated properly, unlikely to result in significant morbidity or mortality. The use of vasoconstrictor agents can influence the duration and even the intensity of the nerve blockade[20].

The prolongation of anesthesia obtained varies with the local anesthetic, its concentration, the type and concentration of vasoconstrictor and the site of injection. Although systemic reactions are generally mild, it should be used the minimal amount of vasoconstrictor agent, above of all in patients with heart disease.

Topical anesthetic creams have positive applications in plastic surgery[21].

For certain procedures, they can replace injected local anesthetics. By replacing injections with a topical cream, the negative effects associated with injections, such as pain, needle anxiety, and edema at the surgical site, are eliminated. A variety of *U.S. Food and Drug Administration*-approved topical anesthetic creams are available for use. Because a topical anesthetic agent will induce anesthesia painlessly, the need for an effective agent is clear. This will serve to eliminate painful injections with lidocaine prior to many dermatologic procedures.

Presently, EMLA (*Eutectic Mixture of Local Anesthetics*) is the most often used method among practicing dermatologists.

Usually during some kinds of plastic surgery, as breast augmentation or reduction, patients report the greatest postoperative discomfort in the first 48 hours.

In a recent randomized, single-blind study patients undergoing breast reduction and receiving intra-operative bupivacaine were discharged home significantly faster and required significantly less narcotic medication while recovering at home[22].

The Authors demonstrated as a corrected dose of intra-operative local anesthetics provides a safe, inexpensive, and efficacious way to significantly shorten the length of post-anesthesia care unit stay. Furthermore, moderate to severe pain is common after ambulatory surgery and is a frequent cause of delayed discharge. Postoperative pain, opioid-related side effects, and time to discharge were less when nonsteroidal anti-inflammatory drugs or local anesthetics were used intra-operatively to prevent pain before patient awakening[23].

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Botulinum toxin in dermatology.

Filippi GM

Institute of Human Physiology, Catholic University, Rome, Italy

Summary

Botulinum toxin in dermatology.

Botulinum toxin type A (Botox) and, recently, type B intramuscular administration are important in the treatment of many neurological disorders. More recently Botulinum toxin A administration was extended to other medical disorders and to some ageing skin evidences.
The action mechanism of this molecule is attributed to a decreased acetylcholine (Ach) release at the alpha motor axon ending. The reduced Ach release decreases muscle contraction. Botulinum toxin A is usually administrated by 1 ml syringes with 1.25-5 units at each injection site after a preplanning about the specific faces areas. Botulinum toxin A in therapeutic doses is a remarkably safe drug with relatively few adverse effects. They consist of weakness, asthenia, dry-mouth and reversible skin alterations. Some Authors say that Botulinum toxin A chemodenervation is less adequate than surgery for the ageing face. An important innovation in Botulinum toxin A use was introduced by performing iontophoresis in palmar hyperhidrosis and by documenting the suppressive effects on sweating. Botulinum toxin A use is rapidly increasing and it is important to keep in mind that Botulinum toxin A is a toxin.

Key words: *Botulinum toxin A; Facial lines; Hyperhidrosis.*

INTRODUCTION

During last twenty years, Botulinum toxin type A (*Botox*) and, recently, type B intramuscular administration became tremendously important in treatment of many neurological disorders. More recently Botulinum toxin A administration was extended to other medical disorders and to some ageing skin evidences, determining an important Botulinum toxin A diffusion in esthetic and cosmetic dermatology (ECD). There is a clear trend to an expansion of the application fields and, consequently, a parallel diffusion of the knowledge about Botulinum toxin A action mechanisms and its potential, even few, adverse effects is hoped.
Botulinum toxin A was initially (1989) approved to pharmacology act on two eye disorders: blepharospasm, a form of uncontrollable blinking and in strabismus, in which an alteration of eye extrinsic muscles motor control determines an eye misalignment.
Later (2000) Botulinum toxin A administration was approved to treat some neurological disorders of neck and shoulder muscle control (cervical dystonia). This step opened neurological diseases signed by spasticity to Botulinum toxin A treatment. A third relevant step was in 2002, when *USA Food and Drug Administration* (FDA) approved Botulinum toxin A administration in frown lines, on the basis of an extended review of studies on the topic showing a frown line decrease lasting up to 120 days[1-6].

ACTION MECHANISMS

Under a pharmacological point of view, Botulinum toxin A is derived from *Clostridium Botulinum* and different serotypes are produced by this organism: A, Botulinum toxin A, C1, D, E, F and G, featured by different action mechanisms and clinical effects.
Botulinum toxin A is considered the most powerful and was also the first to be introduced in clinical practice. The action mechanism of this molecule is attributed to a decreased acetylcholine (Ach) release at the alpha motor axon ending, i.e. at level skeletal muscle endplate. Skeletal muscle contraction can only be determined by the transmission of the electrical nervous signal (action potential) to the muscle fiber, in correspondence of the motor endplate. When the electrical signal is elicited in the muscle fiber, a cascade of chemical reactions performs the transformation of chemical energy (ATP) in mechanical and thermal energy. The transmission of the nervous action potential is guaranteed by nerve ending release of Ach. Such a release is allowed by Ca^{2+} nerve ending inflow which is reduced by Botulinum toxin A administration[7-9]. The consequent Ach release decrease reduces muscle power output and, more generally, decreases muscle contraction (i.e. chemical energy transformation in mechanical energy).
A more sophisticated, complementary, explanation of Botulinum toxin A mechanisms was forwarded by considering a possible a Botulinum toxin A action on spindles receptors, deputed to control motor execution and to concur to calibrate muscle tone[10, 11].
Actually such receptors are equipped with a set of contracting fibers on which Botulinum toxin A can also act, changing afferent muscle information to the central nervous system. Finally, an indirect action of Botulinum toxin A on the Central Nervous System was also suggested[12].

ADMINISTRATION

Botulinum toxin A is usually administrated by 1 ml syringes with 1.25-5 units at

Figure 1

Figure 2*

each injection site after a preplanning about the specific areas. Typically, a total of 25-75 units are administered, only occasionally a patient can receive 100 units. Particular attention has to be paid to the total Botulinum toxin A volume administered and to the area in which this volume is distributed[13]. Finally the injection depth and the sites are determined on the basis of a clinical analysis, the typical face regions in which Botulinum toxin A is injected are reported in Figure 1. Botulinum toxin A dosage is critical both to avoid adverse effects and to guarantee face symmetry. Pictures reported in Figure 2 and 3 show the most common forehead Botulinum toxin A injection sites, while crow's-feet ones are presented in Figure 4 [14].

Figure 3*

Figure 4*

Other regions on which Botulinum toxin A injection shows satisfactorily results include the upper lip, chin, platysma muscle[13,15,16].
Recently, Botulinum toxin A iontophoresis in palmar hyperhidrosis likes to be a particularly interesting administration modality[17].

Adverse events

Botulinum toxin A *"in therapeutic doses is a remarkably safe drug with relatively few adverse effects"*[18], they often consist of weakness, asthenia, dry-mouth and reversible skin alterations. Such effects are often produced by unapproved or nonclinical drugs. Adverse events in treatment of lines in upper face are very rare and a study on 945 subjects[19] reported about 5% of local hematoma and, below 2% of cases, ptosis, local pain, local skin irritation. All these events are spontaneously reversible.

Botulinum toxin A in esthetic and cosmetic dermatology

In the last years esthetic and cosmetic dermatology (ECD) in the world gained a previously unknown and increasing interest. A field which was not pertinent to medical disciplines matured and developed strong and important links with basic sciences, with medicine and is assuming a significant role in prevention. The efforts to attenuate the physiological aspects of ageing are particularly relevant, also with the important aim of separating physiological ageing phenomena from a poor care of our physiological necessities.
In this field cosmetic surgery with its difficulties and complexities saw an erosion in its demand because of the progressive diffusion and improvement of Botulinum toxin A treatment for hyperfunctional facial lines, particularly in the upper face (i.e. glabelar and frown lines and crow's feet). Actually muscle activity, underlying skin face lines has a prominent role in their development and maintaining.
Botulinum toxin A is a paralyzing agent which provokes a functional chemodenervation. If results are important and relevant, progressive and sophisticated attention was focused on a possible loss of mobility in mimic muscles of the treated areas. Digital photography and computerized imaging analysis allow to evidence that Botulinum toxin A injection reduced upward brow mobility by 71% 12 weeks after treatment ending, while frowning was decreased by 57% and the brow to brow distance was reduced of 13%[20].
Three-dimensional studies were also performed to evaluate roughness, anisotropy, number of microsulcus and their with throughout 6 months after Botulinum toxin A injection, showing significant improvements[21].
More complex and automated procedures were also used to verify Botulinum toxin A effects in dynamic conditions (a picture allows only a static study) in a quantitative way (*Automated Facial Image Analysis* AFIA) and evaluate facial expression in its parameter of acceleration, direction, displacement[22].
Results are important and the applied analysis procedures allowed to adjust doses and sites of injection.
Botulinum toxin A injection appears more efficacious to reach to an optimum in rejuvenation in conjunction with fillers, chemical peels to improve superficial texture and remove pigmentations[23-26].
Even though Botulinum toxin A improvements are relevant and evident, some Authors affirm that Botulinum toxin A chemodenervation is less adequate than surgery for the ageing face.
Finally there is a growing interest among men in cosmetic procedures and the number of male patients is increasing even if slowly. The minimally invasive aspects of Botulinum toxin A seem to be particularly attractive in USA, where Botulinum toxin A treatment among men is the first esthetic procedure[27]. The treated areas are the same as in women, however, likely because of their greater muscle mass, men need of higher Botulinum toxin A doses. At the same time, this aspect is considered the first cause of unsatisfactory result in male patient as the doses can be underestimated and clinicians with extensive knowledge knowledge and experience in the topic are needed.

Hyperhidrosis

Localized hyperhidrosis often occurs in the palms, the soles of feet and armpits and, generally, it is increased by psychological stress, while, at the same time, it increases psychological stress. Moreover excessive palmoplantar sweating is a trouble in daily activity. Current methods are ventilation, antianxiety or oral cholinergic blocking agents. In some intractable cases, sympathectomy has been performed. However, recently, Botulinum toxin A is emerging by USA and European studies as an efficacious suppressive agent[28-34].
In particular it was evidenced a 50% sweat reduction on the treated hand at 6 months after Botulinum toxin A injection. In order to obtain a satisfactory result it is often necessary to increase the injection sites and dosage. This

implies an increase in pain injection immediately after administration and, a more persisting reduction of grip strength. Pain can be usually reduced by using ice packs and cold water, to induce a transient desensitization, however these method are often insufficient and some authors recommend median and ulnar block[35]. An important innovation in Botulinum toxin A use was introduced by performing Botulinum toxin A iontophoresis in palmar hyperhidrosis and by documenting the suppressive effects on sweating[17]. This administration technique does not produce pain and it likes very promising. Concerning with the decrease of grip strength, some authors adfirm that can be indentified adequate dosages able to induce a satisfactory hyperhidrosis reduction without compromising grip strength[36].

CONCLUSION

In conclusion the results of from long-term experiences and open-label investigations suggest that the Botulinum toxin A has a favorable safety and tolerability profile across a broad spectrum of therapeutic uses[37]. Severe, even if transient, complications can be evidenced in patients in which more Botulinum toxin A may be required or when previous facial plastic surgery has altered anatomy, and those who have pre-existing neuromuscular disease[38]. A proper injection techniques, appropriate regional Botulinum toxin A dosing, and by being conservative in the overall approach to Botulinum toxin A-mediated facial rejuvenation are cautions to avoid complications.
Botulinum toxin A use is rapidly increasing and it is important that physicians keep in mind that Botulinum toxin A is a *toxin*.

* *Figures are author's responsability.*

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Scar treatment by lipostructure.

Caviggioli F, Klinger F, Forcellini D, Catania B, Salval A, Vinci V, Villani F, Klinger M

Cattedra di Chirurgia Plastica, Università degli Studi di Milano - U.O. Chirurgia Plastica 2
IRCCS Istituto Clinico Humanitas, Rozzano (Milano), Italy

Summary

Scar treatment by lipostructure.

Fat injection has been recently proposed as a promising regenerative treatment for defective and damaged tissues, such as burn scars, irradiated tissues and cicatricial ectropion. The aim of this study is to evaluate the safety and effectiveness of fat injection in burn scars. Eighteen informed voluntary patients (11 males and 7 females) with severe burn scars were selected and treated by Lipostructure®. VAS (Visual Analogue Scale) and VSS (Vancouver Scar Scale) were used to evaluate pain and the other objective and subjective scar features. VAS and VSS scores were obtained at preliminary evaluation, but also at 3, 6 and 12 months follow-up. All patients underwent a lipostructure procedure and futher lipostructure 3 months later. Mean VAS pre-surgery was 5.6, and mean VSS pre-surgery was 11.4. Mean VSS after first treatment was 8.8 (-22.8% from baseline); Mean VSS after second treatment was 6 (-47.4% from baseline). In all patients, satisfaction was excellent at each clinical examination. At 1 year follow-up examination, the tissue regeneration was preserved (mean VSS: 5.3). No complications occurred at the donor or recipient site. This study confirms the reliability and safety of our procedure in burn scars.

Key words: *Scar treatment; Lipostructure.*

INTRODUCTION

Autologous fat graft has been proposed since 1893 and fat injection since the 1920s. For a long time, fat injection for filling purposes, known as lipofilling, led to disappointing results: the injected fat had the tendency to reabsorb, making the results evanescent and unpredictable.

Since 1980, several papers have highlighted different findings on transplantation of fat obtained by liposuction[1-4], but adipocytes viability has been a controversial subject, with survival rates ranging from 30% to 70%[5-7].

In 1992, a turning point occurred when *Coleman*[8,9] described a new technique to improve and standardize adipocytes survival, naming it structural fat grafting or Lipostructure®.

Fat injection has been recently proposed as a promising regenerative treatment for defective and damaged tissues, such as burn scars[18], irradiated tissues[19] and cicatricial ectropion[20]. In addition, fat is abundant in the subcutaneous layer and its harvesting is a safe and simple procedure.

The aim of this study is to evaluate the safety and effectiveness of fat injection in burn scars.

MATERIALS AND METHODS

From December, 2005 to March, 2008, eighteen informed voluntary patients (11 males and 7 females) with severe burn scars were selected and treated by Lipostructure®.

Inclusion criteria were: hypertrofic scars resulting from severe burns occurred ≥ 5 years before surgery, VSS ≥ 9, VAS ≥ 5.

Exclusion criteria were: diabetes mellitus, systemic diseases affecting the normal healing process, smoke, dark skin.

Age and history of the patients were obtained. VAS (*Visual Analogue Scale*) and VSS (*Vancouver Scar Scale*) were used to evaluate pain and the other objective and subjective scar features (Table 1).

VAS and VSS scores were obtained at preliminary evaluation, but also at 3, 6 and 12 months follow-up. After clinical assessment and routine preoperative examinations, all patients underwent a lipostructure procedure and futher lipostructure 3 months later.

Both interventions were performed under continuous intravenous fentanyl infusion associated to local anaesthesia. After tumescent infiltration of 100 mL saline solution, 75 mg of levobupivacaine, 40 mg of mepivacaine and 0.5 mL epinephrine 1:1000, liposuction of the subumbilical area was performed.

An adipose tissue sample of about 60 mL was obtained and processed following *Coleman's* technique (i.e. centrifugated at 3000 rpm for 5 minutes).

Adipocyte-cell fraction was isolated (mean volume first treatment 26.4 mL, mean volume second treatment 23.9 mL) and was equally injected using an 18-gauge angiographic needle with a snap-on wing (by *Cordis®, a Johnson & Johnson Company, N.V. 9301 LJ, Roden, Netherlands*) at the dermal-subdermal junction of the cicatricial area.

All patients were followed up at two weeks, one month, three months, six months and one year after each surgery. The results were photographically documented at each clinical examination.

RESULTS

The average age of patients at injury was 96 months, whereas average age at first

surgery was 306 months. Mean VAS pre-surgery was 5.6, and mean VSS pre-surgery was 11.4. Clinical assessment was performed at three months, six months and 1 year after fat grafting; VAS and VSS of the patients were gathered at each examination (Table 1).
Mean VSS after first treatment was 8.8 (–22.8% from baseline); Mean VSS after second treatment was 6 (-47.4% from baseline).
In all patients, satisfaction was excellent at each clinical examination.
At 1 year follow-up examination, the tissue regeneration was preserved (mean VSS: 5.3).
No complications occurred at the donor or recipient site.

DISCUSSION

Fat graft and fat injection are currently performed in Plastic Surgery.
Lipostructure®, popularized by Coleman in the early 1990s, is nowadays a common and safe surgical technique.
Several variants of the original procedure are being successfully performed all around the world. Clinical and experimental applications are extending far from the original purposes and new indications in regenerative surgery have been proposed.
The safety and effectiveness of autologous fat injection in the treatment of retracted, painful scars[18,20,21] and radiotherapy tissue damage[19] have been reported.
Since the volume injected during our procedure is small, the early results (≤ 3 months) should not be attributed to a "*filler effect*", suggesting that deep biological interactions between transplanted fat and dermal-subdermal structures occur very soon.
On the other hand, long lasting effects (≥ 3 months) should not be attributed to the adipocyte fraction, but to mesenchymal stem cells from the stromal fraction of transplanted fat.

Table 1
VAS and VSS evaluation pre, 6 months and 1 year after surgery

Patient n°	Age at burn injury (in months)	Age at surgery (in months)	VAS pre surgery	VSS pre surgery	mL of adipose tissue inject. at 1 lipostruc.	VAS after first lipostructure	VSS after first lipostructure	mL of adipose tissue inject. at 2 lipostruc.	VAS after second lipostructure	VSS after second lipostructure	VAS at 6 months follow up	VSS at 6 months follow up	VAS at 1 year follow up	VSS at 1 year follow up
1	341	360	5	12	30	1	10	35	0	7	0	6	0	6
2	10	216	6	14	20	2	11	16	1	8	1	8	1	8
3	12	247	5	13	12	1	10	18	1	6	1	6	1	6
4	14	196	5	11	38	1	8	35	0	5	1	4	1	4
5	33	367	5	11	28	1	6	28	0	4	0	4	0	4
6	24	226	7	14	11	3	11	13	1	7	0	6	0	6
7	110	304	6	12	14	1	9	13	0	6	0	6	0	6
8	397	438	6	9	39	1	7	30	0	6	0	5	0	5
9	123	234	5	10	28	1	8	55	0	7	0	5	0	5
10	86	182	5	11	38	1	10	28	0	8	0	7	0	6
11	34	374	6	14	6	2	11	8	0	7	1	6	1	6
12	75	296	7	13	40	2	9	32	0	7	0	7	0	7
13	98	201	6	9	20	1	8	24	0	6	0	6	0	6
14	51	398	6	10	20	1	8	21	1	5	0	4	0	4
15	38	436	5	12	39	1	9	20	0	6	0	6	0	5
16	39	354	6	13	30	1	9	12	0	6	0	5	0	5
17	80	399	5	11	29	2	7	23	0	4	0	4	0	4
18	127	297	6	10	33	2	8	39	1	3	1	3	2	3
Average	***94***	***306***	***5,6***	***11,6***	***27,2***	***1,3***	***8,8***	***25***	–	***6***	–	***5,4***	***0,33***	***5,3***

VSS: The Vancouver Scar Scale consists of four variables: vascularity, height (thickness), pliability, and pigmentation. Each variable has four to six possible scores. A total score ranges from 0 to 14, whereby a score of 0 reflects normal skin.

Recent research has highlighted fat tissue as a source of stem cells.
Human adipose stem cells are an abundant population of pluripotent cells found in the stroma of adipose tissues that have shown a long term vitality, the ability to self-renovate[10], and differentiate into several histotypes of mesenchymal lineage[15-17], in-cluding osteogenic, myogenic, neurogenic[11-13] and hemotopoietic cells[14].
It has been suggested that both the molecular medium and cellular populations of transplanted fat could play a significant role in modulating scar remodelling, inflammation and pain.
In this series of patients, after only three-months follow-up, the clinical appearances and subjective patient feeling (VSS is one of the most frequently used scar assessment scale in clinical studies[22-27]) suggest a considerable improvement of skin texture and thickness; also at 6 months and one-year follow-up improvement of scars quality was preserved. Moreover, patients referred a striking reduction in pain, with a VAS reduction from a mean value of 5.6 to a 0.33 at the one-year assessment. We selected mature (≥ 5 years) scars, in order to standardize the procedure and to have homogeneous results.
This study confirms the reliability and safety of our procedure in burn scars[28, 29].
It is hard to preview future clinical applications, which could include the use of cryopreservation and cultured adipose-derived stem cell, as well as in other fields involving cell-based therapies using hematopoietic stem cells and umbilical cord blood cells.

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Keloids and hypertrophic scars: our experience with fractional CO_2 laser.

Scrimali L, Cassuto DA, Siragò P

University of Catania, Plastic Surgery Unit, Cannizzaro Hospital, Catania, Italy

Summary

keloids and hypertrophic scars: our experience with fractional CO_2 laser.

Keloid scars continue to be a complex and poorly understood subject. The main problem faced by researchers is the lack of an animal model, because keloids affect only humans.
Clinically keloids are distinguished from hypertrophic scars in that, keloids extend beyond the original wound and rarely regress; whereas hypertrophic scars remain within the confines of the original wound and often spontaneously regress. A variety of different types of skin injury can lead to keloid growth, including surgery, ear piercings, lacerations, abrasions, tattooing, vaccinations, injections, insect bites, burns, and any process resulting in skin inflammation (chicken pox, acne, folliculitis, and zoster). Skin or wound tension has also been implicated as a critical factor in keloid and hypertrophic scar formation.
A total of 8 consecutive patients (4 females and 4 males, F:M = 1:1ratio) with 12 scars (12 keloids) were included in this study. All patients were treated monthly with a MiXto SX CO_2 laser, with 13 W of power, 8 SX of index and 40% coverage (density), in association with Same Plast Gel® two times per day.
All patients responded to treatment and had positive results. The overall number of required treatments per scar was 12. All patients completed their treatment course and were followed up for 1 year after the last treatment without any recurrence.

Key words: *Keloids; Hypertrophic scars; CO_2 Fractional laser; Laser and Keloids.*

INTRODUCTION

Keloid scars continue to be a complex and poorly understood subject. The main problem faced by researchers is the lack of an animal model, because keloids affect only humans.
Keloids and hypertrophic scars are abnormal wound responses in predisposed individuals. These fibrous growths result from a connective tissue response to trauma, inflammation, surgery, or burns and occasionally seem to occur spontaneously. Clinically keloids are distinguished from hypertrophic scars in that, keloids extend beyond the original wound and rarely regress; whereas hypertrophic scars remain within the confines of the original wound and often spontaneously regress. Keloids and hypertrophic scars have been reported in people of all races, but a higher incidence of keloids occurs in people with darker skin types, particularly blacks, Hispanics, and Asians. Several reviews have reported the incidence of keloid formation to be 4.5% to 16% in these populations, with an equal male-to-female ratio. Most keloids occur in people between the ages of 10 and 30 years. A variety of different types of skin injury can lead to keloid growth, including surgery, ear piercings, lacerations, abrasions, tattooing, vaccinations, injections, insect bites, burns, and any process resulting in skin inflammation (chicken pox, acne, folliculitis, and zoster)[1,2]. Skin or wound tension has also been implicated as a critical factor in keloid and hypertrophic scar formation[3,4].

MATERIAL AND METHODS

A total of 8 consecutive patients (4 females and 4 males, F:M=1:1 ratio) with 12 scars (12 keloids) were included in this study. Patients ranged in age from 20 to 55 years with *Fitzpatrick skin types* II-IV. The age of scars ranged from 1 to 4 years.
The scars were classified according to the Vancouver Scars Scale (VSS).
Clinical digital photography was performed under standard and cross polarized illumination with a *Canon Eos digital Kiss X camera*. Scars were viewed and evaluated under parallel- and cross-polarized light magnification and were identified as keloids according to their extension compared to the original scar extension.
All patients were treated monthly with a MiXto SX CO_2 laser (*Lasering Srl, Modena, Italy*), with 13 W of power, 8 SX of index and 40% coverage (density), in association with *Same Plast Gel®* two times per day (*Savoma Medicinali SpA, Parma, Italy*).
Slim Evolution is a carbon-dioxide laser (CO_2) with a wavelength of 10.6 nm coupled with MiXto SX fractional system. The laser beam passing through a fractional system is delivered to the scanner handpiece with an articulated arm. Two different scanners inserts with spot sizes of 180 and 300 micron are available. The flexibility of MiXto SX allows working with advanced fractional method at the same time offering the option to use conventional ablation methods.
When fractional irradiation is selected, the *Computerized Pattern Generator* distributes the microspots in a precise square matrix.
The square dimensions vary from 6 x 6 to 20 x 20 mm for the 300 micron spot, and from 5 x 5 to 12 x 12 mm for the 180 micron one.
The density of the spots in the matrix, i.e. percentage of ablated epidermis, can be set from 5 to 40% while the exposure time for each spot varies from 2.5 to 16 msec through an index parameter. Microcrusting occurred after each treatment, a thermal water based sooth-

maturation of the scar will continue up to 12 months from the time of injury[11].
Early forms of fibroblasts persist longer in keloids than in normal scar tissue. In normal wound healing, connective tissue elements regress after the third week, whereas in keloids, fibroblasts proliferate around neovascular formations to form dense masses of collagen. This process can continue for months to years, thus determining the size of keloids[16]. The proliferating activity of fibroblasts is found to be significantly higher in keloids than in hypertrophic scars or in normal skin[16].
Oliver et al.[17] and *Babu et al.*[18] found that keloids derived fibroblasts exhibit as much as a fourfold increase in the rate of fibronectin biosynthesis compared to fibroblasts from normal dermis and normal scars. Fibronectin plays several important roles in wound healing, functioning to promote clot formation, development of granulation tissue, and re-epithelialization. Collagen synthesis in keloids is approximately 20 times greater than in normal unscarred skin and 3 times greater than in hypertrophic scars. 6 It is now known that growth factors play a role in scars contraction. Transforming growth factor β (TGFβ) and platelet-derived growth factor (PDGF) have recently been shown to be key factors in modulating contraction in normal skin fibroblasts. TGFβ strongly promotes the chemotaxis of fibroblasts to the site of inflammation to begin the production of extracellular matrix proteins. The activity of TGFβ is normally turned off when repair is complete. Dysregulation of TGFβ production or activity can cause abnormal fibrosis[19]. TGFβ can regulate its own expression in fibroblasts in an autocrine manner[20].
Younai et al.[21] showed that hypertrophic scar fibroblasts represent a heightened state of normal fibroblasts with an increased level of TGFβ secretion.
Kenneth C. et al.[22] in a recent article described an in vitro model, used to determine the effect of superpulsed CO_2 laser energy on normal dermal and keloid producing fibroblast proliferation and release of growth factors.
Growth factors assayed included basic fibroblast growth factor (bFGF) and transforming growth factor β_1 (TGF-β_1).
βFGF is mitogenic, inhibits collagen production, and stabilizes cellular phenotype.
TGF-β_1 stimulates growth and collagen secretion and is thought to be integral to keloid formation. Growth in a serum-free medium allowed measurement of these growth factors without confounding variables.
Keloid and normal dermal fibroblasts cell lines were established from facial skin samples using standard explant techniques. Samples consisted of three separate keloid and three separate normal dermal fibroblast cell lines. Use of the superpulsed CO_2 laser shortened population doubling times relative to that of controls; the differences were statistically significant in keloid dermal fibroblasts when fluences of 2.4 and 4.7 J/cm^2 were used bFGF was present in greater levels in normal dermal fibroblasts than in keloid dermal fibroblasts. Application of superpulsed CO_2 demonstrated a trend toward increased bFGF secretion in both fibroblast types; the increase was significant in the keloid group at 4.7 J/cm^2.
A consistent trend in suppression of TGF-β_1 was seen in both groups exposed to superpulsed CO_2, with the maximal effect occurring at 4.7 J/cm^2.
Superpulsed CO_2 enhances fibroblast replication and seems to stimulate bFGF secretion and to inhibit TGF-β_1 secretion. Given the function of these growth factors, the application of superpulsed CO_2 may support normalized wound healing.
These findings may explain the beneficial effects of laser resurfacing on a cellular level and support the use of superpulsed CO_2 in the management of keloid scar tissue[22].

CONCLUSIONS

The aim of this study is to demostrate that working in fractional modality with superpulsed CO_2, and spot diamiter of 300 μ reduces the risk of recurrence of scars after treatment. We suppose that treating this way keloids or hypertrophic scars, it's like intralesional excision of the scar, without the risk of radiotherapy. The results we obtain in our experience suggests this to be the safest way to approach patological scars and we hope to confirm this theory with more cases in our activity.

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Clinical and instrumental study for the evaluation of efficacy of an intradermal filler with or without food supplementation.

Sparavigna A

DermIng, Clinical Research and Bioengineering Institute, Monza, Italy

Summary

Clinical and instrumental study for the evaluation of efficacy of an intradermal filler with or without food supplementation.

Aim of the study was to evaluate, clinically and by non-invasive instrumental evaluations, the efficacy and the tolerance of an intradermal filler associated to food supplement on principal ageing/photoageing skin signs. 26 female healthy volunteers were enrolled. They were divided into 2 groups.
Group I (subjects performing intradermal implants with dermal filler associated to *Innéov Re-Age Fermeté* food supplement).
Group II (subjects performing only intradermal implants with *High Fill*).
The study duration was 28 weeks with 5 control visits. During the visits the following clinical and instrumental evaluations were performed: wrinkles grade at level of nasolabial folds and around the eyes, surface microrelief at level of the cheek, skin tonicity, skin brightness, skin replicas at level of nasolabial folds for wrinkles profilometric evaluation.
Clinical and instrumental evaluations confirmed the antiage activity of "*Innéov Re-Age Fermeté* and demonstrated as the food supplement increased the efficacy of the "*High Fill*" intradermal filler.
Treatment tolerance was optimal (final investigators' judgement: 100% = good-excellent); in fact no adverse event related to the tested products occurred during the entire study period.

Key words: *Intradermal filler; Food supplementation.*

PURPOSE

Aim of the study was to evaluate, clinically and by non-invasive instrumental evaluations, the efficacy and the tolerance of an intradermal filler associated to food supplement on principal ageing/photoageing skin signs. Two different experimental groups were compared:

Group I (subjects performing intradermal implants with dermal filler* associated to *Innéov Re-Age Fermeté* food supplement)

Group II (subjects performing only intradermal implants with *High Fill* *).

Selected volunteers, 13 for each study group, were healthy females, with aging or photo-aging skin signs.
It was also aim of this study to evaluate, at the end of the trial, the efficacy and the tolerance of the treatment judged by the volunteers.

MATERIAL AND METHODS

The present study enrolled 26 female healthy volunteers with aging or photo-aging skin signs, who have then been divided into 2 different groups:

Group I with food supplementation
Group II without food supplementation.

These subjects were under dermatological control for 6 months of treatment. During this period the following treatments were performed:
No 2 Intradermal implants with the injectable product, (one-month interval between the implants), for all included subjects.

Food supplement - 2 tables/day, taken in the morning only by subjects included in the Group I, starting one-month before the first intradermal implant for a total of 28 weeks.

Five visits were executed during the study:

T-1 = 1 month before the first intradermal implant
T0 = baseline (1st intradermal implant)
T1 = 1 month after the first intradermal implant (2nd intradermal implant–retouche)
T2 = 2 months after the first intradermal implant
T6 = at the end of the study (final visit, 6 months after the 1st intradermal implant).

To determine the efficacy of the study treatment, during the visits the following clinical and instrumental evaluations were performed mono-laterally at level of the right or left face side randomly (according to a predisposed randomisation list):

- **Wrinkles grade** (visual score) at level of nasolabial folds and around the eyes ("*crow's feet*") using a reference photographic scale:
  0 = No wrinkles
  1 = Very weak wrinkles
  2 = Weak wrinkles
  3 = Quite evident wrinkles
  4 = Evident wrinkles
  5 = Very evident wrinkles
  6 = Marked wrinkles
  7 = Very marked wrinkles
- **Surface microrelief** (visual score) at level of the cheek using a reference photographic scale:

* FILL, F.D.P. Medical srl, Italy, highly purified medical device made of cross-linked hyaluronic acid of non animal origin that is gradually absorbed by the body. Sterile, non pyrogenic, viscoelastic, water insoluble, biologically compatible gel implant, without particulates. Each syringe contains: hyaluronic acid cross linked, 20 mg; sodium chloride, 7.2 mg; sodiummonohydrogen-phosphat-dihydrat, 0.6 mg; water for injection, 1 ml. Viscosity: 6500 mPas.

1 = very regular - The primary lines present all the same depth. The secondary lines are well demarcated and form star like picture (apexes converge of several triangles)
2 = regular - Hiding and loss of secondary lines demarcation. Star-like pictures are still present but with less demarcated secondary lines
3 = irregular - Primary lines irregularity. Strong hiding of lines with low presence of star-like pictures
4 = very irregular - Strong deterioration in the skin. Deep primary lines distorsion and loss of secondary lines

- **Skin tone** (visual score):
  0 = very mild
  1 = mild
  2 = medium
  3 = marked
  4 = very marked
- **Skin brightness** (visual score):
  1 = very opaque
  2 = opaque
  3 = normal
  4 = luminous
- **Skin replicas** at level of nasolabial folds for wrinkles profilometric evaluation.
  This evaluation is conducted through a sophisticated computerised image elaboration. Replicas are illuminated with a 45° incident light, which creates shadows behind crests that can be photographed, digitised and analysed. The shadows are transformed into a grey scale, where grey intensities are directly proportional to shadows intensities and therefore to wrinkle depth. Shadows are detected by thresholding. Defining an area within the image, and tracing a segment of known length in a defined position across the wrinkle and perpendicular to it, it is possible to calculate the profilometric parameters as follows:
  R_a = *roughness average parameter which is the arithmetic mean of all ordinates from mean line of profile*
  R_t = *maximum wrinkles height*
  R_z = *wrinkles depth mean value*
  R_{max} = *maximum wrinkles depth*
  R_{min} = *minimum wrinkles depth*

Moreover, at the end of the study, volunteers' compliance and the possible events which could have interfered to the test result were evaluated.

Regarding treatment tolerance it was:
- recorded the adverse events during the entire trial period;
- evaluated any subjective sign and symptom as erythema, oedema, papules and pustules (dermatological assessment) in basal conditions (T-1), before each intradermal implant (T0, T1), 2 and 6 months after the1st implant (T2, T6).

Statistical analysis of experimental data was carried out as follows:
Evaluation 1 month, 2 and 6 months after the 1st intradermal implant *versus* basal conditions (T-1):
Friedmann test followed by, in presence of statistically significant results, *Tukey test*, for all clinical evaluations.
ANOVA test followed by, in presence of statistically significant results, *Dunnett test*, for all instrumental measurements.
Evaluation 1 month, 2 and 6 months after the 1st intradermal implant *versus* basal conditions (T-1) and *vs* before the 1st implant (T0)
Friedmann test followed by, in presence of statistically significant results, *Tukey test*, for all dermatological evaluations.
Comparison Group I *vs* Group II time by time *Wilcoxon test* for all clinical and dermatological evaluations.
Student t test for all instrumental measurements.

RESULTS

No "*drop-out*" occurred during the study; in fact all included subjects ended the trial as protocol directed.
No other important event which may have interfered to the test results occurred during the study period.

EFFICACY EVALUATION

Clinical evaluations

Statistical analysis *vs* basal conditions (T-1) showed for the Group I (intradermal implants associated to the food supplementation):
- starting from T1 an important and statistically significant (*Tukey test* $p < 0.05$ T1, T2 and T6 *vs* T-1) reduction of nasolabial folds score (of at least 1 degree) in 100% of treated subjects;
- a clinically and statistically significant reduction (*Tukey test* $p < 0.05$ T2 and T6 *vs* T-1) of skin roughness around the eyes (of at least 1 degree) in 77% of cases at T2 and in 78% at T6;
- a statistically significant increase (*Tukey test* $p < 0.05$ T2 and T6 *vs* T-1) of skin tonicity visual score in 77% of subjects at T2 and in 85% at T6;
- an evident and statistically significant improvement of skin brightness score, of at least 1 degree, (*Tukey-test* $p < 0.05$ T1, T2 e T6 *vs* T-1) in 92% of included subjects at T1 and T2 and in 100% at T6;
- a tendencial improvement (no statistically significant variation *vs* baseline was found) of cutaneous micro-relief at T6, corresponding to a reduction of basal visual score in 38% of treated volunteers.

Regarding the Group II (only intradermal implants) was exclusively highlighted:
- a statistically significant (*Tukey test* $p < 0.05$ T1, T2 and T6 *vs* T-1) reduction of nasolabial folds score (of at least 1 degree) in 100% of treated subjects at T1 and T2 and in 92% at T6, index of a very good and persistent filling activity of the injectable product;
- an statistically significant improvement of skin brightness score, of at least 1 degree, (*Tukey test* $p < 0.05$ T2 e T6 vs T-1) in 85% of treated cases at T2 and in 69% at T6.

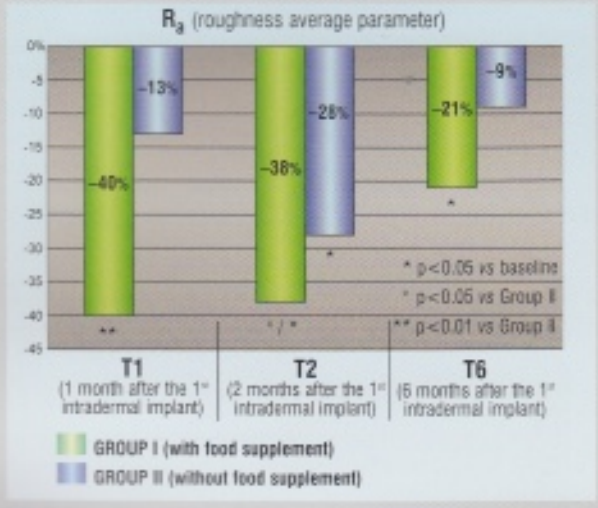
Moreover study groups comparison confirmed the antiage activity of food supplement; in fact the reduction of skin roughness around the eyes, the increase of skin tonicity, the improvement of skin brightness at T2 and T6 and the improvement of cutaneous micro-relief at T6 resulted statistically significant (*Wilcoxon test*) when compared to the group II results at equivalent time-points.

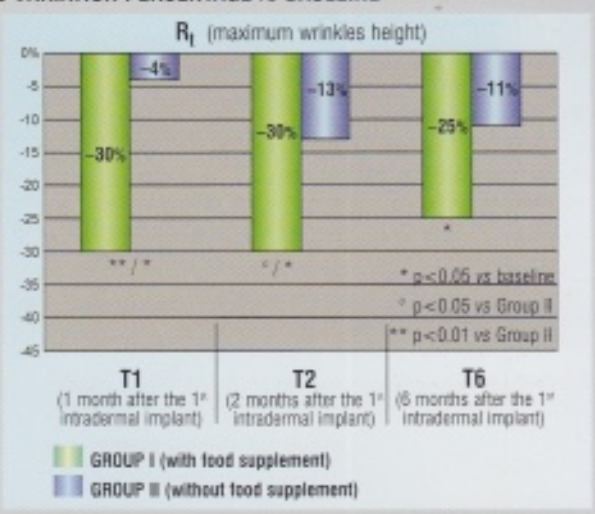
Skin profilometry

The image analysis of nasolabial folds replicas for the Group I (intradermal implants associated to the food supplementation) highlighted at T1, T2 and T6 a clinically and statistically significant reduction (*Dunnett test* $p < 0.05$ *vs* T0) of R_a and R_t parameters, that represent the mean roughness and the maximum wrinkle height (the absolute value between the highest and lowest peaks of a given profile).
The reduction percentages of above mentioned parameters *versus* baseline (T-1) resulted more marked when compared to the ones obtained for the Group II; in particular in Table 1 are summarised, for each study time, the variation percentages of all measured profilometric parameters *versus* baseline (T-1) and the achived statistical significance in comparison to the Group II (*Student t test*).

Obtained results show clearly as the food supplement intake increased the activity of filler product on nasolabial folds which appeared after the 1st intradermal implant and also after the 2nd significantly (*Student t test*) less deep and marked when compared to the Group II; at T6 this result is still present and clinically considerable, although no statistically significant difference *versus* control group was found.

Table 1. PROFILOMETRY: NASOLABIAL FOLDS VARIATION PERCENTAGE *vs* BASELINE





GROUP I (intradermal implants and food supplementation)	VARIATION *vs* BASELINE (%)		
	T1 (before the 2nd intradermal implant)	**T2** (2 months after the 1st intradermal implant)	**T6** (6 months after the 1st intradermal implant)
R_z (mean wrinkles depth)	**+2%** (*vs* –1.3% Group II)	**+3%** (*vs* +2.4% Group II)	**+0.2%** (*vs* +1.2% Group II)
R_{max} (maximum wrinkles depth)	**–2.5%** (*vs* –1% Group II)	**–2.1%** (*vs* –0.1% Group II)	**–2%** (*vs* –0.03% Group II)
R_{min} (minimum wrinkles depth)	**+9%** (*vs* +0.3% Group II)	**+10%** (*vs* +6% Group II)	**+8%** (*vs* +5% Group II)

Volunteer's efficacy judgment

69% of volunteers included in the Group I appreciated the efficacy of intradermal implants associated to the food supplementation on deep wrinkles (8% as very marked, 38% as marked and 23% as medium) and superficial wrinkles (46% as marked and 23% as medium). These percentages are comparable to the ones obtained for the Group II. A more consistent percentage of subjects noted the antiage activity of the food supplement on skin tonicity (69%-15% as very marked, 31% as marked and 23% as medium), skin smoothness (78%-39% as marked and 39% as medium) and skin brightness (85%-8% as very marked, 46% as marked and 31% as medium), that resulted at the end of the trial visibly improved.

TOLERANCE EVALUATION

Dermatological assessment

In Table 2 the percentages of subjects that presented subjective signs and symptoms as slight erythema, oedema are summarised.

For both groups no statistically or clinically significant variation, as well as no worsening of basal conditions was noticed.

Adverse events

No adverse event related to the study products (injectable product or food supplement) occurred during the entire study period.

For subjects n. 8 of Group I and n. 8, 11 and 13 of Group II the medical assessment performed at T2 and at T6 highlighted the presence of

Table 2. TOLERANCE: DERMATOLOGICAL SIGNS

GROUP I (intradermal implants and food supplementation)	SUBJECTS (%)				
	T-1 (baseline)	**T0** (before the 1st intradermal implant)	**T1** (before the 2nd intradermal implant)	**T2** (2 months after the 1st intradermal implant)	**T6** (6 months after the 1st intradermal implant)
Erythema	61%	39%	39%	0%	46%
Oedema	0%	0%	0%	0%	0%

GROUP II (intradermal implants)	SUBJECTS (%)				
	T-1 (baseline)	**T0** (before the 1st intradermal implant)	**T1** (before the 2nd intradermal implant)	**T2** (2 months after the 1st intradermal implant)	**T6** (6 months after the 1st intradermal implant)
Erythema	85%	69%	54%	23%	54%
Oedema	0%	0%	0%	0%	0%

some intradermal little nudules imputable to a temporary thickening of the injectable product at level of the treated area.
This is an expected effect dependent to a slower reabsorption of the filler and it is not considered an adverse event.

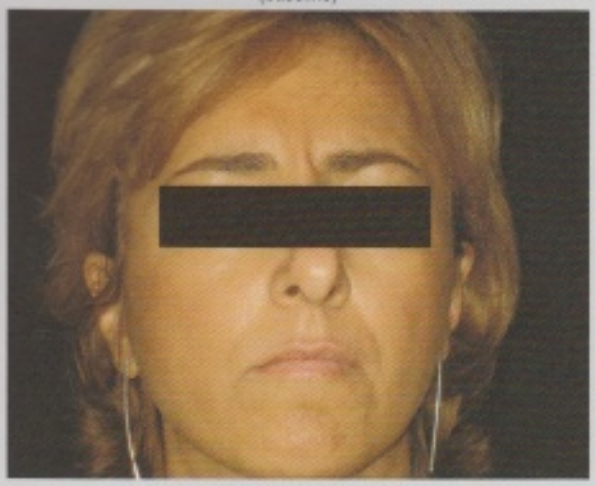
CONCLUSIONS

Clinical and instrumental evaluations confirmed the antiage activity of "*Innéov Re-Age Fermeté*" and demonstrated as the food supplement increased the efficacy of the "*High Fill*" intradermal filler.

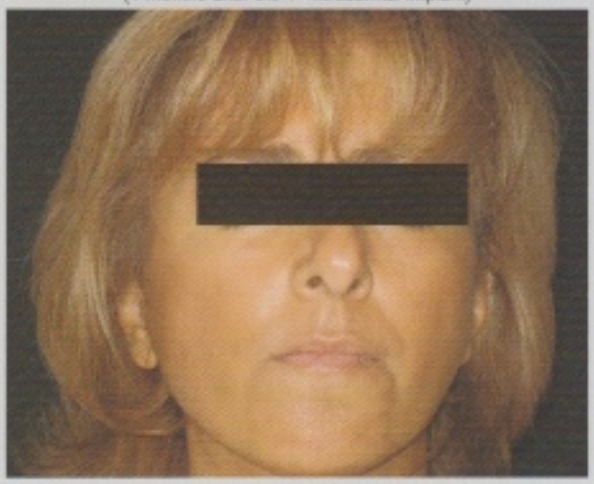
Treatment tolerance was optimal (final investigators' judgement: 100%=good-excellent); in fact no adverse event related to the tested products occurred during the entire study period.

GROUP I (with food supplement)

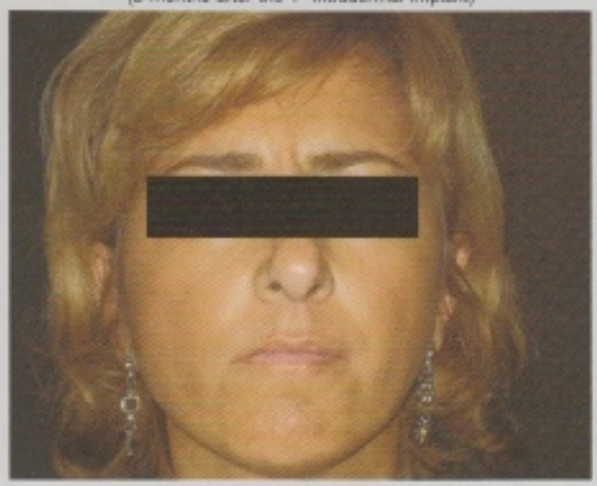
T-1
(baseline)



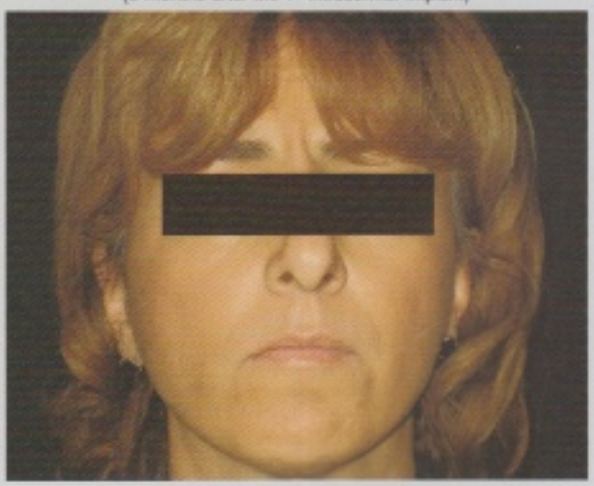
T1
(1 months after the 1st intradermal implant)



T2
INTERMEDIATE VISIT
(2 months after the 1st intradermal implant)



T6
FINAL VISIT
(6 months after the 1st intradermal implant)



LECTURES

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