

Quantifying Depth of Injection of Hyaluronic Acid in the Dermis: Data from Clinical, Laboratory, and Ultrasound Settings

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ABSTRACT

Although manufacturers' instructions for use of dermal fillers ordinarily direct injection in the superficial, mid or deep dermis, or, in some cases, the hypodermis (subcutis), the precise depth of injection may not always be for injectors. In this article, investigators report findings gathered from histopathology, ultrasound, "live" one on one training injections, as well as application of a mathematical formula for depth calculation of the various layers within the dermis. Areas of particular interest are the superficial reticular dermis and the mid dermis. Following the depth measurements detailed by Della Volpe et al in 2012, investigators compare and contrast their own depth findings of the various layers, arriving at the conclusion that the depth of the dermis is not as deep as had been previously assumed. The investigators also develop an argument for the appropriate angles of injection for placement of dermal filler into the various layers, demonstrating that the heretofore widely used angles of 30° and 45° are far more acute than required.

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INTRODUCTION

A wide-sweeping adoption of soft tissue fillers for use in aesthetic medicine has occurred since the introduction of bovine collagen in 1981 and then hyaluronic acid (HA)-based products in 1995.¹⁻⁶ With a panoply of options for HAS now available for aesthetic physicians, dermal fillers products offer treatment options for cosmetic correction of facial lines and wrinkles. Regardless of which filler is being introduced to the medical community, one topic has been an abiding source of interest for some years: depth of injection in the dermis.

Manufacturer instructions as well as in-service education from colleagues nearly always contain directions that any dermal filler product is to be injected at various depths in the skin's dermis (Figure 1).³⁻⁶

Many of us may not know the precise depth of various skin strata. To that end, in this paper we present data a) to identify the depths of the strata; b) explore whether the angle of penetration is appropriate for the stratum selected; and c) argue that the injection depth can be more targeted than we had originally assumed. Data reported have been gathered from ultrasound imaging, biopsies, live injections, and mathematical calculations. Areas of injection and measurement include the nasolabial folds and buttocks in the superficial reticular and/or mid dermis.

Epidermis

This layer consists of stratified squamous epithelial cells. Its mean thickness varies from 0.10 to 0.15 mm, depending on area of the body. Facial skin, for example, is ordinarily thinner than skin on the soles of the feet.

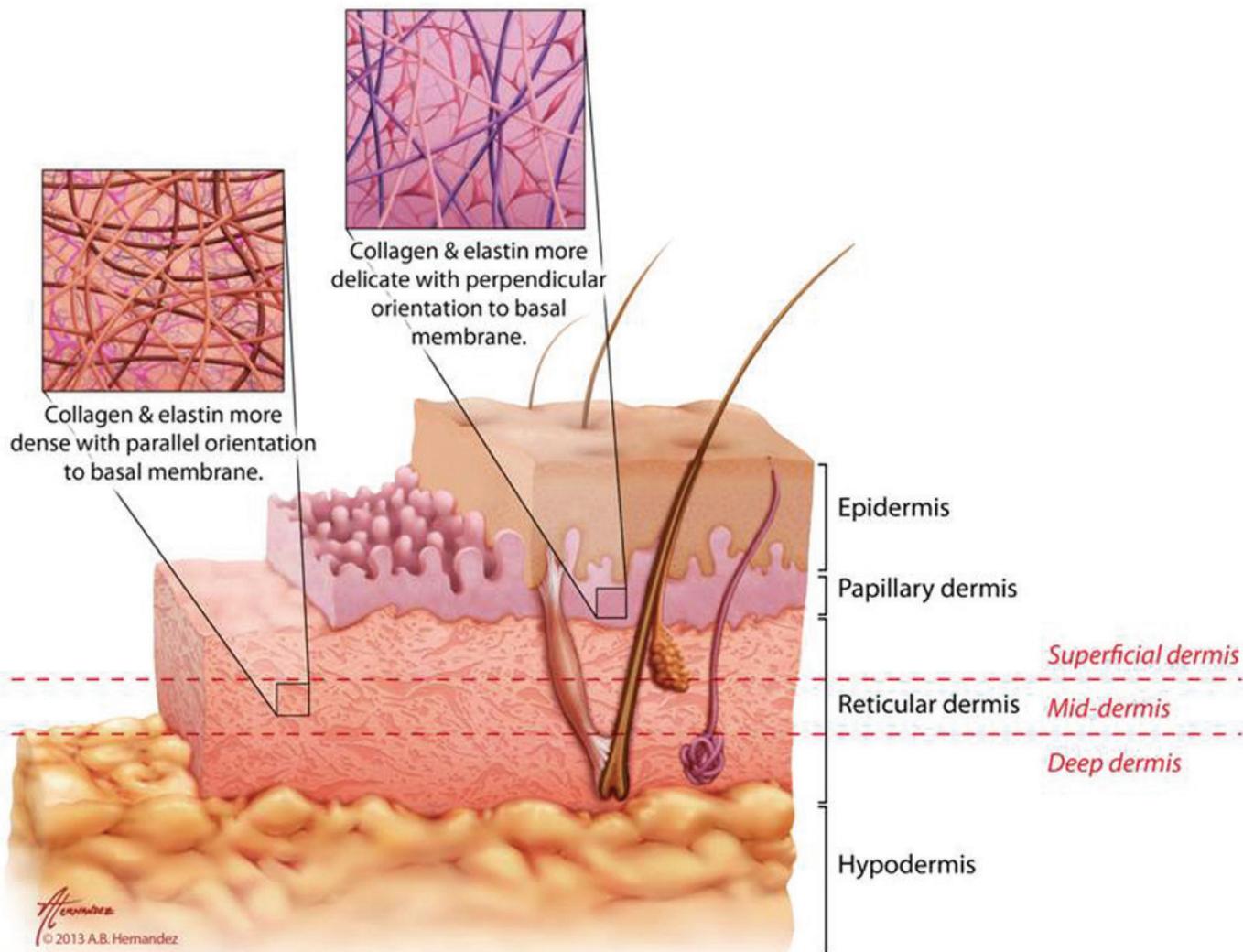
Dermis

This stratum has 2 different layers: the papillary dermis and the reticular dermis, both of special interest for injectors. Each of the layers has a well-defined histological specificity. In the papillary dermis, collagen and elastic fibers are thin and usually somewhat perpendicular to the basal epidermal layer.

In contrast, the reticular dermis is considerably thicker than papillary dermis. Its fibers are more horizontal, ie, more parallel than perpendicular to the basal epidermal layer, unlike the perpendicular ones of the papillary dermis. The thickness of the reticular dermis varies from one body area to another. Della Volpe et al⁷ show dermis thicknesses of 2.56 mm for the cheek and 2.79 mm for the buttock. For the epidermis and the dermis, the thicknesses are 2.72 mm and 2.93 mm, respectively. On certain areas of the dorsum (eg, the back side of the neck and the back), however, the thickness may reach 10.0 mm.

The reticular dermis may be arbitrarily divided in equivalent thirds: superficial reticular dermis, mid reticular dermis, and deep reticular dermis. In our practice, when using HAs, we

FIGURE 1. Layers of the skin. (This illustration originally appeared in *Plast Recon Surg* 2013;132:59S. Used by permission of the artist, Alexandra Hernandez at GoryDetails.com)



generally inject into the superficial stratum for fine lines and wrinkles, particularly for patients with thin skin. For more broadly based wrinkles in normal skin, we generally inject dermal filler into the superficial and/or mid dermis. For deep wrinkles, for folds, and for patients with thick skin, we generally inject into the mid and/or deep dermis.

Hypodermis

This level, also referred to as the subcutis, is a fat layer under the 3 previous layers. Its thickness may reach several centimeters, depending on age, muscle tone, and adiposity of the individual.

Angle and Depth of Penetration

As clinicians, we have been taught (and, in turn, taught others) that injection into the superficial section of the reticular

dermis needs to be at an angle of penetration of approximately 30°. For injection into the mid and deep sections in the reticular dermis, the angle needs to be around 45°. In this article, investigators reports data from multiple experiments and fact-finding projects to explore two questions: 1) Is it possible to inject into the superficial and mid-reticular dermis? and 2) Are the 30° and 45° angles the appropriate angles for penetration into these layers?

Materials and Mathematical Calculations

Materials

Hyaluronic acid (HA) gel fillers

For all the studies and the real live treatments, three HA gel fillers were injected: Restylane® [(RES), Q-Med-Galderma (Uppsala, Sweden)]; Juvéderm® [(JUV) Ultra 3/Juvederm® Ultra XC,

FIGURE 2. Measurement of the implanted needle, using red nail polish (A); real-time injection and measured angle using a protractor (B); US image of implanted needle (C). (Images A and B courtesy of Dr Patrick Micheels and image C courtesy of Dr Stéphanie Besse; all used with permission).

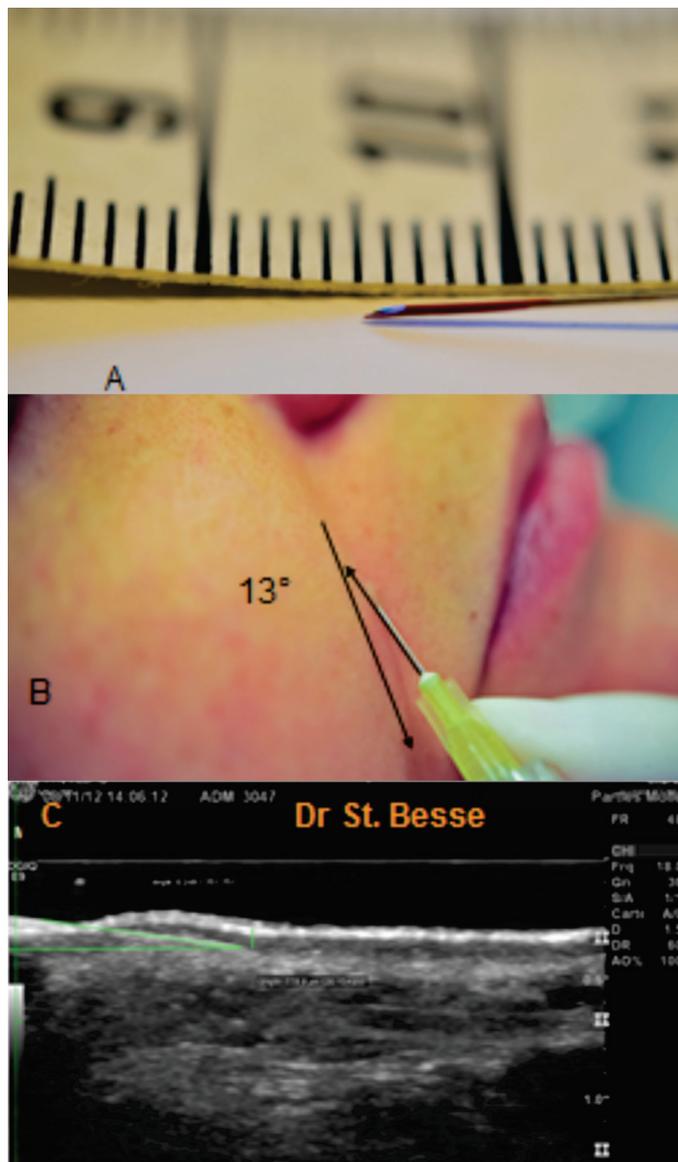
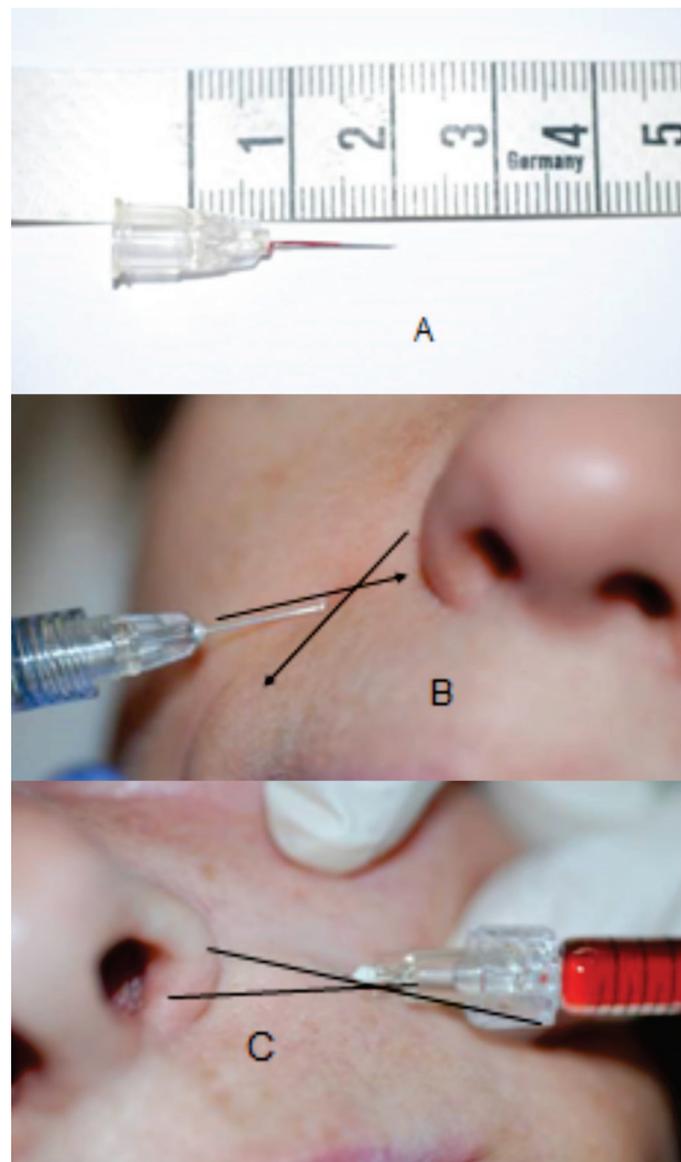


FIGURE 3. Retracted implanted needle with red nail polish visible (A); injection during one-on-one training demonstration, showing intended (superficial dermis) area of injection (B); injection by physician being trained for superficial dermal injection into volunteer subjects (C). Injection at 20.5° by physician being trained. (Images courtesy of Dr Patrick Micheels; used with permission).



Allergan-Cornéal (Pringy, France)); and Belotero® [(BEL) Balance, Merz Pharmaceuticals, GmbH. (Frankfurt, Germany)]/Esthélis® Basic-Antéis S.A. (Geneva, Switzerland)].

Needles

In the studies described here, only Becton-Dickinson needles were used, specifically BD® Microlance 30 G ½ in. (0.3 X 13mm) [lot n° 1009 20 Exp: 2015-08]. These needles have a diameter of 0.3 mm, a total length of 13 mm, and a bevel length of 1 mm.

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Ultrasound imaging

The device for the different ultrasound studies^{12,13} was the *General Electric logiQ E9®* (General Electric Company, Fairfield, CT) with probe *Hockey stick L8 18I®*, 17 mega-Hertz. An interface *SonarAid GeistlichPharma®* [lot 100353], (Geistlich Pharma AG, Wolhusen, Switzerland), was placed over the treated area to obtain a clearer definition of the US image. This *SonarAid* device, placed by investigators, ensures an echoless, undisturbed picture.

TABLE 1.**Della Volpe Calculations of Depth of Cheeks and Buttocks⁷**

	Cheeks	Buttocks
Total skin thickness (epidermis + total dermis)	2.72 mm	2.93 mm
Epidermis	0.16 mm	0.14 mm
Dermis (papillary + reticular)	2.56 mm	2.79 mm
Papillary dermis	~ 0.20 mm	~ 0.20 mm
Reticular dermis	2.36 mm (2.56 mm – 0.20 mm)	2.59 mm (2.79 mm – 0.20 mm)
Each reticular dermis layer	~ 0.79 mm	~ 0.86 mm
Hypodermis	>2.72 mm	>2.93 mm

Angle measurements

Angle of implantation was determined by measuring the penetration angle on profile pictures with a protractor (Rotring®, a transparent resistant geometry set square with fixed grip and precise scaling).

Biopsies

The ultrasound data found in this study was compared to those obtained with biopsies in previous studies.^{13,14}

Photographs

A professional photographer was hired to document live pictures in the office of one of the investigators (PM). The

photographer used a digital camera Nikon D3 with a lens 60 mm 2.8 macro. Investigator PM also photographed colleagues' injection techniques, using a digital camera (NikonD40X with lens AF Micro Nikkor 60mm 1:2.8D). Both the professional photographer and the investigator's images are shown in the Results section.

Measurements during the live treatments

To measure the length of the needle's injection into the skin, simple measuring tape and red nail polish were utilized (Figure 2AB). After the needle had been inserted, the nail polish was applied on the non-implanted part of the needle, close to its skin penetration point. After withdrawal of the needle, the

TABLE 2.**Measurement of injection depth (in mm) for the superficial dermis compared to Della Volpe's histological measurements for the superficial dermis (epidermis [.150 mm] + papillary dermis [.200 mm] + maximum 1/3 of dermis thickness) of between 0.351 mm to 1.13 mm**

Part 1 Real live treatments in PM office			
	Angle	Length	Calculated depth of injection and location
Subject 1	13°	1.80 mm	0.40 Superficial
Subject 2	9°	4.00 mm	0.40 Superficial
Part 2 Real live treatments during "one to one" workshop			
	Angle	Length	Calculated depth of injection and location
Subject 1	32°	5.0 mm	2.6 mm Deep dermis
Subject 2	18°	9.0 mm	2.8 mm Deep dermis
Part 3 Real live treatments; Workshop with 12 colleagues (One physician injected 2 subjects.)			
	Angle	Length	Calculated depth of injection and location
Subject 1	24°	3.0 mm	1.2 mm Mid dermis
Subject 2	25°	3.0 mm	1.3 mm Mid dermis
Subject 3	25°	12.0 mm	5.1 mm Mid dermis
Subject 4	15°	5.0 mm	1.3 mm Mid dermis

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non-red nail polish part of the needle, representing the implanted section of the needle, was determined using the measuring tape (Figure 2A). The angles of penetration were measured with a protractor directly on the pictures (Figure 2B).

To achieve our objectives, we relied on ultrasound images, live pictures, and mathematical formulations. Specifically, we calculated that the depth of penetration can be determined by multiplying the sine (sin) angle of entry times the exact length of the needle's penetration into the skin. Mathematically represented, $depth\ of\ penetration = \sin(\text{angle}) \times \text{length inserted}$. (This formula was provided by Mr B Hadjab [Geneva, Switzerland], an engineer not associated with the project).^{10,11}

Using the theoretical mathematical formula $depth\ of\ penetration = \sin(\text{angle}) \times \text{length inserted}$, an inserted needle length would be 5.0 mm to 8.0 mm. This length is often used by physicians in the clinical setting, with the classical point by point technique of injection—not the retrograde technique of injection. (In the retrograde technique, the entire needle length [13 mm] is implanted in the skin, and the gel is slowly delivered when the injector withdraws the needle.) Using the formula, $\sin 30^\circ \times 5.0\ \text{mm} = 2.5\ \text{mm}$ and $\sin 30^\circ \times 8.0\ \text{mm} = 4.0\ \text{mm}$ for minimal and maximal injection depth. In 45° angle calculation, $\sin 45^\circ \times 5.0\ \text{mm} = 3.5\ \text{mm}$ and $\sin 45^\circ \times 8.0\ \text{mm} = 5.7\ \text{mm}$.

With the “blanching technique” of injection¹⁴ and inserting only the bevel of the needle, the inserted needle length would be 1.1 to 1.5 mm. This distance is just beyond the length of the needle bevel, requiring precise and delicate injection for point by point HA delivery, rather than for retrograde injection. (With the retrograde injection technique, it is impossible to stay in the superficial dermis all along the injection, even with a bent needle.) Using the same formula for calculation, $\sin 30^\circ \times 1.1\ \text{mm} = 0.6\ \text{mm}$ and $\sin 30^\circ \times 1.5\ \text{mm} = 0.8\ \text{mm}$ for injection depth into the superficial dermis. Depths for injection into the mid dermis are as follows: $\sin 45^\circ \times 1.1\ \text{mm} = 0.8\ \text{mm}$ and $\sin 45^\circ \times 1.5\ \text{mm} = 1.1\ \text{mm}$.

In 2012, Della Volpe and colleagues published an article that listed the depths of various layers of the skin of various body

areas.⁷ The Della Volpe measurements in the cheeks and buttocks are shown in Table 1. The investigators in the study reported here assumed that the measurements in the cheeks and the buttocks are roughly equivalent to those in the nasolabial folds. Reference literature with histological data⁷⁻⁹ shows that the mean thickness of the epidermis is 0.15 mm and the mean thickness of the papillary dermis is 0.20 mm. Thus, to inject into the superficial reticular dermis, the needle has to be placed between 0.351 mm and 1.684 mm.⁷ For insertion into the mid reticular dermis with its thin skin, the needle has to be placed between 1.35 mm and 3.018 mm.⁷

Methods of Investigation

Ultrasound

In the 2 ultrasound imaging procedures reported here, the depth of the needle placement was controlled by a specialist in radiology (SB). In the first procedure, the needle was inserted into the superficial reticular dermis.¹² In the second procedure, the needle was inserted into the mid reticular dermis.¹³

In both procedures, the radiologist measured the epidermis and the dermis thickness before needle insertion. After the needle had been inserted, the investigator measured the needle penetration angle, the length of implanted needle section, and the bevel top depth (Figure 2C).

Biopsies

Several studies—two published and one still in preparation—also provide us with histological measurements of epidermis and papillary dermis thickness.¹³⁻¹⁵ In these studies, the thickness of the epidermis and of the papillary dermis—uninfluenced by the injections—has been measured by a specialist in histopathology (DS). These measurements are similar to the ones determined in the Della Volpe data.⁷

Live injections

In the first of 2 live injection procedures, the injector (PM) placed the needle on patients in his office for conventional NLF treatment with no assistance from ultrasound. The needle placement, before any injection, was immediately photographed by

TABLE 3.

Needle penetration measures on live nasolabial treatments, during a “one to one” workshop, comparing calculated depth to Della Volpe’s histological measurements for the mid reticular dermis (epidermis (.15 mm) + papillary dermis [.20 mm] + maximum 2 X 1/3 of dermis thickness of the area being examined) as 1.14mm to 1.93 mm and hypodermis depth of >2.86 mm

	Angle	Length	Calculated depth of injection	Actual location in dermis
Subject 1	24°	9.0 mm	3.7 mm	Hypodermis
Subject 1	33°	9.0 mm	4.9 mm	Hypodermis
Subject 2	35°	5.6 mm	3.2 mm	Hypodermis
Subject 2	35°	5.0 mm	2.9 mm	Hypodermis
Subject 3	35°	10.0 mm	5.7 mm	Hypodermis

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TABLE 4.

Ultrasound and Histological Depths Data (in mm) With Needle Implanted in the Mid Dermis of the Buttock

	Patient's Buttock	Subject G M-5	Subject C P-6	Subject IT
Biopsies	Epidermis thickness	0.10	0.15	No biopsy
	Papillary dermis thickness	0.15	0.20	No biopsy
	Reticular dermis thickness ^o	Mean 5.25	Mean 4.30	No biopsy
US examination preinjection	Dermis thickness at US examination	Mean 3.00	Mean 2.14	Mean 2.33
	Thickness of each dermis layer (1/3)	1.00	0.71	0.77
	Angle of needle penetra-tion (°)	9.99	7.60	8.90
	Implanted needle length (mm)	8.85	9.40	7.21
	Depth of needle top (mm)	1.31	1.20	1.44

^o(after HA gel filler injection)

a professional photographer. Then, the red nail polish and the measuring tape described earlier were used (Figure 2AB).

In the second live procedure, PM observed colleagues' injection during 2 workshops (Figure 3ABC) took close-up photographs, with the colleagues' oral consent. In the one-to-one workshop, the red nail polish and measuring tape were used (Figure 3AB). Only close up photographs were taken (Figure 3C).

Depths of Injection in the Dermis

Superficial reticular dermis injections

In one investigator's private practice setting (PM), NLF of 2 patients were injected by the same injector, with a superficial technique called the "blanching technique."¹⁶ The needle penetrating angles were measured, the inserted needle section was measured, and the depth of injection ($\sin(\text{angle}) \times \text{inserted needle length} = \text{depth of penetration}$) was calculated. Investigators determined that, using the blanching technique, injection into the superficial reticular dermis could be achieved.

Results of the determinations in the live injections in the private practice setting are shown in Table 2 (part 1).

Two other live injection activities focused on determination of depth of injection. In the first activity, a one-on-one workshop between 2 of the authors (PM, MSD), 3 subjects were injected in the nasolabial folds, using a BD[®] 30G half-inch needle. The injector (MSD) typically inserted her needle into what she perceived to be the superficial reticular dermis. Two of the 3 patients were injected on one side in the "superficial" reticular dermis of the NLF. For those 2 subjects, the other side was injected in the "mid" reticular dermis. The 3rd patient was injected only in the "mid" reticular dermis, but with 2 different penetration angles.

Angle of implantation, length of needle inserted, and depth of injection were all reported. Angle of implantation was

determined with the protractor; length of needle part was determined by use of the red nail polish described earlier; and depth of injection was determined by use of the mathematical formula also shown earlier in the paper. With an angle greater than 10° and/or a penetration needle length too long, even the experienced injector appears to be in the deep dermis, not in the superficial reticular dermis.

Results are shown in Table 2 (part 2).

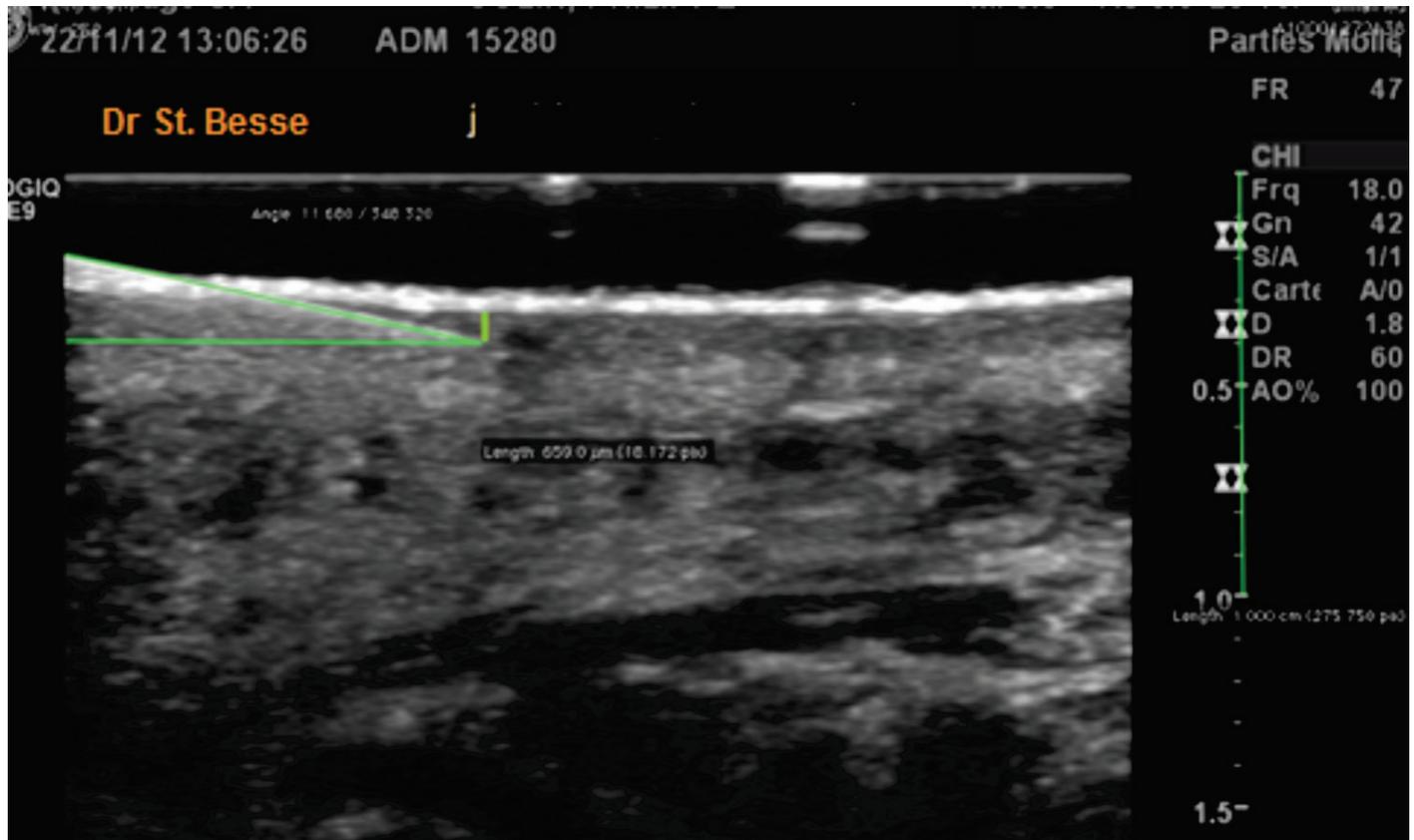
In the second activity, 3 physicians from a group of 12 were randomly selected to attempt to inject precisely into the superficial reticular dermis of 4 patient volunteers (Figure 3C). Measurements showed that, even when colleagues know that they are being closely observed, they are unable to inject in the superficial reticular dermis. Results are shown in Table 2, part 3.

TABLE 5.

Ultrasound Measurements (in mm) in the Nasolabial Area Before Injection in Left (L) and Right (R) Sides

	Subject G M-5	Subject C P-6
Nasolabial epidermis thickness	0.30	0.30
Nasolabial dermis thickness	1.60	1.30
Mean thickness of each dermis layer	0.53	0.43
Needle penetration angle (°)	L 10.13	L 11.44
	R 8.25	R 11.68
Implanted needle length (mm)	L 6.52	L 5.57
	R 6.59	R 7.07
Top of the needle depth (mm)	L 1.04	L 0.983
	R 0.778	R 1.250
Injection theoretical depth (mm)	L 1.3	L 1.1
	R 0.9	R 1.4

FIGURE 4. Ultrasound measurement of angle and depth of needle during injection into a nasolabial fold. (Image courtesy of Dr Stéphanie Besse; used with permission.)



Mid Dermis Injections

Live treatments in the “one to one” workshop training session, the injector (MSD) was asked to inject in the mid reticular dermis as she typically would in her clinical practice.

The length of needle penetration was determined in the similar manner as it was for the superficial dermis injection session, ie, with the red nail polish applied to the needle after the needle had been inserted. The angle of penetration was also determined as it has been previously, ie, with the protractor to measure the angle on the photograph. Investigators determined that, even when the experienced injectors used the conventional angles and a non-retrograde injection technique, the gel was injected too deeply, into the hypodermis (subcutis).

Results of their findings are shown in Table 3.

Ultrasound and biopsy findings in the buttock

In an unpublished and still ongoing mid-reticular dermis ultrasound study,¹³ 11 subjects agreed to have needles and HA gels implanted into the buttocks area. Using the mathematical formula provided earlier, investigators determined that

injection would be at a depth of ~ 1.1 mm to 1.5 mm. Depths required varied. Using Della Volpe’s data, injection in the buttocks had to be between 1.07 mm and 2.0 mm. As a part of the ongoing unpublished study, investigators also calculated that depth in the mid dermis of the buttock for one patient (GM-5) had to be 1.25 mm to 2.25 mm and had to be 1.06 mm to 1.77 mm in the buttock for another patient (CP-6). For the third patient (IT), we had no prior histological data about depth because we had not performed biopsies. Measurements taken from the data-gathering show that investigators were indeed in the mid reticular dermis with these 3 subjects. Data are shown in Table 4.

Ultrasound only findings in the NLF.

In the NLF-injected patients, only ultrasound measurements are available; facial biopsies were not performed. Using Della Volpe’s data, we determined that our needles were to be placed from 1.01 mm to 1.86 mm in order to be in the mid reticular dermis of the nasolabial area. Investigators concluded that placement was indeed in the mid reticular dermis, even though the skin of the subjects was thinner than that presented by Della Volpe. Measurements from 2 subjects are reported in Table 5.

DISCUSSION

What seems clear to us is that the mathematical formula for 30° and 45° injection we had used, ie, $\sin(\text{angle}) \times \text{length of insertion of needle} = \text{depth of penetration}$, will invariably lead us to implant too deeply, especially if we fully implant the needle as we have done in retrograde injection. To inject at the correct depth, the angle of insertion must be changed from 30° to 7°-9° for insertion into the superficial reticular dermis and from 45° to 9°-12° for insertion into the mid reticular dermis. Even a change of a few degrees, we believe, will result in improper placement. For example, using the mathematical formula and the conventional 10° to 12° acute angle, placement will still be in the superficial dermis, ie, 0.2 mm to 0.3 mm. Insertion depth length of implanted needle is equally critical: 1.1 mm to 1.5 mm for superficial reticular injection and 6.0 mm to 8.00 mm for mid reticular injection.

CONCLUSION

Heretofore conventional angle of injection has not proved sufficient for entry into the superficial and/or mid reticular dermis. More acute angles on entry and precise measurement of the length of the needle inserted under the skin are essential to proper placement in the superficial and/or mid reticular dermis.

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DISCLOSURES

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