## Different Injection Techniques of Dermal Fillers: Hyaluronic Acid and Bovine Collagen Gel Suspended Polymethylmethacrylate Microspheres

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**Abstract:**

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Paramount for facial rejuvenation is optimizing facial volume. Most patients prefer a minimally invasive technique for volume replacement and choose dermal fillers.

**Objective:**

Studying dermal filler injection techniques for bovine collagen gel suspended polymethylmethacrylate microspheres or Bellafill (ART) and a hyaluronic acid filler, Restylane Lyft (PERI), using both microcannulas and a dilution of lidocaine with epinephrine and bicarbonate.

**Methods & Methods:**

A prospective study in volunteers seeking ART and PERI fillers to compare standard needle injection techniques to the study method of a diluent of lidocaine with epinephrine and bicarbonate and microcannulas.

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Combination of microcannulas and the diluent revealed less bruising and discomfort. Less swelling was observed using a smaller caliber size blunt tip microcannula compared to a larger bore. With needle injection producing more than mild bruising, the swelling was greater than with a microcannula. The filler injections were easier with less injection force when diluted.

**Conclusions**

ART and PERI are valuable components in a comprehensive facial rejuvenation protocol. Microcannulas and lidocaine with epinephrine and bicarbonate can minimize bruising, discomfort, and swelling with both of these dermal fillers. They can also lower the injection force to improve accuracy of facial volume replacement, while minimizing adverse effects.
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http://mc.manuscriptcentral.com/asjournal
Injection force to improve accuracy of facial volume replacement, while minimizing adverse effects.
Introduction

Paramount for facial rejuvenation is optimizing facial volume. Most patients choose the administration of dermal fillers. The development of different filler substances has seen a surge in options over the past ten years (Figure 1). Most dermal fillers should be termed subcutaneous fillers, since they are injected below the dermis layer of the skin as opposed to into the dermis of the skin.  

There are temporary dermal fillers (less than two-year duration) and a long-term dermal filler that is approved by the Food & Drug Administration (FDA). The long-term filler is a bovine collagen gel suspended polymethylmethacrylate microspheres, known as Bellafill or Artefill (ART). The decision to offer and choose a specific option is typically based on the experience, training, and personal bias of the injector.

ART (Suneva Medical, Inc., San Diego, CA) was approved in 2006 by the FDA for the correction of wrinkles, nasolabial folds (NLF), by volume replacement. The filler in 2014 became the only FDA approved dermal filler for the correction of moderate to severe, atrophic, distensible facial acne scar on the cheek in patients over the age of 21 years. The longest and largest dermal filler scientific study ever performed revealed that 87% of patients were satisfied at 5 years.

In the 5-year post-approval study, no treatment-related serious adverse events (AE) or unanticipated AE’s were noted. The general adverse event profile was similar to previous NLF studies. A total of 1,794 patients have been treated with ART across four U.S. clinical studies with a granuloma rate of 1.2%. The majority of these granulomas

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were mild to moderate in severity with the ongoing granuloma rate at the end of the study of <1%.\textsuperscript{5}

ART is the third generation of methylmethacrylate (PMMA) spheres and the only formulation ever available for use in the United States. These PMMA spheres have a greater uniformity of size and shape and a smoother surface.\textsuperscript{8} The PMMA spheres have a consistent size and range between 30-50 microns (\( \mu \)), removing most spheres smaller than 20 \( \mu \) during processing.\textsuperscript{8}

The smaller the microspheres, the larger their combined total surface area in a given volume. The increased surface area promotes a greater amount of collagen deposition. Art consists of about 20% PMMA microspheres and 80% bovine collagen. The bovine collagen is replaced by the patient’s own connective tissue keeping this 20:80 relationship long-term. Microspheres stimulate collagen production and the resultant microvascularization transforms the area into a ‘living’ implant.\textsuperscript{9}

This ideal microsome size band (30-50 \( \mu \)) makes them large enough to escape phagocytosis, but small enough to be delivered through a 26-gauge needle.\textsuperscript{8} Lemperle et al.\textsuperscript{9} examined the migration and histology of microspheres of different sizes in mice. The study found that PMMA microspheres of \( \geq 40 \mu \) did not migrate, however, smaller microspheres (\( \leq 20 \mu \)) migrated to the lungs and lymph nodes. One milliliter of ART contains 6 million microspheres.\textsuperscript{9}

With regard to temporary fillers, most are made of hyaluronic acid (HLA). This molecule is the most potent humectant molecule on the planet, meaning that it absorbs water, up to 1000 times its molecular weight. All HLA’s from numerous manufacturers demonstrate a host tissue duration of less than two years.\textsuperscript{10}

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An 18-month multicenter, randomized, evaluator-blinded study (n=75) was conducted to evaluate the efficacy and duration of Restylane-L (RES\textsubscript{l}) injected with 2 different retreatment schedules.\textsuperscript{11} Patients were randomized to retreatment of 1 NLF at 4.5 months and retreatment of the other NLF at 9 months. For 97% of patients, improvements seen after the initial treatment with RES\textsubscript{l} persisted for up to 18 months with one retreatment.\textsuperscript{11}

Of the 63 subjects who completed the above 18-month trial, 52 agreed to participate in an 18-month extension study.\textsuperscript{12} The mean volume of RES\textsubscript{l} used at the initial treatment in each NLF was 1.1 ml. This decreased to 0.7 ml per nasolabial fold at the 4.5 and 9-month retreatments and only 0.4 ml for the 18-month retreatment. Blinded evaluator assessments revealed that 94% to 100% of subjects maintained Wrinkle Severity Rating Scale (WSRS) scores 1+ point higher than baseline scores from 2 to 3 years.\textsuperscript{12} Rheological studies have shown greater elasticity, total resistance to deformation, and percent elasticity for RES\textsubscript{l} and Restylane Lyft or Perlane (PER\textsubscript{l}) compared to other hyaluronic acid fillers.\textsuperscript{13,14}

The indications for use (IFU)\textsuperscript{15} of the PER\textsubscript{l} is for placement in the deep dermis to superficial subcutis for the correction of moderate to severe facial folds and wrinkles, such as the nasolabial folds.\textsuperscript{15} It is also indicated for subcutaneous to supra-periosteal implantation for cheek augmentation and correction of age-related midface contour deficiencies in patients over the age of 21 (Figure 3). RES\textsubscript{l} and PER\textsubscript{l} are also indicated for submucosal implantation for lip augmentation in patients over the age of 21. In clinical use, the HLA filler is used anywhere in the face that volume replacement is desired.
A retrospective observational study by Beasley et al.\textsuperscript{16} describes the use of Restylane (RES) mixed with 1\% lidocaine and 1:100,000 epinephrine. The investigators combined 0.2 ml of 1\% lidocaine with 1:100,000 epinephrine with a 1.0 cc syringe of HLA filler (N=439). The authors state this technique is effective for pain control with a high patient satisfaction and no reports of adverse events in this study.\textsuperscript{16}

Weinkle\textsuperscript{17} evaluated the safety of RES mixed with lidocaine-epinephrine compared to RES-only in the treatment of nasolabial folds (n=50). Patients were asked to rate the pain on each side of the face separately, on a scale of 1 to 10 (most pain).\textsuperscript{17} Patients reported an average of 8 on the side where RES-only was injected compared to an average of 2 on the side injected with the RES-lidocaine-epinephrine mixture. The results revealed less bruising on the side of the face injected with the RES-lidocaine-epinephrine mixture.\textsuperscript{17}

A prospective, randomized, phase II, double-blinded study (n=25) compared the safety and efficacy of injecting RES\textsubscript{i} in the nasolabial folds using a blunt cannula to that of a standard needle.\textsuperscript{18} Each nasolabial fold was injected with 0.5 mL of RES\textsubscript{i}, one fold using a 21-gauge, 3-cm blunt cannula and the other fold with a standard 30-gauge, 0.5-inch needle. The fillers were injected subcutaneously in both sides through a single orifice in the cannula side and five to six injection punctures in the needle side. Participants reported less pain, edema, redness, and fewer hematomas on the side injected with the cannula.\textsuperscript{18}

The consensus recommendations with the use of microcannulas for dermal filler placement found distinct patient benefits to include improved safety, decreased risk of ecchymoses, faster return to normal daily activities, and in some patients, an improved
comfort during the injection. The panel stated the safety and efficacy of filler injections ultimately depends on the knowledge and skill of the injecting physician. Microcannulas for dermal filler injection is considered an off-label use.

Material and Methods

Patient History-
Patients presenting for facial rejuvenation completed a detailed medical history. A history of lidocaine or red meat allergy was sought. If the patient does not consume red meat, has not had a surgery or dental procedure where a local anesthetic was used, then a manufacture supplied skin test was recommended. Waiting 28 days after the skin test in order to document the existence of an allergic response is written in the instructions for use brochure from the manufacturer. However, because of the low pretest probability of IgE-mediated local anesthetic allergy and the high incidence of false-positive results, it is unclear whether intra-cutaneous tests have any benefit in the diagnostic approach to local anesthetic allergy.

Aesthetic Consultation-
After receiving patient permission, a comprehensive facial analysis was undertaken. All the pertinent aesthetic anatomical concerns were identified. Those agreeing to compare different injection techniques using both ART and PER fillers were ultimately study patients. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

Prior to treatment, we confirm the completion and review of the dermal filler consent and photograph consent forms, ensure patient photographs are taken, clarify the specific anatomical areas to be treated, and all questions are answered.

Filler injection techniques...
Dermal Filler Volume Replacement Alternatives-
The injector and the patient jointly agree upon the specific filler and amount for each anatomical site. ART is recommended if patient requested a long-term filler. However, if one requested a permanent lip augmentation, a soft silastic lip implant was recommended. The temporary filler recommended was the HLA filler Restylane Lyft. A scientific study comparing HLA fillers revealed that PER$_1$ had the highest gel strength due to the NASHA manufacturing process.$^{22}$

Dermal Filler Syringe Composition-
ART contains about 0.85 ml of the following components: atellocollagen (bovine) 3.5%, phosphate buffer 2.7%, sodium chloride 0.9%, lidocaine hydrochloride 0.3% and water 92.6% with a pH between 6.9 to 7.0.$^7$ Each syringe of PER$_1$ (Galderma, Lausanne, Switzerland) contains a total of 1 ml of stabilized HLA, 20 mg/ml in phosphate buffered saline and 0.3% lidocaine at a pH of 7.0.$^{15}$

Dermal Filler Additives-
Dermal fillers are manufactured containing lidocaine hydrochloride. Lidocaine is classified as an amide-type local anesthetic with vasodilatory properties. Lidocaine with epinephrine has vasoconstrictor effects. The solution contains methylparaben (1 mg) as an antiseptic preservative. Citric acid and sodium metabisulfite may be added as a stabilizer. The solution pH is adjusted by adding sodium hydroxide and/or hydrochloric acid to approximately 4.5 (3.3–5.5).$^{23}$ Lidocaine is manufactured identically, except with an adjusted pH of approximately 6.5 (5.0–7.0).$^{24}$ Thus, when combining a dermal filler with lidocaine with epinephrine, additional buffer of sodium bicarbonate 8.4% is added to create a homeostatic pH between 7.0 and 7.4.

Filler injection techniques...
Standardized Injection Technique Steps-

The injection steps were standardized to minimize variables. A custom ice pack was applied to the treatment site for at least ten seconds. Alcohol swabs cleaned the skin. Injections were initially carried out to 80% of estimated full correction to the immediate sub-dermal space (Figure 1). The filler area was massaged using Arnica Montana gel. The surgeon with the patients input confirm the degree of volume correction and smoothness.

Microcannula versus Needle Injection Methods-

Only one microcannula manufacturer (Dermasculpt™, CosmoFrance, Inc, Miami, FL) was used. The supplied needles for ART are 26 G, 5/8 length, while those supplied for PER1 are 29 G, ½ inch needles.

To determine the ease and accuracy for ART injections, the 26 G needle and different caliper sizes and lengths of microcannulas were examined. The different calibers and lengths included: 27 G, 1 ½ inch (38 mm), 25 G 1 ½ inch (38 mm), 25 G 2 inch (50 mm), 23 G 1 1/8 inch (29 mm). The physician injector ranked the ease of injection as easy, mildly difficult, and moderate to significantly difficult (1-3). Patient subjective discomfort responses, the amount of swelling and bruising were rated as mild, moderate or severe.

Adding Lidocaine with Epinephrine and Bicarbonate-

Lidocaine (1% or 10 mg/ml) with 1:100,000 epinephrine (0.3 ml/syringe) was added to the dermal fillers in hopes of counteracting the potential vasodilatory effects of the lidocaine due to the vasoconstriction properties of epinephrine. The bicarbonate 8.4% (0.05 ml/syringe) was added to buffer the more acidic solution of lidocaine with
epinephrine. The duration of the vasoconstriction clinical effect of epinephrine resolves between 60-90 minutes and does not result in discomfort.\textsuperscript{27}

Results:

ART syringes were injected from the refrigerator directly in five patients using the supplied kit 26 G 5/8 inch needle. Each was noted a significantly difficult to inject score. Laser temperature measurements revealed in five syringes it takes about 20 minutes to reach room temperature laying on the counter and about five minutes with human body contact warming. Once warmed to room temperature, the ease of injection ranged from easy to mildly difficult.

Injecting room temperature ART syringes with microcannulas was tabulated (Table 1). PER\textsubscript{1} injections revealed less syringe tension when diluting the filler with 0.3 cc of lidocaine with epinephrine and bicarbonate (Figures 2 & 3). ART injection was generally easier, however, the diluting process produced clumping. The injection of ART was easier until the point where a clump of the injection material obstructed the cannula or needle lumen. The alternative method, which is the current utilized technique, is to inject the area to be treated with less than 0.5 cc of a diluted lidocaine with epinephrine and bicarbonate solution. This is followed by injection of the unaltered ART syringe, which negated clumping.

The observations of ecchymoses with the microcannula revealed the location of the bruising to be most likely at the entry points created by the sharp needles. The less entry points used, lowered the observation of the existence of ecchymoses. The needle injection method does produce more bruising (Figures 4).

Discussion:
Successful facial volume replacement is related to accurate and sufficient anatomical placement, while minimizing adverse effects (discomfort, swelling, ecchymoses, intravascular injection, granuloma formation). Based on the anatomical areas to be treated, the number of syringes injected, and the type of dermal filler chosen, a combination of microcannulas and needles optimize safety by minimizing soft tissue and vascular trauma and optimize efficacy by precise facial contouring.

Dermal filler accuracy is related to the injectors knowledge of facial anatomy, a metered injection flow, and small lumen caliber of the injection device with low injection pressure. The author believes that the main advantage of needles is the precise injection of small volumes of filler. The blunt tipped microcannulas of longer lengths (1 ½ to 2 inches) than needles (5/8 inch) can be used through one entry point to cover a significant facial surface area using a fanning technique from deep to superficial subcutaneous planes with a multi-directional filler distribution.

Microcannulas\textsuperscript{18,19} are preferred to needles when a larger number of filler syringes are to be injected and a significant facial surface area is to be treated, although they have a higher clinical learning curve. Microcannulas decrease the incidence of ecchymoses (Figure 4), diminish the risk of intravascular injection, lessen discomfort, and in most patients diminish tissue swelling. Using 27 gauge or higher caliber diameter cannulas may eliminate inadvertent intravascular injection with appropriate injection technique.\textsuperscript{19}

To limit adverse effects during dermal filler injection, one should combine slow cannula movement through the soft tissues and a controlled, gentle injection pressure. The gentle advancement pushes vessels aside while moving through the path of least resistance.\textsuperscript{19}
Precise filler placement is heightened by the ease of injection related to the larger lumen, the addition of diluent, and warming ART syringes prior to injection. The author has observed lumen obstruction with ART, not with PER, most commonly with small caliber microcannulas, longer microcannulas (2 inches) and with diluent addition.

When lumen obstruction occurs, an initial attempt to dislodge the obstruction by changing the technique to intermittent short pulses of finger pressure. Avoid excess pressure when the obstruction occurs to prevent the inadvertent disconnection of the syringe and loss of product. Changing to a new needle or cannula or irrigating the same with saline may resolve the obstruction.

Fast absorption of the previously used carrier of gelatin led to agglomeration of the beads, resulting in palpable lumps in certain patients. This problem was addressed by changing to a more viscous collagen solution as the carrier material for the microspheres. This may be the reason when adding the diluent that lumen obstruction occurred. Initial administration of the diluent containing epinephrine followed by the ART syringe injection nullifies this concern.

Those patients with increased subcutaneous tissue resistance make advancement of the microcannula more technically difficult. Patients with increased tissue resistance include those with facial burns, acne scarring, after facial surgery to include barbed suture placement, liposuction, face-lifting and patients who have undergone multiple dermal filler sessions with collagen-stimulating volumizers, such as poly-lactic acid (PLLA). In this patient population, one needs to take care during forward movement of the microcannula and resisting the urge to push harder during significant resistance.

Filler injection techniques
No previous study using ART has evaluated different percentages of lidocaine or using lidocaine with epinephrine with or without bicarbonate. The addition of lidocaine with epinephrine has been shown here and elsewhere with HLA fillers to minimize bruising by vasoconstriction.\textsuperscript{16,27} Another HLA filler study revealed consistent outcomes with less bruising on the side of the face injected with the RES-lidocaine-epinephrine mixture.\textsuperscript{17} However, some consider lidocaine alone as the diluent of choice and place a warning on the use of epinephrine.\textsuperscript{19}

Some injectors believe that adding epinephrine is contraindicated, because potential intravascular injection is hidden by the vasoconstriction. The burning sensation and observed skin blanching might mask signs of vascular compromise during or immediately after filler injection. If intravascular injection occurred, patients would have a vasoconstriction tissue appearance greater than 90 minutes and a complaint of pain that is clinically out of proportion to the procedure. So when the burning sensation and discomfort is a nonentity, there is no assumption of vascular injection with skin blanching alone. The author believes that the diluent of choice for dermal fillers is lidocaine with epinephrine and bicarbonate.

The consensus paper on microcannulas revealed that dilution of HLA fillers decreases injection force through microcannulas with a diameter smaller than 22 gauge.\textsuperscript{19} This diminished force would increase placement accuracy and minimize vascular vessel cannulation, especially in the periobital area.\textsuperscript{8} Although 30 and 27 gauge cannulas can still cannulate a vessel, this complication is unlikely with a 25 gauge microcannula.\textsuperscript{8}

The tear trough area is the most technically difficult area and only facial site of sub-muscular placement. It has the highest risk of complications of over-injection,

Filler injection techniques
ecchymoses, and skin contour irregularities. The microcannula facilitates proper filler placement into the supra-periosteal plane with less risk of globe or vessel injury, and more accurate filler placement of both ART and PER. Berros studied the outcomes of HLA fillers for periorbital hollowing using microcannulas (n=26). The observation was an even distribution of the filler product with an excellent aesthetic improvement (85% subject satisfaction) and a low rate of hematomas as well as post-treatment swelling.

In summary, a diluent solution of lidocaine with epinephrine and bicarbonate and the use of a microcannula increases patient satisfaction, may improve accuracy of facial volume replacement, and minimizes adverse effects of discomfort, bruising, and swelling during dermal filler administration.

Conflict of Interest:

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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Filler injection techniques
Table 1:

Skin Test Data in the Bellafill* Trials

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*Artefill rebranded to Bellafill in the U.S. 2015
§ Data from initial FDA submission, contained in IFU

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Injection ease: E-1 easy, ML- 2 mildly difficult, MD- 3 moderate to significant difficult
Discomfort, Swelling & Bruising: 1 ML-mild, 2 MD-moderate, 3 S-severe

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Filler injection techniques
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Mean | Mean | Mean | Mean |

Filler with the addition of Lidocaine with epinephrine (0.3 cc) and bicarbonate (0.05 cc)

Injection ease: E-1 easy, ML- 2 mildly difficult, MD- 3 moderate to significant difficult
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Figure 1:

Dermal Filler New Technology Timeline

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<td>Restylane</td>
<td>Radiesse</td>
<td>Perlane</td>
<td>Sculptra</td>
<td>Juvéderm XC</td>
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<td>Artefill(RestylaneLyft)</td>
<td>(Bellafill)</td>
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<td>2014</td>
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<td>2016</td>
<td>2017</td>
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<td>Belotero</td>
<td>Restylane Silk</td>
<td>Juvéderm Voluma XC</td>
<td>Voluma</td>
<td>Restylane refine</td>
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<td>Restylane define</td>
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<td></td>
<td>Juvéderm Vollure</td>
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Figure 2

Dermal filler immediate sub-dermal placement of both Bellafill & Restylane Lyft. (Courtesy of Suneva Medical, Inc. 2016).

Figure 3

Artist depiction of wrinkle treatment, micro-aliquot volumes in fine layers (Courtesy of Suneva Medical, Inc.) A. Before B. After

Figure 4

74 yo woman with facial volume loss treated with 6 syringes of Bellafill to midface, vermillion border, premaxilla and pre-jowl sulcus. Microcannula used for Bellafill placement (left side) & Needle Injection (right side & premaxilla). A. B. C. Before After C. D. E.
Dermal filler immediate sub-dermal placement of both Bellafill & Restylane Lyft. (Courtesy of Suneva Medical, Inc. 2016).

677x381mm (72 x 72 DPI)
Artist depiction of wrinkle treatment, micro-aliquot volumes in fine layers (Courtesy of Suneva Medical, Inc.)
A. Before  B. After
Artist depiction of wrinkle treatment, micro- aliquot volumes in fine layers (Courtesy of Suneva Medical, Inc.)

A. Before B. After
74 yo woman with facial volume loss treated with 6 syringes of Belafill to midface, vermilion border, premaxilla and pre-jowl sulcus. Microcannula used for Bellafill placement (left side) & Needle Injection (right side & premaxilla). A. B. C. Before After C. D. E.
74 yo woman with facial volume loss treated with 6 syringes of Belafill to midface, vermillion border, premaxilla and pre-jowl sulcus. Microcannula used for Bellafill placement (left side) & Needle Injection (right side & premaxilla). A. B. C. Before After C. D. E.

1004x1507mm (72 x 72 DPI)
74 yo woman with facial volume loss treated with 6 syringes of Bellafill to midface, vermillion border, premaxilla and pre-jowl sulcus. Microcannula used for Bellafill placement (left side) & Needle Injection (right side & premaxilla). A. B. C. Before After C. D. E.
74 yo woman with facial volume loss treated with 6 syringes of Belafill to midface, vermillion border, premaxilla and pre-jowl sulcus. Microcannula used for Bellafill placement (left side) & Needle Injection (right side & premaxilla). A. B. C. Before After C. D. E.
74 yo woman with facial volume loss treated with 6 syringes of Belafill to midface, vermillion border, premaxilla and pre-jowl sulcus. Microcannula used for Bellafill placement (left side) & Needle Injection (right side & premaxilla). A. B. C. Before After C. D. E.
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