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Research Article

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Behaviour of Hyaluronic Acid Gels Injected Under Ultrasound Guidance in he Mid and Deep Reticular Dermis, The Hypodermis, And in The Muscle, Near the Bone: Comparative Observation on Day 0

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1. Abstract

1.1. Aim: Hyaluronic acid (HA) gels are injected into the superficial, minor deep dermis, into the hypodermis (subcutaneous fat, subcutis) and intramuscularly, near the bone. We already documented the behaviour of some gels injected into the superficial reticular dermis. This new ultrasonographic (US) study of HA gels, indicated to fill up wrinkles and creases, or to correct the volume of the face, gives us an outline of their behaviour during injection into the medium and deep reticular dermis, into the fat and during deep intramuscular administration, near the bone.

1.2. Subjects:

- For the mid and deep dermis: 4 Caucasian subjects:
 3 women, 1 man.
- > For the hypodermis: we have already described our observations, ex-vivo and in-vivo.
- For deep intramuscular injection, near the bone: 2 Caucasian women.

1.3. Materials and methods: Cohesive, partially cohesive and non-cohesive hyaluronic acid (HA) gels were injected into the mid and deep reticular dermis under ultrasound guidance, in the gluteal region. To study the hypodermis, the injections of cohesive and partly cohesive gels were administered in the abdomen and breast.

For the observation of the behaviour of HA volumizing gels, injected deep in muscle, near the bone, we injected a partly cohesive gel into the temporal hollow.

1.4. Results: When injected into the mid or deep reticular dermis, opposed to injections in the superficial reticular dermis, all the HA gels were found to leak into the hypodermis. During hypodermal injection, the behaviour of the tested HA gels is distinctly less specific than during their injection in the superficial reticular dermis, or even mid dermis. There is no interference with the interlobular fibres. The gels take the same aspect, in the form of a ball or a sausage, following the injection technique. Injected deep in the muscle, near the bone, the gel is located in between muscular fibres, or within the insertion of the deep temporal fascia, on the temporal crest. Its ultrasonographic aspect is hetero-hypo-echogenic compared to the adjacent non-injected zone.

1.5. Conclusion: After injection into the mid and/or deep reticular dermis, all examined gels escape into the hypodermis. This raises the following questions.

- In our daily practice, do we inject at the correct depth, as recommended in the instruction manual and labels of HA gels?
- More in particular are retrograde injections with needles and micro-cannula, as frequently Observed during clinical demonstration, truly intradermal?
- > Are the recommendations for injection and product labels well-thought and well-written?
- > If the filler is mainly deposited sub-dermally, how can the improvement of that area are explained?

These questions warrant new studies, to understand more precisely what happens when we treat the wrinkles of our patients with hyaluronic acid-based fillers. An ex-vivo study carried out by the University of Geneva, an in-vivo study with 1 subject and another in-vivo study in a larger study population were previously published, describing the behaviour of HA gels injected into the fat. Gels have a less specific behaviour in the fat tissue than in the dermis. Via deep intramuscular injection, near the bone, we observed an oblong papule in two subjects, hetero-hypo-echogenic in comparison with the overlying and underlying structures. A 2-years study including 4 subjects is currently being finalized.

2. Keywords:

Hyaluronic acid; Mid and deep reticular dermis; Hypodermis; Deep IM route; Near the bone

3. Introduction

The operating manuals of HA filler gels specify the superficial reticular dermis, mid reticular dermis or deep reticular dermis, as recommended level of injection, depending on gel concentration, cross-link ingrate and clinical indications [1-8]. We noticed that these texts have evolved after the introduction on the market, including changes to the suggested depth of injection. In some previous studies, HA gels behaviour injected into superficial reticular dermis was compared [9-14]. Some gels were studied during their injection in mid reticular dermis [11,12]. However, until today, no comparative studies on the diffusion of HA gels were carried out, when injected into mid and/or deep reticular dermis. We studied 3 HA filler gels and 2 gels specifically designed for

volumizing treatments, injected in the mid and deep dermis, the hypodermis, and deep in muscle, near the bone [15,16]. Some of the gels have been approved by the Food and Drug Administration of the United States of America; for others registration is pending. All gels have a CE mark and have been registered by "Swiss Medic" (Swiss Agency for Medicinal products and Medical devices). Santer, Vandeputte, Micheels, and others published ex-vivo and in vivo studies on the behaviour of HA fillers in the subcutis [17-19]. Several publications describing the complications of HA fillers showed the presence of these HA gels in the hypodermis [20-22]. We included our observations on 2 subjects during injection a volumizing HA gel in the temporal fosse, to correct skeletonization of aging faces. We described the behaviour of HA gels, in gluteal area of 4 subjects, under ultrasound guidance, on Day 0, in mid or deep reticular dermis, following the instructions in the product labels.

4. Materials and Methods

4.1. Disinfection

The skin was disinfected twice with Hibidil[®] (non-alcoholic solution of chlorhexidine 0.5 mg/1 ml-LAB CPS CITO PHARMA SERVICES GMBH, Uster-Switzerland).

4.2. Injections

Injections were carried out according to the instruction in the product labels, with needles included in the package, i.e. 29G, 30½G or 27G, in mid reticular and/or deep reticular dermis. In the hypodermis, injections were carried out with a27G needle or with a 27G cannula. In the temporal hollow, we used the 23G needle, included in the product package.

4.3. Pictures

Macrophotography of the zone to be injected was taken before and after the injection, using a digital Nikon® D40x camera, with an AF NIKKOR 60 mm lens (Figure 1 and 5).



Figure 1: Above: Before injection.

- (A) Drawing of the injected area.
- (B) Ultrasonographic dermis measurement 1= epidermis (50.0 μm) dermis (270.0 μm).

Below: Before injection.

- (C) In the mid dermis, needle placed.
- (D) In the deep dermis, after injection.
- (E) After injection and needle withdrawal.

Figure 2: Image showing levels of sectioning in the axial plane of the cadaver's right femur (Author's own work). Consent for images to be taken was provided by the donor registration programme at the University of Birmingham, licensed by the Human Tissue Authority number 12236 (Anatomy).

4.4. Ultrasound (US) equipment

We used a General Electric logiQ E9[®] ultrasound instrument equipped with an Ice hockey Stick L8 18i[®] probe (GE HEALTHCARE, Little Chalfont, United Kingdom) 17 MHZ [11-14]. We applied a "no-touch" technique by using a lot of gel–Dispogel[®] from Disposan AG, Dietikon Switzerland-avoid in gany direct contact between probe and skin. Ultrasonographic assessment was performed before injection, to measure the thickness of the dermis to be injected. One image was saved of the needle or the cannula, before injection, and two after injection, first with the needle or the cannula in place, then after withdrawal. All injections were filmed and recorded (Figure 1).

4.5. HA fillers

4.5.1. Mid and deep intra dermal injections: The behaviour of non-cohesive gels NASHA®, cohesive CPM®, partly cohesive Vycross®, injected into the mid and/or deep reticular dermis, was studied.

4.5.2. Non-cohesive HA gels: Cross-linking technology NASHA® (Non-Animal Stabilised Hyaluronic Acid), Galderma. Uppsala-Sweden: -Restylane® lido, batch n° 14066-1, exp 2018-05-31 FDA 2010. Restylane Perlane® lido, batchn°12863-1, exp 2017-02 FDA 2010.

4.5.3. Partly cohesive HA gels: Cross-linking technology Vycross®, Allergan, Pringy-France.

Volbella®, batch n°V15LA60047, 2017-12 - FDA registration pending. Volift®, batch n° V17LA50183, 2017-04 – FDA registration pending. Juvederm® Voluma Lido, batch n°VB20A50346, 2017-07, FDA registered.

4.5.4. Cohesive HA gels: Cross-linking technology CPM[®] (Cohesive Polydensified Matrix[®]), Merz Aesthetic, Geneva-Switzerland. CPM[®] without lidocaïne is FDA registered.

Belotero* Balance lido, batch n°346060 / 3, 2017-06 - FDA registration pending.

Belotero $^{\circ}$ Intense lido, batch n°546031 / 7, 2016-10 - FDA registration pending.

Belotero $^{\circ}$ Volume lido, batch n° 547024/4, 2016-12 - FDA registration pending.

4.6. Injection via deep intramuscular (IM) route, near the bone, in the temporal pit (IMbo)

Globally cohesive gel, cross-linking technology IPN-LIKE*, Vivacy, Archamps-France: Stylage* XL with lidocaïne, batch n° LXE1829F, and 2021-03 was injected, through a 23G needle.

4.7. Injection via deep intramuscular route, near the bone, in the temporal hollow

Partly cohesive gel, cross-linking technology IPN-LIKE[®], Laboratory Vivacy, Archamps-France: Stylage[®] XL with lidocaine, batch n^o LXE1829F-2021-03 was injected, through a 23G needle.

4.8. Injection in the hypodermis

We will remind HA gels behaviour injected in the subcutaneous fat thanks to previous studies:

Ex-vivo: 3 different gels injected with a needle by P.M: NASHA®, CPM®, and VYCROSS® Volumising gel [17].

In-vivo: a) First observation: P.M. injected gels with a cannula and with a needle: CPM® Volumising gel, Vycross® Volumising gel [18].

b) In J. Vandeputte and coworkers's study, gels CPM® Volumising gel and Vycross® Volumising gel were injected with a 22G cannula [19].

4.9. Subjects

All subjects were given both oral and written explanation and gave a written consent. The study was conducted in accordance with the Helsinki Declaration.

4.9.1. Mid and deep reticular dermis injections: - 3 Caucasian female subjects, medium age of 52 years (range: 64-41 years). 1 Caucasian masculine subject (50 years).

2 different HA gels were injected into the left and right gluteal region, under US guidance, into the mid and/or deep reticular dermis. Some injections were performed as much in accordance with the instructions on the product labels as possible, others according to the main author's preferred injection technique.

the demographic data of subjects, the injected region, the injection depth and the different gels tested.

4.9.2 Subcutaneous injections ex-vivo: 3 models were used: pork skin, wastes of abdomino plasty and of face-lift of 5 female subjects, age ranging from 55 to 65 years.

4.9.3. Subcutaneous injections in-vivo: 1 Caucasian female subject, 66 years-old in 2016 (subject 1), and 5 Caucasian female subjects in 2017, medium age of 45.6 years (range: 34-55 years).

4.9.4. Deep intramuscular injection, near the bone: Two female subjects from 46 and 49.5 years in 2019.

the demographic data of subjects injected by PM, the different injected gels in-vivo in the subcutis, deep in muscle, near the bone.

5. Results

5.1. In the mid reticular dermis

Due to the small number of measurements contributing to the mean cross-sectional area at each level (n=2), the confidence intervals for the true mean at each level are very wide. The lower confidence interval for the true mean at Level 4 was adjusted from -3061.62 to 0 as this represents a value for cross-sectional area so cannot be negative. The mean cross-sectional area at Level 2 was 4230.08 mm2 (95% CI, 3698.89-4761.27). This was not statistically significantly different (p=0.14) from the mean cross-sectional area at Level 3. However, the small number of specimens (n=2) contributing to the mean at each level reduces the reliability of this comparison.

The mean cross-sectional area at Level 4 was 3527.43 mm2 (95% Cl, 0-10116.48) (Lower Cl adjusted from a negative value to zero due to the units being mm2). Like the mean cross-sectional area at Level 2, this was not statistically significantly different (p=0.14) from the mean cross-sectional area at Level 3.

The percentage decrease in cross sectional area when passing superiorly



Figure 2:

The gels, injected following their use leaflet, in the mid dermis. Green arrows : Gel in the fat. Red arrows, air bubbles. Yellow arrows: Gel in the dermis (A) NASHA[®] (B) VYCROSS[®]

(C) CPM[®]

5.1.1. Non-cohesive HA gels: Restylane[®] lido Originally, Restylane[®] lidohad to be injected into the mid or superficial reticular dermis (1995-+/- 2010). Currently, it is indicated for injections in mid reticular dermis and under the labial mucous membrane [1]. Dermal thickness, measured before injection: 2.2 mm. During injection in mid reticular dermis, we observed some diffusion with minimal escape of Restylane[®] Lido into the hypodermis. Gel leakage is variable, trans-sonic, perpendicular to the cutaneous surface. Dimensions: 7.3 mm X 6.0 mm. The papule was hypo-echogenic compared with the non-injected adjacent dermis, with irregular borders. The average dimensions of the papule were: 4.2 mm X 2.0 mm. After injection, the gel was palpable as a small nodule, with a light in duration of the injected zone.

Restylane Perlane[®] lido: Originally, Restylane Perlane[®] lido had to be injected into the mid and deep reticular dermis (1999 -+/- 2010). At present-2019-, it is injected in the deep reticular dermis [2]. Dermal thickness, measured before injection: 2.0 mm. During injection in the mid reticular dermis, a small intradermal papule appeared, with a diameter of 1.2 mm, hypo-echogenic compared with the non-injected adjacent dermis, irregular, oblong, discreetly trans-sonic. Gel leaked into the hypodermis quickly, perpendicular to the cutaneous surface, with well-delimited borders and a diameter of 1.8 mm X 7.6 mm.

5.1.2. Partly cohesive HA gels: Volbella®: Volbella® is indicated for injections in the superficial and mid reticular dermis [6]. Dermal thickness, measured before injection: 2.0 mm. Injection into the mid reticular dermis led to the development of a small intradermal papule (5.0 mm X 1.0 mm), hypo-echogenic compared with the non-injected adjacent dermis, well-delimited. There was a well-delimited escape into the subcutis, as well very precociously, oblique to the skin surface. The dimensions measured are: 8.0 mm X 2.0 mm [14].

Volift[®]: Volift[®] has to be injected in the mid reticular dermis [7]. Dermal thickness, measured before injection: 3.2 mm. During injection in the mid

reticular dermis, there was minimal gel escape towards the hypodermis with dimension: 3.0 X 2.5 mm. The oblong papule (4.0 mm X 1.0 mm) was iso-echogenic, discreetly visible compared to non-injected adjacent dermis. No shadow cone was observed.

Juvederm[®] Voluma: This gel can be injected in the deep reticular dermis, the hypodermis and deeply, in the muscle, near the bone. [8]. we do not inject Juvederm[®] Voluma into the mid reticular dermis; this gel is not indicated for being injected into this part of the dermis.

5.1.3. Cohesive HA gels: Belotero[®] Balance lido: Belotero[®] Balance lido was injected in the superficial reticular dermis and the mid reticular dermis [3] 2016. Dermal thickness, measured before injection: 1.8 mm. During injection into the mid reticular dermis, we observed: a. The presence of air bubbles.

b. A moderate escape in the hypodermis (3.0 mm X 4.0 mm).

c. An oblong papule (3.0 mm X 12.0 mm), hetero-echogenic (hyper-and hypo-echogenic), without progressive homogenization of its ultrasound aspect, compared with the non-injected adjacent dermis.

Belotero® Intense lido: Belotero® Intense lido must be injected into the deep reticular dermis [4]. However, PM has a habit of injecting this gel also into the mid reticular dermis, very carefully, and has been doing so since its launch on the Swiss market, in 2007. Dermal thickness, measured before injection: 3.2 mm. The gel showed high viscosity. During injection, a moderate escape in the hypodermis was observed; dimensions: 3.0 X 2.5 mm. The papule was iso-echogenic compared with the non-injected adjacent dermis. We noticed neither a shadow cone nor a posterior reinforcement. Average dimensions of the intra dermal papule are 4.5 X 10.0 mm.

Belotero® Volume lido: Belotero® Volume lido can be injected in the deep reticular dermis , in the hypodermis and close to the bone [5]. This gel was not injected into mid reticular dermis.

5.2. In the deep reticular dermis



Figure 3: The gels, injected following their use leaflet, in the deep dermis. Green arrows : Gel in the fat. Red arrows: air bubbles.

Yellow arrows: Gel in the dermis.

(A) NASHA®

(B) VYCROSS®

(C) CPM®

5.2.1. Non-cohesive HA gels: Restylane[®] lido: Dermal thickness, measured before injection: 2.2 mm. On injection into the deep reticular dermis, similar to injection in the mid reticular dermis, a considerable amount of Restylane[®] lido escapedin the hypodermis, in a direction perpendicular to the skin. Dimensions: 8.0 mm X 4.0 mm. The papule is oblong (1.9 mm X 3.8 mm), slightly hypo-echogenic compared with the non-injected adjacent dermis. A shadow cone was observed, possibly due to the structure of the gel (non-cohesive formed by dense particles of reticular hyaluronic acid). After injection, the gel was almost impalpable. Restylane[®] lido: Dermal thickness, measured before injection: 2.0 mm.

In the deep reticular dermis, the gel escaped into the hypodermis, (20.0 mm X 10.0 mm). It is hypo-echogenic compared with the non-injected adjacent dermis, well-delimited, and it is deposited parallel to the cutane

ous plan. The skin papule itself measured 6.0 mm X 2.0 mm, with no visible shadow cone.

5.2.2. Partly cohesive HA gels: Volbella[®]: Dermal thickness, measured before injection: 2.0 mm. From the beginning of injection, there was an important escape, already at the beginning of injection, with irregular deposition of gel in the subcutaneous fat, not very visible and badly defined, oblique to the skin surface (11.0 mm X 17.0 mm). In the dermis, a bulky hypo-echogenic papule (8.0 mm X 11.5 mm) was observed.

Volift[®]: Dermal thickness, measured before injection: 3.2 mm. The papule with the dimensions 10.1 mm X 4.0 mm, is hyper-echogenic compared with the non-injected adjacent dermis. Due to the fluid proportion of composition of the gel (which enableacoustic waves to travel at higher speed and hit the posterior wall of the papule), there was a slight a coustic enhancement posterior to the papule. A moderate escape of gel in the hypodermis (7.0 mm X 2.0 mm), parallel to the cutaneous surface was found.

Juvederm[®] Voluma: Dermal thickness, measured before injection: 1.5 mm. On injection in the deep reticular dermis, there is an immediate an important escape of gel into the hypodermis (7.8 mm X 1.8 mm). Its aspect is trans-sonic, hypo-echogenic compared with the non-injected adjacent dermis. The gel diffuses horizontally in the upper part of the subcutaneous fat. After injection, there is an oblong hypo-echogenic papule of 9.0 mm X 3.0 mm.

5.2.3. Cohesive HA gels: Belotero® Balance lido: Dermal thickness, measured before injection: 1.8 mm. No papule was noticed during injection of Belotero® Balance lido in the deep reticular dermis. On the contrary, there was an immediate escape of gel towards the superficial hypodermis. The deposit had a heterogeneous aspect, polylobular aspect, and was oriented parallel to the skin surface. Dimensions : 15.0 mm X 3.7 mm.

Belotero® Intense lido: Dermal thickness, measured before injection: 3.2 mm. Again, on injection injected into the deep reticular dermis, we noticed a leak of the gel into the hypodermis, always parallel to the skin. Dimensions: 87.7 mm X 8.0 mm. Compared with the non-injected adjacent dermis, the papule (0.38 mm X 6.6 mm) appears hyper-echogenic. A discreet posterior reinforcement is noticed.

Belotero[®] Volume lido: Dermal thickness, measured before injection: 2.2 mm. Air bubbles were noticed during injection. In the deep reticular dermis, a considerable portion of Belotero[®] Volume lido quickly diffuses into the subcutaneous fat. Escape is perpendicular to the cutaneous plan, irregular, badly delimited and hardly identify able. Dimensions: 7.0 X 5.0 mm. The US aspect of the small papule (2.8 mm X 1.4 mm) is heterogeneous. The gel is not palpable after its deposition in the deep skin. Here we also observe a discreet posterior reinforcement.

5.3. In the hypodermis

5.3.1. Ex-vivo: In classical histology, stereo-microscopy and full-field optical coherence tomography (OCT), 3 HA gels, cohesive, partly or non-cohesive injected, in 3 skin models used for this study, present a globally similar deposition in the fat, looking as a homogenous bolus, without harming the trabecular and inter-lobular fibres, when injected through a needle.

5.3.2. In-vivo: Non-cohesive HA gel: We did not inject this type of gel into the hypodermis. Partly cohesive and cohesive HA gel. Gels injected into the hypodermis form broader plaques than when injected into the dermis. Juvederm[®] Voluma: looks like an extended deposit, badly delimited. On US, it appears to be heterogeneous, from hypo- to very hyperechogenic.

5.3.3. Cohesive gel: Belotero[®] Volume lido: The gel looks like elongated lobules, distinctly delimited, in string of pearls, with an US aspect of going from quasi an echogenic to slightly heterogeneous. Deep intramuscular injections, near the bone.

5.3.4. Partly cohesive gel: Stylage XL[®] lidocaïne: We notice some air bubbles, because we did not purge the syringe. The latter may be due to the stress of injecting in half-light, also near the bone, with a bent needle, to make it clearly shown on the ultrasound (Figure 4). From the beginning of injection, the gel took, the form of a droplet, with regular contours, polycyclic, pushing back the overlying tissues. It was hypo-echogenic, with clear posterior reinforcement (Figure 5).



Figure 4: Schema of needle placement for bolus injection of HA gel in the temple area.



Figure 5: (A) Partially cohesive HA, needle placed (yellow arrow).(B) After injection cohesive HA gel, après retrait de l'aiguille.(C) Before injection, needle placed (red arrow) close to the bone in the

temple area- partially cohesive HA gel. (D) Immediate post injection picture , close to the bone, of a partially cohesive HA gel.

5.4. Side effects

Injection in mid and deep reticular dermis.

5.4.1. Subject 1: After injection of CPM[®] Belotero[®] Balance with lidocaine into the left buttock, and Vycross[®] Juvéderm[®] Voluma to the right, subject 1 showed no pain during the course of injections. Papules remained visible and palpable, but normal-coloured during several weeks.

5.4.2. Subject 2: Subject 2, injected with CPM® Belotero® Intense and Vycross® Volift®, felt a light during the injection of Vycross® in the mid and deep reticular dermis. The papules of both gels, injected in mid reticular dermis, remained palpable for some months, whereas skin colour remained normal (Figure 4). They were not sensitive to touch. On the left, the developed papula became slightly itchy occasionally.

5.4.3. Subject 3: Subject 3 felt light pain during injection, both intradermal midand deep, of NASHA® Perlane®-lidocaine. On both sides, papules with NASHA® Perlane®-Lidocaïne and Vycross® -Volbella®, injected in the mid reticular dermis, remained palpable for nearly 2 months, but without any pain.

5.4.4. Subject 4: On the right, subject 4 felt some pain during the injections of NASHA® Restylane®. She also had pain later on, especially after injections in the mid reticular dermis, for 4 days. A small haematoma was noticed in the zone of deep intradermal injection. At the end of the 4th month the papules became completely invisible and not palpable. On the left, the papule of CPM® Belotero® Volume, administered in the deep reticular dermis, was still visible and palpable after 5 months (inflammatory reaction, blue grey dyschromia?) [23] (Figure 6).



Figure 6:

- (A) Papable normal colored papule, after mid reticular dermis injection of CPM® Belotero® Intense lidocaine and Vycross® Volift®.
- (B) Long lasting redness (blue-grey dyschromia, inflammatory reaction?) after CPM® Belotero®Volume in the deep dermis.
- (C) 2 palpable, visible, normal colored papule (Vycross® Juvederm®Volu ma).
- (D) CPM® Belotero® Balance lido in the mid dermis.

5.5. Injection in the hypodermis

A part from some bruises, and some light discomfort on the day of injection, no side effects have occurred.

5.6. Deep Intramuscular injection, near the bone

A light to moderate pain is felt. For a few minutes some heaviness is noted in 2 subjects, in the temporal region. There were no injection side effects, either bruising or haematoma.

6. Discussion

Since 2013, Micheels and co-workers study the behaviour of HA gels, during injection into the reticular superficial dermis [10-14]. This depth of injection in accordance to the instructions in the products labels, described in the operating manuals of HA gels in the moment of their commercialization [1-8]. With time, these operating manuals were changed, and for most

HA fillers, except for 2 gels of different cross-linking technology [14], the recommended depth of injection today is mid and/or deep reticular dermis, or even deeper if the indication is the correction of volume. We demonstrated that after injection into the superficial reticular dermis, the studied gels do not escape into the subcutaneous fat, except Vycross® Volbella® [10-14].

In this study, when injected into the minor deep reticular dermis, all the tested HA gel sleak into the subcutis to some extent.

6.1. In the mid reticular dermis

6.1.1. Non-cohesive HA gels: 2 tested gels from the NASHA® ranges howed early escape into the hypodermis, perpendicular to the skin surface. Leakage is more important when injected into the deep reticular dermis. This could be due to smaller resistance of this skin layers compared to the superficial reticular dermis. However, a part of the gel stays in the dermis. On US, it is visible as a hypo-echogenic papule, compared with the non-injected adjacent dermis.

6.1.2. Partly cohesive HA gels: The 3 HA gels designed for mid and/or deep intradermal injection show an escape in the hypodermis, indeed more important for the least reticulated product, whereas minimal for the most cross-linked one. This is probably due to the rheological properties of gels based on Vycross® technology.

The 3 Vycross[®] HA gels diffuse in the fat.

> For Vobella[®], escape is early and important.

> Volift[®] shows less escape, parallelto the skin surface.

> For Juvéderm® Voluma, escape is also precociously, in a plane parallel to the skin. However, the gel remains present in the dermis, visible in the form of an oblong papule, hypo-echogenic compared with the non-injected adiacent dermis.

6.1.3 Cohesive HA gels: In the mid dermis:

As for partially cohesive gels, we do not inject the gel Belotero[®] Volume, in the mid reticular dermis. For the 2 other products, there is an escape of gel in the hypodermis, parallel to the skin plane. Air bubbles during the injection of the less cross-linked product (Belotero® Balance lidocaïne) were observed. This may explain the heterogeneous US aspect of the developed papule. The more concentrated and cross-linked product (Belotero® Intense lidocaïne) seems, for the tested syringes, to be the most optimal (absence of air bubbles, iso-echogenic papules, compared with the non-injected adjacent dermis).

6.2. In the deep reticular dermis

For the less cross-linked products, all injected material leaks into the subcutaneous fat. This therefore seems prove that Belotero® Balance should be injected into the superficial reticular dermis. It can be injected into the mid reticular dermis, if escape in the hypodermis is acceptable. The 2 other products show an important escape in the hypodermis during their injection in mid reticular dermis. We noticed air bubbles in the volumizing formulation. Papule shave a heterogeneous (air bubbles) or hyper-echogenic aspect, compared with the non-injected adjacent dermis. The occurrence of a palpable, red to purple papule of CPM® Belotero® Volume seems to confirm that this gel should be injected into the fat or in deep in muscle, near the bone.

6.3. In the hypodermis

All studied gels seem to show distinctly fewer variations in their distribution and ultrasonographic aspect than in the dermis.

6.4. Deep intramuscular, near bone

Along-term study with a larger number of subjects and with more filler is needed to draw a conclusion. A 2-year study is under way of revision, with 4 subjects injected at the level of temples hollows with a globally cohesive ael.

7. Conclusion

In this comparative study, we injected several formulations of 3brands of hyaluronic acid gels, to which lidocaine is added during production. The gels were injected under ultrasound guidance, into the mid and/or deep reticular dermis, into the hypodermis and near the bone, in accordance with the instructions on the product labels. Whenever injected deeper than the superficial reticular dermis, the HA fillers designed for intradermal injection, but not the volumizing gels, leaked into the hypodermis. This could be due to the higher resistance of superficial reticular dermis, possibly as a consequence of the composition and direction of collagen fibres and elastin. In fat tissue, the behaviour of the tested HA gels is distinctly less specific than during their injection in the superficial reticular dermis, or even mid dermis. Near the bone, in the temporal fossa, the tested gel takes the shape of an oblong papule, hypoechogenic relative to the surrounding and underlying non-injected structures, deposited between the bone and the muscular fibres. In reality, we are still at the beginning of our knowledge as for the actions of gels of hyaluronic acid in the field of the aesthetics.

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