ORIGINAL RESEARCH

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Comparison of Artecoll, Restylane and silicone for augmentation rhinoplasty in 378 Chinese patients

Abstract

Purpose: Dermal fillers have been proven to be safe in soft tissue augmentation; however, their efficacy in modeling the noses of Asian patients has not been demonstrated.

Methods: In this study, 378 patients were included and underwent augmentation rhinoplasty (Artecoll, n=126; Restylane, n=126 and silicone implants, n=126). The subjective and objective outcomes were evaluated on day 1, and months 1, 3, 6, and 12 after injection rhinoplasty.

Results: All patients achieved significant improvement in nasal shape and contour immediately after surgery. Patients treated with Restylane failed to maintain the nasal shape and contour 1 year after surgery, whereas patients undergoing Artecoll rhinoplasty completely maintained the post-treatment nasal shape and contour. More patients with silicone implants experienced adverse events and the severity of these events was greater in the silicone group compared to those in the Restylane and Artecoll groups.

Conclusion: Artecoll rhinoplasty has a low incidence of adverse effects and the shape and contour of the nose are maintained for a prolonged period.

Manuscript submitted 10th October, 2013
Manuscript accepted 15th July, 2014

Clin Invest Med 2014; 37 (4): E203-E210

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East-Asian noses differ anatomically from Caucasian noses. Typically, the East-Asian nose is characterized by a wide low dorsum, poor nasal tip projection and cartilaginous support and retracted columella [1, 2]. Detailed anatomical studies have also revealed thick lobular skin with abundant subcutaneous fatty tissue, small osteo-cartilaginous framework and weak and thin lower lateral cartilages in the East-Asian nose [3, 4]. Asian patients seeking cosmetic improvement of their noses often demand a higher and narrower nasal dorsum, a more projected and well-defined tip and a narrower alar base.

Since 1920s, physicians have attempted to use a wide range of materials, including vaseline, aluminum, ceramics, gold, silver, platinum, celluloid and ivory, for augmentation rhinoplasty. Some materials have been widely used over different time periods - and the exploration of the use of these materials has continued for almost 100 years [5-8]. Because of excessive tissue stimulation, high extrusion rates and brittleness, each of these materials was eventually abandoned. In 1940s, silicone fluid injections were used clinically and, after continuous improvement, a solid implant form was developed and is still widely used in plastic surgery for augmentation rhinoplasty and genioplasty and as silicone rubber shells in breast implants [7-10].

In addition to silicone, a variety of biomaterials has been developed and these materials are currently in use for rhinoplasty. Since its introduction into clinical practice in the 1970s, hydroxyapatite has been widely adopted clinically due to the resemblance of its inorganic component to human bone tissue as well as its excellent biocompatibility [11]. Allogeneic tissue augmentation, using bone and/or cartilage from fresh cadavers, is an alternative implant material for rhinoplasty. After surgery, the allogeneic bone and cartilage acts as a temporary mechanical support but is eventually replaced by autologous bone [6]. Specially treated heterologous tissues, such as bovine nasal cartilage, bovine costal cartilages and calf sternum, have also been used in human rhinoplasty [9]. Autogenous bone is one of the augmentation materials that has been used in rhinoplasty from the very beginning; it is rarely used in primary cosmetic nose surgery today although it is still recommended for complicated nasal deformities or severe saddle nose correction. Costal cartilage is the most commonly used cartilage graft, followed by auricular cartilage and nasal septum cartilage [8].

An alternative and non-surgical technique for nasal augmentation is the use of injectable tissue fillers; i.e., subcutaneous injections to enhance and beautify the nasal shape. Safety should always be considered first, so any filler material should be non-toxic, non-immunogenic and tissue-biocompatible. Filler substances can be divided into three categories: 1) tem-

porary fillers that will be absorbed within 4-6 months (such as collagen and hyaluronic acid) [8], 2) semi-permanent fillers (such as hydroxyapatite and polylactic acid microspheres) that will be absorbed within 9-12 months [11], and 3) permanent fillers (such as fluid silicone, polyacrylamide and poly(methyl methacrylate)-microspheres) that are non-absorbable and will remain in the tissues permanently [10]. Theoretically, a permanent filler should be preferred for augmentation rhinoplasty, as it does not require ongoing re-treatments but provides a new and improved nasal shape without change in appearance over time. Nevertheless, autologous fat transplantation, collagen injections and hyaluronic acid injections have become the three leading techniques in the cosmetic filling [12-14] and they have their own benefits and shortcomings.

In 1996, Artecoll ('CE-mark') was approved by the European Union, and introduced to China in 2002. By the end of 2011, a total of 71,508 ml of Artecoll had been used in 38,456 Chinese patients who received treatment to improve wrinkles, skin depressions, and facial contour deficiencies [15]. With the increased awareness of Artecoll's action and refinements in physicians' injection skills [13], its applications have expanded gradually from simple deep dermal wrinkle correction to broader indications such as facial feature shaping and structure contour modeling. In order to objectively evaluate the efficacy of Artecoll on the shape and contour modeling through augmentation rhinoplasty, 378 patients recruited through the Department of Plastic Surgery were included in a study that ran between 2003 and 2011. Rhinoplasties were performed using Artecoll or hyaluronic acid (Restylane) injections or solid silicone implantation (Artecoll, n=126; Restylane, n=126 and solid silicone implant, n=126).

Materials and Methods

General data

A total of 1918 Chinese patients with a simple congenital saddle nose and a wide and low dorsum, poor nasal tip projection and poor cartilaginous support received either solid silicone implant surgery or Restylane or Artecoll injections between January 2003 and December 2011. Of the 1074 patients who were operated on by insertion of silicone implants, 126 of them provided informed consent for inclusion in this study and had adequate clinical data available. The first 126 cases from the 563 patients injected with Artecoll and the first 126 cases from the 281 patients injected with Restylane who provided informed consent and for whom adequate clinical data were available were also included in the study. Each patient was in-

FIGURE 1. Augmentation rhinoplasty: A the filler is injected between deep dermis and periosteum; B modeling the nasal tip by a filler; and, C the new nasal contour is fixed with a one-day splint.

formed about the risks and benefits of all procedures. Each patient paid for the products and the fee for medical care.

The efficacy of nasal dorsum augmentation and tip contour modeling was evaluated. Prior to surgery or injection, the history of allergies, endocrinologic, hematologic and immune diseases was recorded. If patients developed common acute diseases, no surgery was performed until they recovered completely. This study was approved by the Research Ethics Board of our hospital.

Medical records of these patients were reviewed to collect surgery and anesthesia-related information, details on preoperative and postoperative care, and treatments out of hospital. The patient characteristics included age, gender, etiology, surgical site, operational procedures, dose of fillers, possible complications and surgical repair methods for complications (when necessary).

The subjective and objective outcomes of augmentation rhinoplasty were evaluated on day 1 and at 1, 3, 6 and 12 months after surgery and photos were taken at all visits

Injection of Artecoll and Restylane

Artecoll was obtained from Hafod B.V. (Rotterdam, The Netherlands) and Restylane was obtained from Q-Med AB (Uppsala, Sweden). Note that Artesense and Artecoll are different names for the same product. After the fourth generation production, Artecoll was changed to Artesense worldwide, with the exception of mainland China. Topical anesthesia cream was applied to the patients 30-60 minutes before injection. A 27-G needle (0.5 mm) was used to determine the thickness of the dermis. The "tunneling technique" [16] was employed to deliver the implant between periosteum and subdermis while withdrawing the needle slowly during injection. Slow

and continuous withdrawal under constant injection pressure is crucial to achieve even filler placement and to avoid the occurrence of irregularities and nodules. Scratching the needle tip on the periosteum under pressure may assure the product delivery in the right subcutaneous plane (Figure 1a). If the needle hits the dermal layers and the skin turns pale, the injection should be stopped immediately and the material in the pale part must be spread out evenly. After each injection, any potential small, palpable irregularities should be modeled in place (Figure 1b). An external fixation with a thermoplastic splint for 24 hours was used to help shape the entire nose (both nasal dorsum and nasal tip) (Figure 1c).

Insertion of Silicone Implants

Under local anesthesia with 2% lidocaine, an incision of about 1 cm was made on the upper wall of the right nasal columella. Separating the skin from the periosteum up to 0.5 cm below the line connecting the two eyebrows creates a tight pocket for silicone implant insertion. A custom-made silicone implant, obtained from Winner Corporation (Shanghai, China) was chosen and trimmed according to the defect of the nose and the desire of the patient. After insertion of the implant, the columellar incision was sutured. An external fixation with a thermoplastic splint for 24 hours was used to help shape the entire nose (both nasal dorsum and nasal tip).

Clinical Assessment

The efficacy of injections or surgery was evaluated according to the assessment of the cosmetic improvement of the nasal augmentation and the degree of satisfaction by the patients and doctors, using comprehensive assessment scores.

TABLE 1. Clinical characteristics of patients in different groups

Group	Patient (n)	Sex (F/M)	Age	Location	Dose (ml)
Silicone	126	112/14	31.3±7.5	dorsum	implant
Restylane	126	120/6	29.2±6.9	dorsum	1.75±0.43
Artecoll	126	119/7	30.2±7.1	dorsum	1.14±0.28*

*P<0.01, Restylane *versus* Artecoll

Adverse Events after Augmentation Rhinoplasty

Adverse events (AEs) were categorized into acute and delayed effects. Acute AEs were usually mild and of short duration, mostly self-limiting and included erythema, ecchymosis, pain, itching, bleeding, swelling and infection. In most cases, no treatment, or only symptomatic treatment, was required. Delayed AEs are usually severe and rare and included allergic reactions, hypertrophic scars, thrombosis, inflammation and granulomatous reaction. All delayed AEs require further treatment. Permanent fillers are more prone to causing foreign body reactions such as granulomas.

Pathological Examination

At 12 months after surgery, a 2×3×3 mm³ specimen was collected from patients who experienced delayed AEs. Tissue samples were embedded in paraffin and processed for H.E staining and subsequent histological examination.

Statistical Analysis

AEs were described as total counts of events and subjects experiencing adverse events. The number of treatments and the quantity of product were compared by using an independent *t*-test. Non-parametric tests were used for comparisons of rates. Mann-Whitney *U*-test was employed to compare the surgical improvements and patient and doctor satisfaction on the basis of observer-rated and investigator-rated "Rhinoplasty Assessment Scale" scores among groups. Rater reliability for observer "Rhinoplasty Assessment Scale" ratings was analyzed using intra-class correlation. A value of *p*<0.05 was considered statistically significant.

Results

A total of 378 patients received augmentation rhinoplasty and had complete clinical information. No patient was lost to follow-up. There were no significant differences with regard to the gender, age, and outcome expectations among the three groups (Artecoll, Restylane and silicone). All patients received

augmentation and shaping of the entire nose (the nasal dorsum and the nasal tip). The dose of Artecoll used was significantly lower than that of Restylane (*p* <0.01), but the same effect was achieved (Table 1).

Adverse Events

Patients receiving silicone implants experienced significantly more nasal and upper facial traumatic reactions, skin swelling or intense pain (requiring oral pain medication) during the first week after surgery. Nasal hematomas occurred in 32 patients of the silicone implant group but resolved within two weeks. Silicone implants had to be removed in six patients due to infection and silicone implant exposure was found in another four cases. Conspicuous red angiogenesis was observed in 10 patients: six patients had nasal deviation, two showed hyperplastic capsule formation and two developed nasal tissue granulomas. Symptomatic treatment and re-operations were performed due to these complications.

In the Restylane and Artecoll groups, acute AEs, including mild swelling, pain and redness, occurred at all injection sites and lasted for 1-3 days. In the Restylane group, two patients experienced mild hyperpigmentation at the injection site but this resolved spontaneously within 6 months and three patients developed mild subcutaneous nodules, which disappeared within half an hour after hyaluronidase injection. One patient developed infection, two had hematoma and one presented with nasal deviation. Within one year after injection, Restylane was completely absorbed in 89 patients (70.6%) and the patients' noses returned to pre-treatment shape.

In the Artecoll group, the number of AEs was significantly lower: only one patient had subcutaneous bleeding, which resolved within one week, one patient developed a 0.5 mm³ subcutaneous nodule, which disappeared within two weeks after one injection of 0.5% triamcinolone. No acute/chronic allergic reactions, inflammatory granulomas, skin infections, abscesses, infarction or other serious complications were found in these patients (Table 2).

Efficacy of Augmentation Rhinoplasty

Significant improvement was objectively noted in the nasal shape and contour immediately after surgery or injection in all the patients who stated that they were satisfied with the outcome. As the number of delayed AEs increased, the nasal shape and contour were compromised, and the cosmetic results also reversed. Some patients could not tolerate the AEs, especially those patients treated with silicone implants, and they complained about the significant traumatic response, skin swelling,

TABLE 2. Complications and adverse events after augmentation rhinoplasty

Group	Patient (n)	infection	hematoma	extrusion	displacement	completely absorbed	nodule	granuloma	telangiectasia
Silicone	126	4.76(6)	25.40(32)	3.17(4)	4.76(6)	0	1.59(2)	1.59(2)	7.93(10)
Restylane	126	0.79(1)	1.59(2)	0	0.79(1)	70.63(89)	2.38(3)	0	0.79(1)
Artecoll	126	0	0.79(1)	0	0	0	0.79(1)	0	0

intense pain and impaired life and work. Patients receiving Restylane had significantly fewer complaints about their AEs than those treated with silicone implant. By 1, 3 and 6 months after rhinoplasty, all of these patients had subjective improvement, which was consistent with the evaluation by the physician. Twelve months after rhinoplasty, Restylane was completely absorbed in 70.63% (n=89) of patients and improvement in nasal structure disappeared.

Patients in the Artecoll group did not complain about AEs. Subjective efficacy increased gradually, peaking at 12 months, and was significantly superior to that in both the silicone implant and Restylane groups (Table 1,2).

Imaging Examination before and after Injection

During the first year, findings in image examination before and after rhinoplasty were compared among the three groups. Artecoll injection was found to be superior to either Restylane injection or silicone implants with regard to maintaining nasal shape and contour, incidence of AEs and degree of subjective satisfaction (Figures 2 and 3).

Follow-Up

Silicone implants with a preformed and tailored shape provide a straight contour, which may be prone to shifting. The solid silicone puts great pressure on the skin of the nose tip, causing

FIGURE 2. A-F: Complications after silicone implant injection: A, bleeding; B, infection; C, extrusion; D, local swelling and shift; E, displacement; F, lack of the tip. Adverse events after Restylane injection: G, allergy; H, infection; I, completely absorbed.

FIGURE 3. Nasal shape before and after nasal augmentation with Artecoll: A, before augmentation; B, 1 day after augmentation; C, 12 months after augmentation).

FIGURE 4. Nasal height among three groups after augmentation ($\Delta p < 0.05$ vs. Restylane at 3 months; at $\Delta\Delta p < 0.01$ vs. Restylane at 12 months). The average nasal height after Artecoll and Restylane injections were lower than that after silicone implant injection at all time points (** $p < 0.01$)

swelling and congestion of the skin, with the risk of perforation. In contrast, augmentation with Restylane or Artecoll exerts no pressure on the nasal skin and has the advantage of mold ability during the first week post-treatment. Small irregularities and defects could be improved by further filling. After surgery or injection, patients were followed up for one year, the nasal elevation after Artecoll injection remained nearly consistent, while elevation with Restylane injection was significantly compromised ($P < 0.01$) (Figure 4). Specimens were collected at 12 months after surgery, and histological examination showed the Artecoll poly(methyl methacrylate) (PMMA) particles were completely encapsulated with autologous collagen, while Restylane was completely absorbed. Chronic inflammation was found around some silicone implants with thickened capsule (Figure 5).

Discussion

For nearly a century, physicians have investigated the use of different solid and injectable materials for use in augmentation rhinoplasty; however, many materials cause pain and other AEs in patients [17]. Liquid paraffin was used as filler material but was discontinued when it was found that paraffinomas developed years after injection [10]. Similarly, in the 1930s, vaseline was injected for soft tissue filling of different body parts, but was discontinued when tumor-like proliferation occurred 6-8 years after injection. In 1953, Baronders reviewed the use of

FIGURE 5. Histological examination at 12 months after nasal augmentation (H.E staining, x25): A, hyperplasia and dermal cyst in the capsule surrounding silicone implant; B, inflammatory response to injected PAAg; C, completely absorbed Restylane at 12 months; and, D, completely encapsulated PMMA by autologous tissue.

liquid silicone for soft tissue augmentation and concluded that the chronic inflammation observed after liquid silicone injection was unacceptable [10,17]. In 1975, bovine collagen was introduced into clinical practice as wrinkle filler [18] and in 1981, Zyderm® (a bovine collagen product) was approved by the FDA [19]. In 1994, a modified sodium hyaluronate gel from Q-Med AB Sweden was approved in the Europe [11]. In 1996, Artecoll (CE-mark) was approved by the European Union (EU) and has been used in the EU and worldwide since then [16]. In 1996, polyacrylamide (PAM) was introduced into clinical practice as Aquamid® [20]. In 2004, Restylane (a haluronic acid filler from Q-Med AB, Sweden) was approved in the USA by the FDA. In October 2006, ArteFill® was approved by the FDA and this new permanent filler was found to possess significant advantages over absorbable substances.

An ideal filler material for soft-tissue augmentation should have the following characteristics: (1) safe, with good biocompatibility; (2) exhibit tissue stability; (3) capable of maintaining a fixed volume and flexibility; (4) be stable against dissolution and phagocytosis; and (5) show no migration or dislocation [16]. An analysis of all injectable fillers used in the past 10 years has revealed that each have their own advantages and disadvantages [13].

Hyaluronic acid and collagen are stromal components of the skin. They have hydrophilic properties and can increase the volume and flexibility of the dermis [21]. Some of the currently

available products are synthesized during bacterial fermentation of sugar (i.e., Restylane) [10]. A study comparing Restylane and Zyplast® showed that AEs, such as ecchymosis, swelling and pain, caused by Restylane are more severe than those caused by Zyplast [22]. Restylane may also cause itching and subcutaneous discoloration at the injection site. Soparkar *et al.* [21] reported that hypersensitivity to bacterial hyaluronic acids occurred in 0.005% to 0.42% of patients. One advantage of this filler is that hyaluronidase can be used to treat early complications. The primary drawback of hyaluronic acid is its complete absorption within 6-12 months; therefore, hyaluronic acid does not meet the requirements of maintaining long-term efficacy in augmentation rhinoplasty. If its degradation time could be prolonged to five years, Restylane may become the filler of choice.

Radiesse (calcium-hydroxyapatite) is a semi-permanent injectable filler with low solubility and a longevity of 9-12 months. Few AEs have been reported and the incidence of immunologic reactions is extremely low. On the other hand, it can cause a high incidence of submucosal nodules in soft tissue when spread unevenly [11]. Radiesse appears radiopaque on X-rays and may interfere with facial imaging.

Aquamid is marketed as a permanent filler. Although the polyacrylamide polymer is non-toxic, the acrylamide monomer may be neurotoxic and teratogenic [12]. Furthermore, polyacrylamide hydrogel may migrate and cause inflammation and granulomatous reactions. A reported complication rate was 6.74%, especially when it was used for breast augmentation where it may cause granulomas in the surrounding tissues and hyaline degeneration [12].

Nasal augmentation with solid silicone implants has been performed for more than 70 years and is still being widely used by plastic surgeons. Its advantages include easy shaping, short operation time and feasibility for all nose shapes [1,2]; however, there is a high incidence of complications, such as shifting and dislocation of the implant and bleeding and infection after operation. Furthermore, it is prone to cause teleangiectasia over the nasal tip; thus, straight silicone implants are not recommended for tip surgery alone.

Artecoll is a safe and predictable permanent injectable filler and has been used clinically over the past 15 years and in over 500,000 patients world-wide [23]. Artecoll has been found to work quite well in correcting facial wrinkles (such as forehead lines, frown lines, fishtail lines, lower lid shadows, nasolabial folds, fine perioral wrinkles and cervical folds), acne scars and traumatic depressions in ear lobes, nasal bridge and columella, alar depressions, sunken cheeks, small lips and receding chins [23]. Artecoll is composed of 20% v/v PMMA

microspheres (with a diameter of 32-40 microns) suspended in a solution of 80% v/v bovine collagen (from BSE-free herds in Australia) and 0.3% lidocaine. Once the smooth PMMA microspheres enter the subdermal soft tissues, they are covered by fibrin and later by macrophages and fibroblasts, which produces a fine collagen capsule around these millions of microspheres. The capsule not only avoids phagocytosis by macrophages, but minimizes the irritation of soft tissues and dislocation [16]. Within 1-3 months, the collagen is gradually degraded and completely replaced by the host tissue, while the PMMA will not be degraded and remains permanently at the injection site [13].

The 32-40 micron PMMA microspheres in the Artecoll represent the ideal particle size; large enough to avoid phagocytosis [24,25] and small enough to successfully pass through the 26 G to 31 G diameter needles. Microspheres in this size range also possess other advantages: smaller microspheres have a larger total surface area, which stimulates the generation of more collagen. When the average diameter of microspheres is 40 microns, the new autologous connective tissues ingrowth will reach about 80% by volume but when the diameter of microspheres increases to 100 microns, the new connective tissue is only about 56% by volume [24]. The primary advantage of collagen as a carrier is its ideal viscosity [25] that keeps the PMMA microspheres evenly suspended and also leaves spaces between the well-aligned microspheres to facilitate the ingrowth of the tissues. It is interesting that the effective results of the Artecoll injection are superior to the surgical procedure. The former technique uses less material and is easier to mold than the latter. Other biological wrinkle fillers, such as Zyplast and Restylane are metabolized and absorbed completely within 6-12 months [26,27].

Adverse Events

Artecoll has been used in China for more than 10 years and 38,456 patients have been treated with it. The incidence of severe AEs is less than 0.05% [28]. In the present study, of the 126 Artecoll-treated patients, only one developed a subcutaneous hematoma at the injection site and one showed transient nodules (disappearing after massage). The incidence of AEs was significantly lower than that in both the Restylane and the solid silicone implant groups. Granuloma formation after Artecoll treatment is a reported complication, but very rare: only four cases of granuloma were reported after injection of an earlier generation of Artecoll, and two of the patients with potential granuloma were treated with intralesional corticosteroid (triamcinolone) injections. Surgical resection should be the last option [29].

Conclusion

Our results showed that all 378 patients had significant improvement in nasal shape and contour immediately after surgery or injection. Our results also confirm that Artecoll is a safe soft tissue filler for augmentation rhinoplasty and superior to both Restylane injections and solid silicone implants. With a lower incidence of AEs, Artecoll additional advantages over the other two treatments for augmentation rhinoplasty. Similar results are expected in other patient populations.

Acknowledgments

This study was supported by the National Natural Science Foundation of China (No.81071563, 81272102).

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