

Soft Tissue Augmentation: A Clinical Comparison of Injectable Soft-Tissue Fillers for Volume-Augmentation

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ABSTRACT

While injectable fillers for volume-augmentation have been extensively marketed, there are few published reports comparing the clinical efficacy and cost effectiveness of multiple injectable agents for soft-tissue augmentation.

We present our experience in treating 93 patients with the use of 5 common injectable agents in our locality: Restylane, Juvederm, Bio-alcamid, Esteform and Amazingel for soft tissue augmentation in different parts of the body. We analyze the injection characteristics of each filler, including injection volume, complication rate, revision rate and longevity. The clinical efficacy and patient satisfaction were evaluated.

INTRODUCTION

Early signs of aging include a deepening of facial folds, an increase in muscle-induced wrinkling and even a loss of facial volume. These changes are caused by alteration of the extracellular matrix of the connective tissue and skin. Loss of volume of the subcutaneous tissue also contributes to this process in the face and other parts of the body. The youthful face has a soft, full appearance, as opposed to the flat, pulled, two-dimensional look often achieved by more traditional surgical approaches [1,2]. Different strategies have been developed to reduce the visible effects of these alterations. One common strategy is to refill altered connective tissue matrices or subcutaneous tissue by injection of different agents to enhance contours, either intradermally or subcutaneously [2].

First attempts for subcutaneous filler materials were made in 1960s and 1970s with the use of silicone oil, with devastating results in many cases [2,3]. Since then, many different materials have been used for this purpose which can be categorized under these groups; biological, synthetic and the off-label use of synthetic materials. The biological materials are further divided into autologous, allogenic, or xenogenic transplants [1,2,3].

Autologous fat has to be harvested by liposuction and processed before injection and all reports

on successful fat grafting have been anecdotal, with no statistics on the "take" of fat have been published, otherwise, there would be no need for artificial fillers [1,3].

Although the number and variety of products being developed and evaluated for soft tissue augmentations are impressive, yet the ideal filler has not been found; neither have physician agreed on the properties that would be appropriate for all fillers [4,5]. These agents should be; non-toxic, non-carcinogenic, non-immunogenic, biocompatible and not be reabsorbed or degraded by the host organism, with predictable results for permanence, bulk and behavior. Although permanence would clearly be a virtue, it could also be a negative if the filler used did not age appropriately as the patient's soft tissues became ptotic and attenuated, so it should have long-lasting results but yet non-permanent. The material has to stay at the site of injection without migrating into the surrounding tissues. It should be safe, in-expensive and easy to use with minimal downtime [1,2,4,5,6].

Hyaluronic acid derivatives are currently available and provide safe and effective soft-tissue augmentation. They do not require pre-injection skin testing and produce reproducible, longer-lasting, non-permanent results compared with other fillers specially collagen [1,5,7]. Both collagen and hyaluronic acid are removed by phagocytosis over a period of 3-24 months [1,3].

Polyacrylamide hydrogel has been used extensively for body contouring for more than fifteen years. It is injected subcutaneously and approved for facial or body contouring under different brand names [2,3].

Key components to optimal filler administration include proper anatomical evaluation, changing or combining various fillers based on the carrier substance and its particle size, altering the depth

of injection, using different injection techniques, host defense mechanism, the injected area if there is a constantly moving wrinkle, host defense mechanism and co-administration of butulinum toxin type A when indicated [6].

MATERIAL AND METHODS

Ninety three patients, aged between 21 and 63 years, underwent soft tissue augmentation in different body regions for different causes. They were collected from the outpatient clinic at El-Minia University Hospital, our Private clinic, El-Minia, Egypt and the outpatient clinic at "The Consulting Center for Plastic Surgery", Riyadh, KSA, in the period from March 2006, to April 2008.

Subjects with facial contour deformities or soft tissue deficiencies caused by aging, acne, trauma, surgery, or other causes were included. Persons presented with pregnancy, lactation, connective tissue disorders, skin disorders, uncontrolled diabetes mellitus, compromised immune functions or acute inflammatory disease, known drug abuse or allergy, or mental disorders were excluded from this study. The primary areas treated were lips, nasolabial folds, malar eminence, sunken cheeks, marionette lines, pre-mental or lateral orbital depressions, acne scars, surgical soft tissue defects and other sites.

Materials used in this series of cases were five agents among the most commonly used fillers in our practice, namely; Restylane, Juvederm, Bio-alcamid, Esteform and Amazingel.

Restylane (Q-Med Co., Sweden) was used for superficial wrinkles, lip contouring or augmentation, or on top of Perlane injection. Perlane (Q-Med Co., Sweden) was used for naso-labial fold or malar augmentation. Juvederm (Allergan, Pharmaceuticals Inc., Irvine, California, USA) was used for superficial wrinkles, naso-labial fold, malar augmentation, or lip contouring and augmentation. Bio-alcamid (Polymekon Co. Ltd, Brindisi, Italy) was used in Mala, cheek, or chin augmentation. Esteform (Safe Fill Co. Ltd, Ukraine) was used for cheek, malar, or chin augmentation. Amazingel (Merrystone Medicine Science and Technology Development Co. Ltd, China) was used for cheek, malar, chin augmentation and around lateral orbital wall.

The amount of injectable material ranged between 1-30ml according to the area to be treated. The revision dose ranged between 1-10ml.

Gel injection (colorless gel that was provided in sterile container) was performed under local anesthesia infiltration at site of entry port of the injection needle with 0.5ml of "Xylocain 1%" or through a nerve block to the area to be treated. The filler was administered to the intra-dermal or subcutaneous tissue using a thin 23-30-gauge needle. Injection starts in a retrograde manner when the needle is withdrawn again. Different injection techniques were used; the linear threading injection, the serial puncture injection, the fan technique, or the cross-hatching method. Immediately after injection, gentle manipulation of the augmented tissues ensures an even distribution of the filler. In areas with a thicker subcutaneous space, the filling with the Polyacrylamide gel starts with deeper injections to fill the lost volume of tissue. After finishing injection, the site of the entry port of the injection needle was dressed with a small piece of "Steri-strip" tape. Patients were advised not to touch the treated area for next 24-48 hours and avoid sleeping on their faces. After 24 hours, they can wash their faces gently [1,7].

Next follow-up session for revision was after 7-10 days. If some bruises or ecchymosis appeared, patients were advised to use a topical vitamin K oxide ointment with gentle massage, tangentially and upwards. They were examined for possible adverse events. After that, they were followed-up about every 2 months. Standardized photographs were taken before injection and at follow-up visits. Appearance, softness and overall patient satisfaction were recorded.

The outcome was categorized to be "excellent", "very good", "good" or "bad" by another investigator. Patient satisfaction with the results was assessed to be "very satisfied", "satisfied", or "not satisfied" [2].

RESULTS

A total number of 93 patients were treated by injectable fillers. Of the treated patients, 74 were female (79.6%), with a mean age of 37.8 ± 7.1 years (\pm SD), 19 persons were male (20.4%), with a mean age of 42.3 ± 6.4 years (\pm SD) (Table 1). The youngest woman was 21 years old and the oldest woman was 63 years old. The youngest man was 24 years old and the oldest was 53 years old. Five patients were lost for follow-up.

The amount of injectable materials ranged from 0.8-30ml in the first session. For revision, the injected amount ranged from 1-10ml.

The esthetic outcome was judged by a second investigator to be "excellent" in 29 (31.2%) and "very good" in 37 (39.8%). In 17.2 percent, results were judged to be good (16 cases). In 11 of the cases (11.8%), it was considered bad, in the form of no or only very little effect resulted after injection (Table 2). The best results, with the highest patient satisfaction, were found in cases injected with Restylane for lip augmentation (30 out of 36 cases). The least results were encountered with cases injected with Bio-alcamid for malar augmentation (5 cases) (Table 3).

Tables (5,6) shows the types of fillers injected in this series with their distribution as a single filler or combinations. In Table (7), shows the sites of injection of the fillers.

Adverse events were observed in 32 cases (34.4%) (Table 4). They were most commonly

presenting as moderate or severe pain that occurred with injection in 12 patients (12.9%) but disappeared 2 to 5 minutes after injection without treatment. Transient local tissue reaction or edema was observed in 8 cases (8.6%) but resolved spontaneously, and a hematoma formation in 5 cases (5.4%) that resolved either spontaneously or after massage with vitamin K oxide cream. Five patients developed early unwanted collections [three patients (3.2%) had persistent visible mucosal lip nodules, but no one required intervention and two cases (2.15%) with gel accumulation and lump formation in nasolabial fold and cheek that needed withdrawal]. In another case (1.07%), a slight change of skin color at the site of injection was observed. Another patient, with the longest follow-up period (Fig. 1A,B,C,D), developed a sterile abscess with gravitation of the material that needed drainage. No severe adverse effect related to the material injected was reported.



Fig. (1-A): Pre-injection view.

Fig. (1-B): Post-injection view of Malar and cheek injected with Bio-alcamid (16 months).

Fig. (1-C): Abscess formation on left side of cheek (22 months).

Fig. (1-D): After drainage of the abscess.



Fig. (2-A): Pre-injection view of Malar and anterior cheek depression.

Fig. (2-B): Post-injection view after Bio-alcamid injection (three weeks).



Fig. (3-A): Pre-injection view of lateral-orbital depression.

Fig. (3-B): Post-injection view after injection of Amazingel (two weeks).



Fig. (4-A): Pre-injection view of a facial post-traumatic wound.



Fig. (4-B): Post-injection view after injection with Perlane 1ml.



Fig. (5-A): Pre-injection view of Malar atrophy.

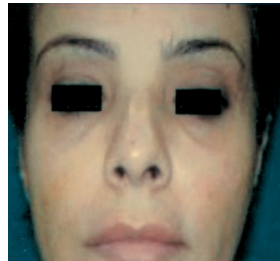


Fig. (5-B): Post-injection view of Mala and tear trough with Amazingel injection (10 days post-op).



Fig. (6-A): Pre-injection view of facial asymmetry.



Fig. (6-B): Post-injection view after correction with Esteform 10cc.

Table (1): Sex distribution of cases injected with one filler or more.

	Total	One filler	Two fillers
Female	74	54	20
Male	19	12	7
Total	93	66	27

Table (2): The esthetic outcome.

Esthetic results	Cases	%
Excellent	29	31.2
Very good	37	39.8
Good	16	17.2
Bad	11	11.8

Table (3): Patient' satisfaction.

Satisfaction	Type of filler						Total %
	R	P	J	B	E	A	
Very satisfied	30	13	7	2	12	16	66.66
Satisfied	5	6	5	2	6	4	23.33
Not satisfied	1	2	1	5	2	1	10.00

Table (4): Adverse effects.

Adverse effect	Cases	Percentage
Pain (During or after injection)	12	12.90
Transient reaction or edema	8	8.60
Hematoma	5	5.37
Mucosal nodule	3	3.22
Lump accumulation	2	2.15
Discoloration at site of injection	1	1.07
Development of a sterile abscess	1	1.07
Total	32	34.40

Table (5): Type of filler injected either alone or combined with other filler.

Type of filler injected	Alone	Combined with another filler	Total
Restylane	19	17	36
Perlane	6	15	21
Juviderm	8	5	13
Amazingel	13	8	21
Esteform	13	7	20
Bio-alcamid	7	2	9
Total	66	54/2=27	120-27=93

Table (6): Distribution of combined fillers (more than one filler in the same case).

Combined fillers	R + P	R + E	P + A	J + A	J + B	Total
Females	7	6	3	2	2	20
Males	3	1	2	1	0	7
Total	10	7	5	3	2	27

R: Restylane. A: Amazingel.
 P: Perlane. J: Juviderm.
 E: Esteform. B: Bio-alcamid.

Table (7): Treated areas in the studied cases.

Area	Number of cases	%	Type of filler injected					
			R	P	J	B	E	A
Lip	36	30.00	26	–	10	–	–	–
Naso-labial fold	25	20.83	7	15	1	–	1	1
Chin	7	05.83	–	2	–	2	1	2
Peri-orbital depression	2	01.66	–	–	–	–	–	2
Cheek	20	16.66	–	–	–	–	10	10
Mala	20	16.66	3	2	2	7	2	4
Peri-mental depression	4	03.33	–	–	–	–	3	1
Breast augmentation	1	00.83	–	–	–	–	1	–
Gluteal augmentation	1	00.83	–	–	–	–	1	–
Mons pubis augmentation	2	01.66	–	–	–	–	1	1
Post-traumatic depression	2	01.66	–	2	–	–	–	–

DISCUSSION

Today, cosmetic physicians have a much larger armamentarium of techniques and materials to improve facial and body contours, ameliorate wrinkles and provide esthetic rejuvenation to the face. Soft tissue fillers have provided esthetic surgeons with an effective means to addressing patient requests for non-surgical facial rejuvenation [8]. There are a plethora of excellent products that are appropriate for filling, augmenting and recontouring. However, as with any esthetic product or procedure, success is dependent on thorough understanding of the filling agents available, their indications and contraindications, as well as having thorough knowledge of implant technique to provide the patient with esthetically pleasing results [1-7].

The rationale for the use of hyaluronic acid products relates to the fact that the substance is ubiquitous in human tissue. Most of the bioengineered hyaluronic acid products are produced by tissue extraction or biosynthesis from non-animal source. They are a glycosaminoglycan biopolymer cross-linked into long, repeated, un-branched polyanionic chains. It binds water molecules which lead to increased skin hydration and turgor. Their usefulness for esthetic indications is achieved by varying the molecular weight, increasing cross-linking and concentration, which may increase the persistence/residence time but also, may be attributed to the reactions to these products. So, a critical balance must be achieved to minimize these adverse

events. Now, they replaced animal or human-derived collagen as the standard injection materials without the need for skin testing [5,6]. They offer the potential of longer lasting results, but long-term outcome in larger number of patients is not yet known [4-6]. Also, they can be used at the same time with facial surgical procedures to complement and enhance the overall results [2,6].

Restylane and Juvéderm are produced from bacterial fermentation sources. Restylane is considered the benchmark of all hyaluronic acid products. No skin testing is required before use. It has an excellent safety profile and is considered to be close to the ideal filler in many respects, but ultimately require periodic maintenance therapy to maintain the desired effect [5]. Early clinical and efficacy studies were reported from Italy and Sweden. After improvement of the injection techniques, reports of redness, swelling, localized granulomatous reactions, bacterial infection, or acneiform lesions started to appear. In mid-1999, Restylane reformulation was done with decrease in adverse events. Reports with delayed or theorized hypersensitivity reactions were published, but this could be avoided by slow and gentle injection. Reports of granulomatous reactions also appeared, but it was claimed that this is due to less precise and forceful injection [9-18].

In this study, Restylane was the first choice for isolated lip augmentation procedures or correction of vermilion border and fine wrinkles. Care is always taken to ensure that the product is not injected into a vessel, especially at the peri-ocular area [5]. Perlane, which is a Restylane with higher density, [6] was found to be ideal for blunting the prominent nasolabial folds and lip augmentation.

Juviderm is considered the second generation of hyaluronic acid fillers that uses the particle suspension technology. It contains the highest concentration of non-animal and cross-linked hyaluronic acid. It is believed to be less likely to yield visible lumps when injected more superficially [6]. It is believed that time should be spent injecting not massaging. Post-injection massage frequently results in a decreased final correction because of the forceful displacement of the material deep both peripherally and into the subcutaneous space [4,6]. The choice between Restylane and Juviderm in this series depended upon the cost and availability.

Polyacrylamide hydrogel contains a 2.5 percent polymer backbone of cross-linked Polyacrylamide and a 97.5 percent content of sterile water is bound in a non-covalent fashion. They are not degraded

by enzymatic activity during turnover of the extracellular matrix, thus longer lasting [2,3]. They can cause foreign body reaction, soft-tissue proliferation and formation of granulomas [3,19].

At the beginning of this series, Bio-alcamid was used as a permanent filler in 9 cases. It was found that it is expensive, difficult during injection, causing moderate to severe pain to the patient. Although it lasts for the longest period in this series, the site of injection is hard on touch and the implant might be apparent. These results are contradictory with those found by Abd El-Mageed, [20] and this might be due to the short follow-up period in that study. We no longer use Bio-alcamid in our institution.

Esteform is less expensive, easier in injection, can last for a reasonable period and is considered as a good alternative to Bio-alcamid. It was mostly used in wider areas as cheek depressions, gluteal or supra-pubic.

In an effort to improve the longevity of fillers, the merge of resorbable and non-resorbable components into an injectable compound is a logical one [4]. We used Amazingel as an example of this marriage. It was found to be less expensive and a lot easier to inject, especially if injected periocular (Fig. 3A,B), but its longevity is questionable. It loses some of its bulk early and then stays in a quiescent form for a variable period.

The overall experience in this study demonstrated that Restylane and Juvederm are ideally suitable for treatment of vermilion border, lip augmentation and fine lines. Perlane was found to be very good in ameliorating nasolabial fold and glabellar creases and also, post-traumatic wounds (Fig. 4A,B) Amazingel was suitable for augmentation of the mala, cheeks, pre-orbital depression, tear trough and chin (Fig. 5A,B). Also, it was good in correction of nasolabial fold, labia majora and mons pubis. Esteform was a good choice in gluteal region and breast augmentation. It was also used in mala and cheek augmentations (correction of facial asymmetry, Fig. 6A,B). Erythema, edema and ecchymosis were common immediately after treatment of most of the cases in this study, especially with hyaluronic acid products, but resolved in all patients within 2 weeks.

It is believed that when BTX-A is used in combination with hyaluronic acid fillers in the appropriate patient, it can restore facial appearance by the dual mechanisms of reflation and relaxation [1,4,6,21-23]. We had Combination of BTX-A injec-

tion with different types of fillers in this series. The results are beyond the scope of this article and will be discussed in another one.

Conclusion:

Most available fillers appeared to be clinically safe, easy-to-use, highly effective and well tolerated, when used for soft tissue augmentation, although may exhibit undesirable rare clinical side effects. The effect of tissue enhancement lasted over the follow-up period of most of the cases.

As regard the Polyacrylamide hydrogel, Bio-alcamid was found to be expensive, difficult during injection, causing moderate to severe pain to the patient. Although it lasts for the longest period in this series, rigidity was observed in the filled areas with an obvious artificial appearance. Esteform and Amazingel were good alternatives, but might require periodic maintenance therapy. As regard hyaluronic acid products, Restylane and Juvederm were ideally suitable for treatment of vermilion border, lip augmentation and fine lines. Perlane was found to be very good in ameliorating nasolabial fold and glabellar creases.

Although all of the used fillers were safe, the concepts of their long-term volume persistence and how they compare with each other remain largely anecdotal. Additional experience with longer follow-up need to be evaluated in the future and will help determine the most appropriate use and long-term safety of these fillers.

REFERENCES

- 1- Broder K.W. and Cohen S.R.: An overview of permanent and semi permanent fillers. *Plast. Reconstr. Surg.*, 118 (3s): 75-145, 2006.
- 2- Von Buelow S., von Heimburg D. and Pallua N.: Efficacy and safety of Polyacrylamide hydrogel for facial soft-tissue augmentation. *Plast. Reconstr. Surg.*, 116 (4): 1137-1146, 2005.
- 3- Von Buelow S. and Pallua N.: Efficacy and safety of Polyacrylamide hydrogel for facial soft-tissue augmentation in a 2-year follow-up: A prospective multicenter study for evaluation of safety and aesthetic results in 101 patients. *Plast. Reconstr. Surg.*, 118 (3s): 85s-91s, 2006.
- 4- Eppley B.L. and Dadvand B.: Injectable soft-tissue fillers: Clinical overview. *Plast. Reconstr. Surg.*, 118 (4): 98e-106e, 2006.
- 5- Dover J.S., Carruthers S., Carruthers J. and Alam M.: Clinical use of Restylane. *Skin Ther. Lett.*, 10 (1): 5, 2005.
- 6- Rohrich R.J., Ghavami A. and Crosby M.A.: The role of hyaluronic acid fillers (Restylane) in facial cosmetic surgery: Review and technical considerations. *Plast. Reconstr. Surg.*, 120 (6s): 41s-54s, 2007.

- 7- Alam M. and Dover J.S.: Management of complications and sequelae with temporary injectable fillers. *Plast. Reconstr. Surg.*, 120 (6s): 98s-105s, 2007.
- 8- Klein A.W.: Soft tissue augmentation 2006: Filler fantasy. *Dermatol. Ther.*, 19 (3): 129-133, 2006.
- 9- Shafir R., Amir A. and Gur E.: Long-term complications of facial injections with Restylane (injectable hyaluronic acid). *Plast. Reconstr. Surg.*, 106: 1215, 2000.
- 10- Matarasso S.L. and Herwick R.: Hypersensitivity reaction to non-animal stabilized hyaluronic acid. *J. Am. Acad. Dermatol.*, 55: 128, 2006.
- 11- Lupton J.R. and Alsters T.S.: Cutaneous hypersensitivity reaction to injectable hyaluronic acid gel. *Dermatol. Surg.*, 26: 135, 2000.
- 12- Micheels P.: Human anti-hyaluronic acid antibodies: Is it possible? *Dermatol. Surg.*, 27: 185, 2001.
- 13- Leslie B.: View from America: Dermal fillers. *J. Cosmet. Dermat.*, 3 (4): 249, 2004.
- 14- Lowe N.J., Maxwell C.A. and Patnaik R.: Adverse reactions to dermal fillers: Review. *Dermatol. Surg.*, 31: 1616, 2005.
- 15- Duffy D.M.: Complications of fillers: Overview. *Dermatol. Surg.*, 31: 1626, 2005.
- 16- Fernandez-Acenero M.J., Zamora E. and Borbujo J.: Granulomatous foreign body reaction against hyaluronic acid: Report of a case after lip augmentation. *Dermatol. Surg.*, 29: 1225, 2003.
- 17- Friedman P., Mafong E.A., Kauver A.N. and Geronemus R.G.: Safety data of injectable non-animal stabilized hyaluronic acid gel for soft tissue augmentation. *Dermatol. Surg.*, 28: 491, 2002.
- 18- Lowe N.J., Maxwell C.A., Lowe P., et al.: Hyaluronic acid fillers: Adverse reactions and skin testing. *J. Am. Acad. Dermatol.*, 45: 930, 2001.
- 19- Kesselring U.K.: Efficacy and safety of Polyacrylamide hydrogel for facial soft-tissue augmentation. (letters) *Plast. Reconstr. Surg.*, 118 (2): 562-563, 2006.
- 20- Abd El-Mageed M.: Evaluation of the safety and efficacy of Bio-alcamid for facial soft tissue augmentation. *Egypt J. Plast. Reconstr. Surg.*, 31 (2): 129-137, 2007.
- 21- Klein A.W. and Fagien S.: Hyaluronic acid fillers and butulinum toxin type A: Rationale for their individual and combined use for injectable facial rejuvenation. *Plast. Reconstr. Surg.*, 120 (6s): 815, 2007.
- 22- Coleman K.R. and Carruthers J.D.: Combination therapy with Botox T.M. and fillers: The new rejuvenation paradigm. *Dermatol. Ther.*, 19 (3): 177, 2006.
- 23- Wise J.B. and Greco T.: Injectable treatments for the aging face. *Facial Plast. Surg.*, 22 (2): 140, 2006.