Observational Study

LIP AUGMENTATIONS WITH AGAROSE DERMAL FILLER: A 10-YEAR EXPERIENCE

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ABSTRACT

The process of facial aging is generally derived from intrinsic and extrinsic processes. The most significant changes occur in the dermis, where the amount of glycosaminoglycans and proteoglycans decreases. In general, aging is an atrophy process. The lips are the foundation on which the remainder of the perioral region is centered. The aging process of the lips begins with a proliferative phase from birth to pubescence; full, youthful-appearing lips are a direct effect of glandular and muscular hypertrophy. After puberty, a gradual atrophy of these structures occurs. The aging process includes the skin and supporting structures such as the teeth, muscles, and bone. Lip rejuvenation for the treatment of perioral rhytids is a procedure commonly requested by patients who are typically older than 50 years of age, smokers, or former smokers. The present study analyzed the use of the agarose gel for perioral rejuvenation. Newer advances in the use of fillers include agarose gel. A general increase in the indications for the use of soft tissue augmentation techniques was reported. Agarose gel has proven to be a reliable and predictable tool for perioral rejuvenation.

KEYWORDS: *filler, rejuvenation, perioral tissues, agarose, gel*

INTRODUCTION

The appearance of the mouth, teeth, and surrounding tissues provides insight into a number of factors such as age, social status, hygiene, and physical well-being and, in general, can even affect and influence one's perception and attitude (1). These structures are the most exposed parts when speaking and contribute to the first general impression, playing an important role in every occasion and conversation (2).

Teeth can hugely impact the aesthetic appeal of a smile, and the techniques used to improve their appearance, such as veneers, ceramic crowns, and the less invasive composite restorations, are fundamental in case of extensive tooth loss, diastema's closures, malpositions, and in the treatment of imperfect odontogenesis and severe dyschromia. It is also important to note that the aesthetic and functional results should be achieved using minimally invasive restorative techniques, preserving structures that contribute to defining and supporting the smile.

Color plays a pivotal role in the aesthetics of the lower third of the face; the idea of the white and perfectly shaped teeth spread during the Roman civilization. Patrician women were used to whiten their teeth by rubbing them with cloths soaked in urea-related compounds. Teeth tend to become darker over time, and white teeth have always been

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associated with a youthful smile. These changes are followed by the modification of lips and surrounding soft tissues derived from physiological aging. Teeth shape and related pathologies can also have a fundamental impact on the smile's appearance. In addition, the consequences of an improper vertical dimension, overjet, and overbite can cause irreversible changes to the muscles and skin of the perioral region. It can be deduced that rejuvenation or remodeling of the perioral region for the dentist represents a complementary intervention in addition to dental treatment. Various techniques such as peeling, connective tissue massage, biostimulation, and electroporation with collagen precursors and fillers are employed for this aim (3).

Fillers are widely used in dentistry as a complementary intervention to dental treatment, especially in complex prosthetic rehabilitation. They are divided into resorbable and non-resorbable. Absorbable fillers tend to be degraded by the action of certain enzymes, which reduce their tissue-supporting effect within 3-8 months. Permanent fillers guarantee a long-lasting effect and have a higher percentage of complications (temporary or permanent) that limit their clinical use (4).

Fillers made their appearance in the 1960s in the form of silicone oil. Today, increasingly innovative and technologically advanced materials ensure the integrity and complete biocompatibility of such products.

Soft tissue augmentation techniques began in 1893 when Neuber (5) used autologous fat, which did not guarantee adequate stability. In 1977, Knapp (6) introduced the purification of bovine collagen, and from this point on, it started to be used as filler. It was approved for this specific use by the Food and Drug Administration (FDA) in 1982, and it was, for many years, one of the few resorbable fillers available. Porcine-origin fillers represent another alternative with no risk for BSE transmission and no requirement for intradermal skin testing before use (7).

The introduction of hyaluronic acid has led to a considerable increase in dermatologists, dentists, and plastic surgeons using this type of filler. They started to be used to correct imperfections related to pathologies such as facial asymmetries and lipoatrophy in AIDS patients and even for the rejuvenation of perioral tissues (8). The latest filler proposed by scientific research is the agarose gel, created to enhance durability and eliminate the side effects observed with other fillers (9). Agarose is a saccharide polymer composed of repeated units of 3,6-anhydro-L-galactose and D-galactose. Due to its physical properties, agarose in water forms a hard gel with a 3D plastic mesh that is slowly resorbed and easily extruded through a 30-32 G needle. It is reabsorbed from the site of application by macrophages. After enzymatic destruction by galactosidase, an enzyme belonging to the glycosidase family, it is degraded through the pentose phosphate pathway at the level of the macrophages, platelets, and reticuloendothelial system (RES).

Due to its ability to retain numerous molecules and fluids, agarose gel can increase the volume of soft tissues. In addition, it has a longer duration than hyaluronic acid and collagen since there is no corresponding enzyme to reabsorb it. Its degradation only occurs after being processed by macrophages and then subjected to the action of galactosidases. This mechanism, therefore, guarantees longer-lasting results. Although the desired effect tends to decrease from the 4th month, the duration of agarose gel is 8/11 months. Its injectable, painless (isotonic and isosmotic), colorless, and transparent nature makes it an ideal material for soft tissue correction.

This article aims to share the experience gained over 12 years in using filler to create a pleasant smile in harmonious relation with the perioral tissues.

MATERIALS AND METHODS

Two hundred seventy patients needed volumetric lip augmentation (Fig.1). Agarose gels with concentrations of 1.5 and 2.5 from the companies Ghimas (Easy-Filler, Casalecchio di Reno-Bologna, Italy) and SIFARMA S.p.A (Easy-agarose, Milan, Italy) was used. Special 'total emptying' syringes allowed the use of the entire gel during the treatment.

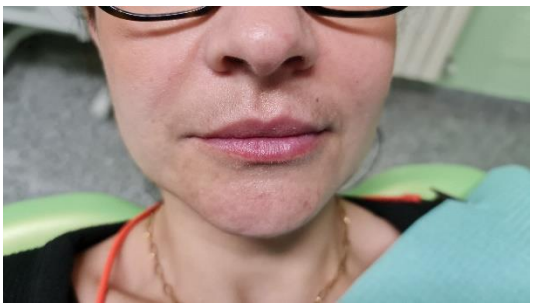

Fig. 1. *Before treatment.*

Patients treated with oral anticoagulants and suffering from severe systemic diseases, such as dialysis patients, were excluded. After the dental treatment, the patients were proposed to eliminate or diminish the skin perioral manifestations induced by chrono/photoaging and worsened by the dental pathologies.

The target area was disinfected and well-illuminated; any residual make-up was carefully removed. In some cases, especially in asymmetries, the area was highlighted with a dermographic pencil before starting the treatment to maintain the references. The needle was inserted into the mid-deep dermis, with the bevel pointing outward beneath the target zone. The correction was performed using the linear technique, releasing the product as the needle was withdrawn. A slow injection was carried out to achieve a better placement of the product in the desired sites, reducing trauma.

In some cases, the treated area was subjected to a gentle massage to promote the homogenous distribution of the material and to correct any excess. In addition, a further infiltration of agarose was performed after 1 or 2 weeks to correct slight asymmetries derived from an uneven distribution of the material (Fig. 2). All patients were advised about the need for periodic follow-ups.

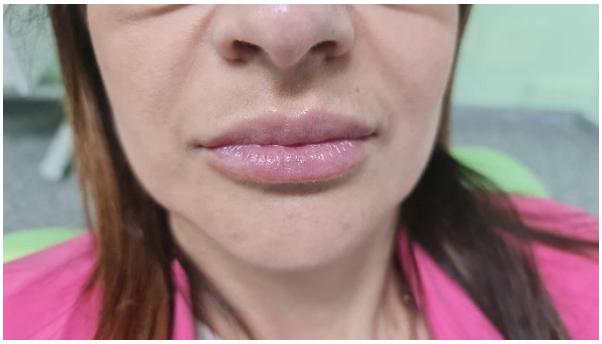

Fig. 2. *After treatment with agarose gel, a marked improvement was noted despite an initial situation difficult to resolve with fillers alone.*

The infiltrations were performed with a 30 G needle into the papillary dermis, preferably with a microponfi or 'nappage' technique and bleaching if necessary. The insertion angle was about 10° (as much as possible parallel to the skin surface), and the amount of material injected depended on the depth of the wrinkle. The infiltration was stopped as soon as the wrinkle was lifted by the agarose (100% correction). 0.6 ml was often sufficient to treat the entire perioral region. After 5 months, the lip's volume was diminished, but the result was still satisfactory. Adjustments were performed with a 0.5 ml syringe.

RESULTS

Two weeks after the first treatment, patients showed a significant improvement in lip volume (Fig. 2). The results remained unchanged for about 4 months after the first infiltration. The effects slowly but gradually wore off from this moment, so the treatment had to be repeated at 6 months (Fig. 3).

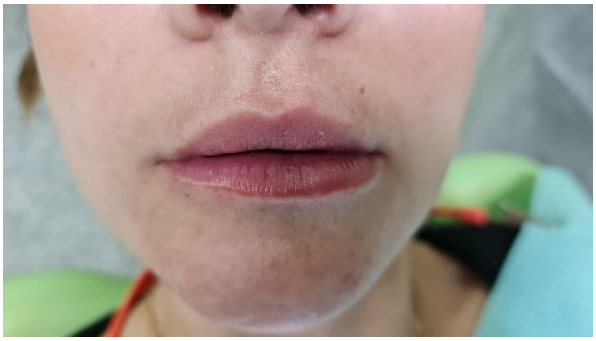

Fig. 3. *After 6 months a reduction in lip volume was observed, a situation requiring further adjustment with agarose filler.*

Dryness, roughness, and the "cigarette-paper" appearance of the epidermis considerably regressed. Tissue elasticity and hydration were significantly increased over the entire treated area. Furthermore, teeth appearances had a more harmonious relationship with the perioral soft tissues, and the results were defined as excellent by both the clinician and the patient. There were no important side effects, and erythema, edema, and ecchymosis related to the needle trauma were transient and regressed within a few days. None of the complications associated with using other fillers, such as nodular reactions, over-infections, abscesses, ulcerations, or migrations, were reported.

DISCUSSION

In the present study, agarose gel allowed attenuation or even erasing the main signs of aging by improving the harmony of the oral and extraoral tissues. As it affects the skin and the entire musculature of the lower third of the face, the perioral region aging is a fundamental issue for the dentist. Drooping labial commissures, undefined mandibular rim, and anterior and downward sliding of the muscle mass of the zygomatic region (with a subsequent drooping buccal corners and accentuation of the nasolabial groove) are the main effects of the aging process. Various conservative/minimally invasive and safe techniques, such as agarose gel, have been adopted to prevent or treat these effects.

Wrinkles are probably the most obvious 'photodamage' blemish and the least tolerated, as they are most often associated, in the collective imagination, with the aging phenomenon. The pathogenesis of wrinkles depends on the area of the skin where they occur. The tension of the mimic muscles plays a fundamental role in preventing folds in the overlying skin of the forehead, glabellar, periocular, neck, and décolleté areas. The correction of skin damaged by photo-exposure alterations or by dental disorders, which can affect the perioral zone, requires numerous methods and substances capable of attenuating or eliminating their effects. Generally, using filler alone is not enough to resolve wrinkles. In such cases, peeling, electroporation, ionophoresis, and botulinum toxin type A have proven to be effective adjunctive therapies (10). The documented numerous complications associated with the use of permanent fillers, such as silicone oil and then acrylamide (11), have led many dentists to not use these valuable tools.

Currently, the recent introduction of cross-linked hyaluronic acid and agarose gel has led to an increased interest among dentists and patients. The ideal filler should be biocompatible, non-toxic, non-allergenic, sterile, stable at the injection site without migrations to the adjacent areas, and easy to handle without side effects. All these characteristics are fully satisfied by the agarose gel. The biocompatibility of agarose is well known. The gel is well tolerated by cells and tissues and, in contrast to other vehicles suspended in solvents, it does not induce immune system responses (12).

In the present study, unwanted complications (e.g., nodule formation, foreign-body granuloma, or areas of necrosis), described often with the use of other fillers (13), were not observed. It is also worth mentioning that agarose gel is currently highly used as a biocompatible vehicle in numerous different fields of application in medicine and is employed as the main substrate in various biocompatibility tests, such as in cytotoxicity (14), genotoxicity (15), mutagenesis (16), sensitization (17) and subcutaneous implantation tests (18).

The extensive literature on the biocompatibility of agarose also highlights its safety in the different research fields, from 3D tissue growth (19) to its clinical use as a substrate for controlled drug delivery systems (20). Agarose gel fillers comprise a variable percentage of agarose (1%, 1.5%, or 2.5%), with the remainder comprising injectable water and sodium chloride. These formulations are essential for maintaining biocompatibility and preventing immune system stimulation or allergic reactions. The infiltration into the dermis enables partial replenishment of the hyaluronic acid physiologically lost and restoring the skin tone (21, 22). The product is injected into the dermis to provide a viscoelastic supplement to the extracellular matrix of the connective tissue, thereby increasing the tissue volume. Perioral soft tissue augmentation techniques represent additional therapeutic tools available to the dentist. The lower third of the face can significantly influence the overall aesthetic appearance, and the smile, along with other face regions and the neck, represents the starting point for treatment plans in dentistry.

Harmonization of the face begins with a smile, which may help to increase mental and physical well-being, self-esteem, and the ability to relate (23). An aesthetically pleasing smile increases awareness of oneself and one's abilities; it has a gratifying effect and satisfies the need for security and fulfillment that characterizes the man of the third millennium.

In recent years, the awareness of the social value of the smile has led to a progressive increase in requests for teeth whitening, veneers, and other treatments on perioral tissues that play a key role in defining the smile. Adequate lip volume, the absence of perioral wrinkles, and elastic, hydrated skin are all major elements of a beautiful and harmonious smile. Teeth appearance must also have a correct dimensional relationship with the gingival and perioral soft tissues in a 'golden' or divine proportion. The smile plays a crucial role in defining the emotional state of the individual, but it is also a great tool for communication, both verbal and non-verbal.

For all these reasons, cosmetic dentistry techniques are procedures that are increasingly in demand by patients. Dentists are driven to pay attention to the perioral soft tissues since dental treatment alone can improve the appearance of the smile. Still, an intervention in the perioral tissues allows them to harmonize and recreate the right golden ratio (12). A direct therapeutic intervention limited to the teeth would accentuate the existing discrepancies between the oral and extra-oral tissues. The patient would appear with 'youthful' teeth, while the lips and surrounding tissues would appear dehydrated, drooping, and have a dull, aged appearance.

CONCLUSIONS

Especially in complex prosthetic rehabilitations, the benefit of a combined approach in perioral tissue rejuvenation is evident. Clinical cases of patients treated with dental and perioral tissue rejuvenation procedures were presented. The results showed that the combination of the techniques mentioned above led to patient-pleasing outcomes.

The treatment of such conditions with agarose gel appeared to be a valid tool, capable of increasing perioral soft tissue volume without undesirable side effects and without requiring frequent infiltrations. By positively modifying the patient's physiognomy without incurring any risk of complications, the agarose gel was reported as an effective therapy for the rejuvenation and the correction of chrono or photo-induced alterations in the perioral region.

The results obtained from using agarose gel are satisfactory and comparable to those obtained from using other gels (24).

REFERENCES

1. Graber LW, Lucker GWilliam. Dental esthetic self-evaluation and satisfaction. *American Journal of Orthodontics*. 1980;77(2):163-173. doi:https://doi.org/10.1016/0002-9416(80)90004-4
2. Rufenacht CR. *Fundamentals of Esthetics*. Quintessence Pub. Co; 1990:373.
3. Iorio-Siciliano V, Ramaglia L, Isola G, Blasi A, Salvi GE, Sculean A. Changes in clinical parameters following adjunctive local sodium hypochlorite gel in minimally invasive nonsurgical therapy (MINST) of periodontal pockets: a 6-month randomized controlled clinical trial. *Clinical Oral Investigations*. 2021;25(9). doi:https://doi.org/10.1007/s00784-021-03841-8
4. Dadzie OE, Mahalingam M, Parada M, El Helou T, Philips T, Bhawan J. Adverse cutaneous reactions to soft tissue fillers--a review of the histological features. *Journal of Cutaneous Pathology*. 2008;35(6):536-548. doi:https://doi.org/10.1111/j.1600-0560.2007.00853.x
5. Neuber F. Fettransplantation Bericht uber die Verhandlungen der Deutscht Gesellsch Chir. *Zentralblatt fur Chirurgie*. 1893;22:66.
6. Knapp TR, Kaplan EN, Daniels JR. Injectable collagen for soft tissue augmentation. *Plastic and Reconstructive Surgery*. 1977;60(3):398-405.
7. Shoshani D, Markovitz E, Cohen Y, Heremans A, Goldlust A. Skin Test Hypersensitivity Study of a Cross-linked, Porcine Collagen Implant for Aesthetic Surgery. *Dermatologic Surgery*. 2007;33:S152-S158. doi:https://doi.org/10.1111/j.1524-4725.2007.33355.x
8. Bezzola A, Micheels P. Esthelis®, acide hyaluronique de conception suisse. Premiere etude complete des caracteristiques physicochimiques et essais cliniques. *Journal de Medecine Esthetique et de Chirurgie Dermatologique*. 2005;32(125):1120.
9. Fernández-Cossío S, León-Mateos A, Sampedro FG, Oreja MTC. Biocompatibility of Agarose Gel as a Dermal Filler: Histologic Evaluation of Subcutaneous Implants. *Plastic and Reconstructive Surgery*. 2007;120(5):1161-1169. doi:https://doi.org/10.1097/01.prs.0000279475.99934.71
10. Diamond A, Jankovic J. Botulinum toxin in dermatology - beyond wrinkles and sweat. *Journal of Cosmetic Dermatology*. 2006;5(2):169-169. doi:https://doi.org/10.1111/j.1473-2165.2006.00250.x
11. Narins RS, Jewell M, Rubin M, Cohen J, Strobos J. Clinical Conference: Management of Rare Events Following Dermal Fillers-Focal Necrosis and Angry Red Bumps. *Dermatologic Surgery*. 2006;32(3):426-434. doi:https://doi.org/10.1111/j.1524-4725.2006.32086.x
12. Scarano A, Carinci F, Piattelli A. Lip augmentation with a new filler (agarose gel): a 3-year follow-up study. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology, and Endodontics*. 2009;108(2):e11-15. doi:https://doi.org/10.1016/j.tripleo.2009.04.025
13. Jesús Fernández-Aceñero M, Zamora E, Borbujo J. Granulomatous Foreign Body Reaction Against Hyaluronic Acid: Report of a Case After Lip Augmentation. *Dermatologic Surgery*. 2003;29(12):1225-1226. doi:https://doi.org/10.1111/j.1524-4725.2003.29392.x
14. Belpaeme K, Delbeke K, Zhu L, Kirsch-Volders M. Cytogenetic studies of PCB77 on brown trout (Salmo trutta fario) using the micronucleus test and the alkaline comet assay. *Mutagenesis*. 1996;11(5):485-492. doi:https://doi.org/10.1093/mutage/11.5.485

15. Cho YS, Hong ST, Choi KH, Chang YH, An Sik Chung. Chemopreventive Activity of Porphyrin Derivatives Against 6-Sulfooxymethylbenzo[a]pyrene Mutagenicity. *PubMed*. 2000;1(4):311-317.
16. Marczylo T. Protection against Trp-P-2 mutagenicity by purpurin: mechanism of in vitro antimutagenesis. *Mutagenesis*. 2000;15(3):223-228. doi:https://doi.org/10.1093/mutage/15.3.223
17. Naziruddin b, Durriya S, Phelan D, et al. HLA antibodies present in the sera of sensitized patients awaiting renal transplant are also reactive to swine leukocyte antigens 1,2. *Transplantation*. 1998;66(8):1074-1080. doi:https://doi.org/10.1097/00007890-199810270-00018
18. Gu Y, Tabata Y, Kawakami Y, et al. Development of a New Method to Induce Angiogenesis at Subcutaneous Site of Streptozotocin-Induced Diabetic Rats for Islet Transplantation. *Cell Transplantation*. 2001;10(4-5):453-457. doi:https://doi.org/10.3727/000000001783986693
19. Amedee J, Bareille R, Jeandot R, et al. Evaluation of cell colonization on biomaterials: preventing cell attachment to plastic containers. *Biomaterials*. 1994;15(12):1029-1031. doi:https://doi.org/10.1016/0142-9612(94)90086-8
20. Wang W, Gu Y, Miyamoto M, et al. Effect of Basic Fibroblast Growth Factor on Insulin Secretion from Microencapsulated Pancreatic Islets: An In Vitro Study. *Cell Transplantation*. 2001;10(4-5):465-471. doi:https://doi.org/10.3727/000000001783986521
21. Ghersetich I, Lotti T, Campanile G, Grappone C, Dini G. Hyaluronic acid in cutaneous intrinsic aging. *International Journal of Dermatology*. 1994;33(2):119-122. doi:https://doi.org/10.1111/j.1365-4362.1994.tb01540.x
22. Scarano A, Puglia F, Cassese R, et al. Hyaluronic acid fillers in lip augmentation procedure: a clinical and histological study. *Journal of Biological Regulators and Homeostatic Agents*. 2019;33(6Suppl2):103-108.
23. Albino JE, Tedesco LA, Conny DJ. Patient perceptions of dental-facial esthetics: shared concerns in orthodontics and prosthodontics. *The Journal of prosthetic dentistry*. 1984;52(1):9-13. doi:https://doi.org/10.1016/0022-3913(84)90172-0
24. Cantisano-Zilkha M, Bosniak S. Hyaluronic acid gel injections for facial rejuvenation: A 3year clinical experience. *Operat Tech Oculoplast Orbital Reconstr Surg*. 1999;2:177-181.