Five Fluorouracil, Hyaluronidase and Triamcinolone in the Nasal Region.

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Abstract: The use of five fluorouracil (5 FU) as antifibrotic started in the 1960s, in hands of ophthalmologists, to prevent adherence after glaucoma and pterygium surgery. In 1999 Fitzpatric presented his experience in keloids and hypertrophic scars, making a great contribution to their treatment. Fibroblasts main function is collagen synthesis; in vicious scar the amount of collagen is normal, but what is altered is the ratio between collagen subtypes. The use of triamcinolone, the previous standard treatment produced different degrees of atrophy and telangiectasias. Infiltration is done in the center of fibrosis, weekly for the first month, then every 15 days until reaching the desired result. Softening, loss of volume and of retraction is seen since the first session. Also pain and itching disappears. Biopsy of treated scars has organized collagen fibers and less fibroblasts compared to non treated scars. Clinical applications: hypertrophic scars or keloids fixed to deep planes, "supratip" post rhinoplasty fibrosis, post rhinoplasty fibrosis (as preparation for other treatments), foreign body granulomas, and post burn retractions. The use in supratip deformity when secondary to rhinoplasty fibrotic scar has proven very effective, and also as preparation for surgical (secondary rhinoplasty) and no surgical (bioplasty) procedures. Our experience in the treatment of nasal scars, fibrosis and retraction with 5 FU is favorable. The results of infiltration with 5FU, hyaluronidase and triamcinolone in low dose have clinical and histological demonstration of collagen synthesis reduction and reorganization of collagen cicatrizal fibers.

Keywords: corticosteroids, fibrosis, fibrosis histopathology, fibrosis treatment, five fluorouracil, fibroblasts, foreign body granulomas, healing, hyaluronidase, hypertrophic scar, keloids, nasal aesthetics, nasal dermatology, nasal deformity, nasal reconstruction, post rhinoplasty fibrosisburn sequelae, scar, scarring disorders, supratip deformity.

INTRODUCTION

Since Fitzpatrick[1] published his work with five fluorouracil (5FU) in 1999 we included it in our daily practice. The most frequent use of this drug is for treatment and prevention of hypertrophic scars, keloids and foreign body granulomas[2].

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The particular anatomy of the skin in each nasal subunit makes scarring process completely different among them (Fig. 1). The skin of the tip is thick, has follicular units and sebaceous glands, whereas the dorsum skin is thin with almost no subcutaneous tissue. Because of these, the nasal tip skin uses to react violently to injury, with an important inflammatory process and residual edema that generates unaesthetic deformities. The dorsum skin uses to react softly to injuries, with light inflammation and scarring, but strong adherence to deep structures due to its thin composition. The etiology of scarring in the nose are:

Congenital (angioma)

Traumatic

Surgical

Infectious

Implants

Fig. 1- Anatomical structure of nasal tip and dorsum
Fibroblasts proliferation and migration play a major role in wound healing. Their main metabolic function is collagen, elastin and proteoglycans synthesis. Fibroblasts suppression in hypertrophic scars and keloids is essential since collagen synthesis is increased by 14% and 20% respectively compared to normal skin. Other studies show a higher amount of fibroblasts without significant increase in collagen synthesis, but with altered proportions between collagen I, III, and IV. This studies also show an increase production of fibronectin by fibroblasts. The local increase of collagenase inhibitors has also been reported.

Local steroids have been the gold standard treatment for nasal inflammatory and fibrotic processes for years, but its use has important side effects and complications. Triamcinolone usually generates different grades of skin atrophy and telangiectasias in the nasal tip and ala.

5 FU is a citostatyc antimitabolite drug, that inhibits cell proliferation by:

Inhibition of thymidylate synthase avoiding DNA synthesis.

Incorporation in RNA and DNA altering is function.

Interference with glycosyltransferases altering cell membranes (Fig. 2).

It has been proved in laboratory tests that 5 FU produces a slight reduction of collagen synthesis in normal fibroblasts but a drastic reduction in altered ones, as in Dupuytren illness[3]. Apparently it also inhibits the collagen synthesis stimulation effect of TGF1 (transforming growth factor).

5 FU has been used for years in treatment of premalignant and malignant lesions of skin and mucosa due to its selective toxicity for dysplastic epithelium and fibroblasts. The first application of 5 FU was as an antifibrotic to prevent fibrous scarring after glaucoma surgery and to avoid relapse in pterigion surgery in the sixties[4, 5, 6, 7, 8, 9]. In February of 1999 its use was reported to prevent fibrous adherence after tendon reconstructive surgery. One month after Fitzpatrick published his seven year experience of over a thousand patients with 5 FU in hypertrophic scars and keloids. This magnificent work encourage our team to include it in our office with positive results. Since Lambros published his work in 2004 [10] our team also added hyaluronidase. Fig.2- Molecular structure of 5 FU

This last is an enzyme that increases connective tissue permeability by hyaluronic acid hydrolysis. Hyaluronic acid is a polysaccharide of connective tissue and other
specialized tissues as the umbilical cord and the vitreous humor. Hydrolysis is done between the C1 of glucosamine and C4 of glucuronic acid. This reduces temporarily the intercellular cement viscosity, promoting diffusion of injected solution, exudates and transudates facilitating absorption.

Triamcinolone is a steroid, it diffuses through cell membranes binding with cytoplasmic receptors that are translocated to the nucleus generating the transcription of proteins that are responsible of their effects. It reduces tissue response to inflammation, reducing it symptoms without treating the specific cause. To do this it reduces the white blood cells (WBC) migration to the affected tissue. The most important effects are:

Inhibition of phagocytosis.

Inhibition of liberation of lysosomal enzymes and inflammatory mediators.

Reduction of capillary permeability and WBC adhesion to capillary endothelium.

Reduction of blood concentration of T-cells, eosinophils and monocytes.

Reduction of immunoglobulin binding with cellular receptors.

In the past 14 years we have been using a preparation of 5FU, hyaluronidase and triamcinolone for the nasal area and we have not had the complications and side effects observed with steroids monotreatment.

TECHNIQUE

5 FU (Fluorouracil- Filaxis 500mg) is presented commercially as ampoules of 10 ml containing 50 mg per ml. Triamcinolone (Kenacort-A-BSM) is used in its acetonide form of 40mg/ml, and is commercialized in ampoules of 1ml (Fig. 3). Hyluronidase (Unidasa Roux Ocefa) is commercialized in ampoules that contain 500 UI of testicular ovine freeze dried powder hyaluronidase. We use 2.7ml of 5 FU and 0.3ml of triamcinolone to reconstitute hyaluronidase (5 FU
solution). For the application a 0.3 or 0.5 ml Luer lock syringe and 30G needle are preferred. This allows a better dosage and correct plane of infiltration. We had never used more than 0.5 ml of the solution in the nasal area per session. The infiltration is done with multiple punctures in the “heart” of the fibrotic lesion. The first month one session is done per week, then is spaced to every fifteen days. The improvement is evaluated with 3 parameters: hardening reduction, loss of volume and reduction of cutaneous retraction. Positive changes are observed since the first session, not only in the above parameters but also in aesthetics and pain-itching symptomatology. Some cases are complemented with kinesiology treatment in order to obtain a better functional and cosmetic result.

HISTOPATHOLOGY

If after finishing the treatment a surgical procedure was needed to improve the result, the surgical piece was send to the pathologist and compared to non treated scarring tissue resections. Results informed reduction of fibrosis and rearrangement of collagen tissue in the treated pieces. These results are illustrated in the images. In the tissue of the right side of the scar proliferation of fibrous tissue, great amount of fibroblasts and collagen fibers forming tangles is seen (Fig. 4). In the tissue of the left, treated with 5 FU solution, there are less fibroblasts, and the collagen fibers adopt a parallel disposition (Fig. 5).
CLINICAL APPLICATIONS

Hypertrophic scars or keloids fixed to deep planes

"Supratip" post rhinoplasty fibrosis

Post rhinoplasty fibrosis (as preparation for other treatments)

Foreign body granulomas

Post burn retractions

Hypertrophic scars or keloids fixed to deep planes

The nose, being a mid facial and projected structure, is exposed to trauma that leave scarring sequels in the skin. Traumatic scarring if healed by second intention generates unaesthetic scars. The use of 5 FU, triamcinolone and hyaluronidase for hypertrophic scars and keloids in the nasal area is in our hands more effective and safe than the use of steroids.
Fig. 6- Nasal tip scar after cartilage graft infection and extrusion. Frontal view before and after 5FU injection and dermabration.

alone. When this scars are fixed to deep planes, the infiltration is done as preparation to subcision and then a filler as Polymethylmetacrilate (PMMA) is used to prevent the relapse of the adherence.

"Supratip" post rhinoplasty fibrosis

One of the most frequent complications of rhinoplasty is the healing fibrosis that is formed over the time known as “fibrous supratip”. It can be the result of a bad executed rhinoplasty or defective healing process. Is very frequent among beginners and even experts still have this complication. There are many causes of supratip deformity and each demand a specific treatment. Bahman Guyuron [11] conducted a clinical and histological study to unmask the surgical causes of this deformity. This study shows that clinical supratip is observed in 9% of primary and 36% of secondary consults of rhinoplasty. In primary cases the deformity is the result of: tip inadequate projection, caudal dorsum over projection, lateral inferior cartilages cephalic orientation, or a combination of these. In secondary cases the deformity is the result of: sub correction or overcorrection of caudal dorsum, over resection of medial valve, sub projected
tip, or a combination of these. The histophatological study of the supratip soft tissue demonstrated significant fibrosis in 14 from 16 secondary patients and 13 of 23 primary patients. The supratip deformity can be avoided through appropriate resection of caudal dorsum (in order not to leave dead space), nasal tip projection and joining with stitches the subcutaneous tissue over the cartilages in the supratip area. When early diagnosed, if the tip has adequate projection and the supratip tissue can be collapsed by pressure, the elective treatment is compressive tape. If after 6 weeks the response is not positive 0.2 to 0.4 ml of 5 FU solution is injected in the deep (Fig 8 and 9)

subcutaneous tissue. This infiltration can be repeated monthly until reaching the desired result (The judicious use 5 FU solution can help in most supratip Fig.9- Fibrose supratip after previous procedure solve after 5 year with 0.3 ml of 5FU single injection. Frontal view. Lateral view.
deformities caused by fibrosis when the caudal septum and the tip cartilages are strong. If the cartilaginous frame is weak, infiltration will not solve the problem. Infiltration can reduce a big supratip to a small one, but with an important risk of skin atrophy.

Other authors as Gruber [12] prefer to start with infiltration after 4 to 6 weeks of surgery, when most edema has disappeared. He uses 1 to 2 mg of triamcinolone (0.1 to 0.2cc of triamcinolone 10mg /cc) in the supratip or other fibrous area. Pastorek [13] uses small steroids dose during and immediately after surgery having excellent results in his hands. If a severe supratip deformity is the consequence of inadequate cartilage resection or sub projection of the tip, a surgical correction or bioplasty are needed. Sheen[14] suggested in 1979 that most supratip deformities were caused by caudal dorsum over resection. He proposed then the use of cartilage graft to correct this deformity.

Nowadays it is widely accepted that healing fibrotic tissue formed to fill the dead space is the most frequent cause of supratip deformity post rhinoplasty. But it was not until Guyuron's work that this was scientifically confirmed.

Fig. 10- Patient with 3 previous rhinoplasties. Three applications of 5 FU solution were done.
Post rhinoplasty fibrosis, as preparation for other treatments

After several surgical procedures, the nose can be involved in different grades of fibrosis turning the skin hard and inelastic. Before performing a secondary rhinoplasty or a bioplasty we prefer preparing the area with some applications of the 5 FU solution in order to soften the tissue (Fig. 10).

Foreign body granulomas

The use of fillers in the nasal area is a very popular method to correct slight deformities. There are many different materials and each of them produce a different degree of fibrotic reaction in the tissue. In most cases, this is a controlled reaction and lead to the expected result. But in some cases, an over reaction of patient immune system, bad application technique or the chemistry of the material used, provoke the formation of foreign body granulomas, resulting in unaesthetic deformities.

The use of triamcinolone in this cases can generate skin atrophy, thus turning the deformity more visible. When the filler used is hyaluronic acid, pure hyaluronidase should be infiltrated as stated by Brody [15]and Hirsch [16]. Infiltration is done with 100 UI in the area of hyaluronic acid excess (Fig. 11). This dissolves the acid, solving the fibrosis. When alloplastic materials were used, we preferred the 5 FU solution for infiltration because it does not have the side effects of steroids monotreatment. The application has a double effect, the pharmacological effect of the drugs, and the mechanical effect of disruption by the fluid pressure.

Post burn retractions

The nasal skin usually gets affected in facial burns. The scarring retraction can deform the tip, ala or both, stretching the nostrils. We use the 5 FU solution infiltration in these fibrous areas in order to increase the tissue elasticity and prepare them for secondary procedures as PMMA bioplasty or compound auricular graft.

COMPLICATIONS

The use of 5 FU solution, in young patients mostly, can cause tissue necrosis. This is relatively frequent in keloid treatment, resulting in ulcers or brown stains in the application spots. However in the nasal region we have not observed this complication, mainly because of the low dosage. In this way, by using progressive treatment instead of aggressive one, side effects are kept to minimum.

CONCLUSIONS

Through this chapter we presented our experience in the treatment of scars, fibrosis, retractions and deformities over the nasal skin. The results of our 14 year experience
with 5 FU solution (5 FU, triamcinolone and hyaluronidase) has the histopathological demonstration of effectiveness in collagen fibers synthesis reduction and fiber rearrangement, thus explaining the positive clinical effect.

CONFLICT OF INTEREST
None Declare

ACKNOWLEDGEMENT
None Declare

BIBLIOGRAPHY


