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A double-blind, clinical evaluation of facial augmentation treatments: a comparison of PRI 1, PRI 2, Zyplast® and Perlane®

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KEYWORDS
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Summary *Background:* Facial wrinkles are caused by weakening of the sub-dermal collagen support layer. Dermal fillers can be used to treat wrinkles, and this double-blind, randomised, single-centre study compared four fillers: PRI 1, PRI 2 (both porcine collagen), Zyplast® (purified bovine collagen) and Perlane® (cross-linked hyaluronic acid gel).
Methods: 79 females (aged 25–55 years) with wrinkles in the upper lip line border were randomised to PRI 1 (19 patients), PRI 2 (19 patients), Perlane® (23 patients), Zyplast® (18 patients). Patients were assessed at 1 week and 1, 3, 6, 9 and 12 months using 2D images and by mathematically derived facial volume changes using 3D stereophotogrammetry.
Results: All treatments produced larger, less wrinkled, more prominent lips. PRI 1, PRI 2 and Zyplast® showed similar lip volume gains, with Perlane® showing the greatest upper lip volume increase. All treatments were comparable for rates of decrease in upper lip volume post-treatment, however, Perlane® maintained higher lip volume gains at each time point. Investigators indicated PRI 1 was significantly easier to deliver than Zyplast®. Patient satisfaction scores were similar, though there was a trend towards greater dissatisfaction for PRI 1 and PRI 2 at month 9 ($p = 0.052$). Treatment was well-tolerated, with 'cold sore' being the most common adverse event.
Conclusions: Results showed that PRI 1 and PRI 2 were comparable to Perlane® and Zyplast® as dermal fillers. Further rigorous studies are required to establish the performance of dermal

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fillers and patient acceptability. We propose the utilisation of stereophotogrammetry for assessment of volume changes.

External factors (e.g. exposure to the sun and pollution) and internal conditions (e.g. ageing and genetic factors) contribute to weakening of the natural collagen support layer and fat lying just beneath the skin, causing facial lines and wrinkles. Initially fine wrinkle lines may be discrete but gradually they become grouped and multidirectional.

Wrinkles limited to superficial dermal creasing are commonly termed lines (partial thickness) or furrows (full thickness) which are the visible effects of deep dermal creasing caused by repeated facial movement and expression, combined with dermal elastosis. They are perpendicular to the direction of underlying facial muscles and occur with ageing as nasolabial folds, radial lip lines, marionette lines, lines in the corners of the mouth and nasolabial folds as a result of smiling. Concomitant movement of the muscles around the lips during smoking or chewing can also cause radial lip and marionette lines. Superficial wrinkles respond to treatments such as chemical peeling, dermabrasion and laser resurfacing, whilst preferred treatments for deeper wrinkles comprise facial surgery, botulinum toxin treatment or injectable dermal fillers.

The objective of this double-blind, randomised, single-centre study was to compare the effectiveness of four dermal fillers: PRI 1 and PRI 2 (two new materials derived from porcine collagen with PRI 2 having a greater degree of cross-linking than PRI 1), Zyplast® (purified bovine collagen) and Perlane® (cross-linked hyaluronic acid gel) for lip augmentation, as measured by lip volume change. Efficacy was assessed using mathematically derived facial volume and shape measurements using 3D stereophotogrammetry and ratings made from 2D images using the rating scale developed by Catherine Knowles-Clark (CKC Scale) (Table 1).

Materials/patients and methods

The study was approved by the local ethics committee and patients provided written informed consent prior to participation in any study-specific procedures.

Patients included in the study were all females aged 25–55 years with similar clinical features of facial wrinkles which were suitable for treatment with facial filling agents in the upper lip line (vermillion) border.

Patients were required to refrain from any further facial cosmetic surgery or treatments throughout the study and any treatments that could result in facial swelling (e.g. laser hair removal, dermabrasion or dental procedures). Those patients assigned to Zyplast® were also required to have a negative collagen skin test which was performed by the investigator administering the injections. To preserve the study blinding, this investigator was not involved in any patient follow-up and patients assigned to PRI 1, PRI 2 or Perlane® treatments received a similar saline skin test.

Patients were excluded if they were unable to fulfil the study requirements, if they had a known allergy to any collagen or hyaluronic acid product, they had a positive skin test reaction or had a known allergy to local anaesthetic. Patients with a history of connective tissue (auto-immune) diseases, any active malignancy over the past five years, presence of any facial scar tissue, facial deformity, active acne, eczema, rosacea or visible signs of herpes virus were also excluded. A history of cosmetic surgery or botulinum toxin injections six months prior to study entry, use of oral steroids or anti-retroviral therapy were not permitted.

Patients attended a pre-screening visit one month prior to treatment and those who fulfilled the study entry criteria were randomised by using a computerized Interactive Voice Response (IVR) system designed by the Robertson Centre for Biostatistics, Glasgow University, to one of the four treatment groups comprising injections to the upper lip line (vermillion) border (Group A: PRI 2, Group B: Perlane®, Group C: PRI 1 or Group D: Zyplast®). The IVR was accessed using a push button telephone; the system provided both randomization and unblinding facility for the

Table 1 CKC classification scale

Size			
Score	Letter	Description	
−2	V	Very thin	≤1:15
−1	T	Thin	1:15–1:10
0	M	Medium sized	1:10–1:7
1	F	Full	1:7–1:4
2	E	Extremely Full	>1:4

Vermilion body	
Score	Description
−1	Tight almost unlined
0	Rounded with natural lines
1	Less rounded with fine lines
2	Flattening with moderate wrinkles
3	Severe wrinkles

Vermilion border	
Score	Description
−1	Protruding and/or creating peri oral shadow.
0	Distinct and intact, with/without shadow from mid lower lip.
1	Distinct but broken by fine lines, with/without shadow from mid lower lip.
2	Indistinct and broken by moderate lines with/without shadow from mid lower lip.
3	Indistinct and severely lined, with/without shadow from mid lower lip.

study, which was available 24 hours a day, 7 days a week for the duration of the study. To standardise treatment procedures, an independent practitioner performed the injections on all patients and local anaesthetic (injection or topical cream) was used as appropriate. Volumes of product used varied according to patient age and desired cosmetic effect, but typically ranged from 1.5—3.0 mL.

Patients were assessed post-operatively at 1 week and then 1, 3, 6, 9 and 12 months post treatment by an independently qualified blinded assessor. During these time points, both 2D and 3D facial images were taken and a review made of any adverse events. All patients received pre- and post-treatment facial wrinkle assessment based on photographs, which were assessed using the CKC scale by five independent observers (Table 1). At each time point, the average rating from all observers was calculated and the change from the mean baseline rating was used as the response variable in all analyses.

In addition, mathematically derived facial volume was assessed using the 3D stereophotogrammetry method.[1—3] The method is based on the same principle by which humans perceive depth. Analogous to the interpretation of the slight disparity between the images viewed by two eyes, the disparity between two cameras at an angle to each other can decode to create a map of depth, provided the geometry of the camera configuration is known. This ultimately produces a photorealistic life-like model that could be manipulated in the screen using a separate software programme known as the Facial Analysis Tool (FAT). All images were taken in a standardised manner in a dental chair with the head rested on the headrest and the patient staring at their own reflection on a mirror mounted opposite. This equipment was carefully calibrated prior to each capture session to ensure all images were standardised. All patients were required to remove makeup, close their eyes, clench their teeth for 10 seconds, lick their lips and allow their teeth to part but keeping the lips together to achieve a natural rest position. The image was then captured without warning. A specially designed software (Facial analysis tool) was utilised, (Figure 1) to allow accurate digitisation of anatomical landmarks around the lip for volume measurements. At each time point, the change from the baseline volume was used as the response variable.

All four treatments were assessed in terms of investigator's opinion as to ease of application, pressure required, ease of needle gliding into the skin, ease of judging degree of correction, how well the patient tolerated pain, and the degree of immediate post-treatment erythema and swelling. Patients were asked to provide treatment satisfaction scores using a 5-point rating scale at each visit, and, in addition, patient assessment of the degree of pain of injection was evaluated at the time of treatment.

Statistical analysis

The primary objective was to identify the longevity of the effects of the four different treatments using assessor ratings, as well as volume and shape measurements derived from 3D image capture.

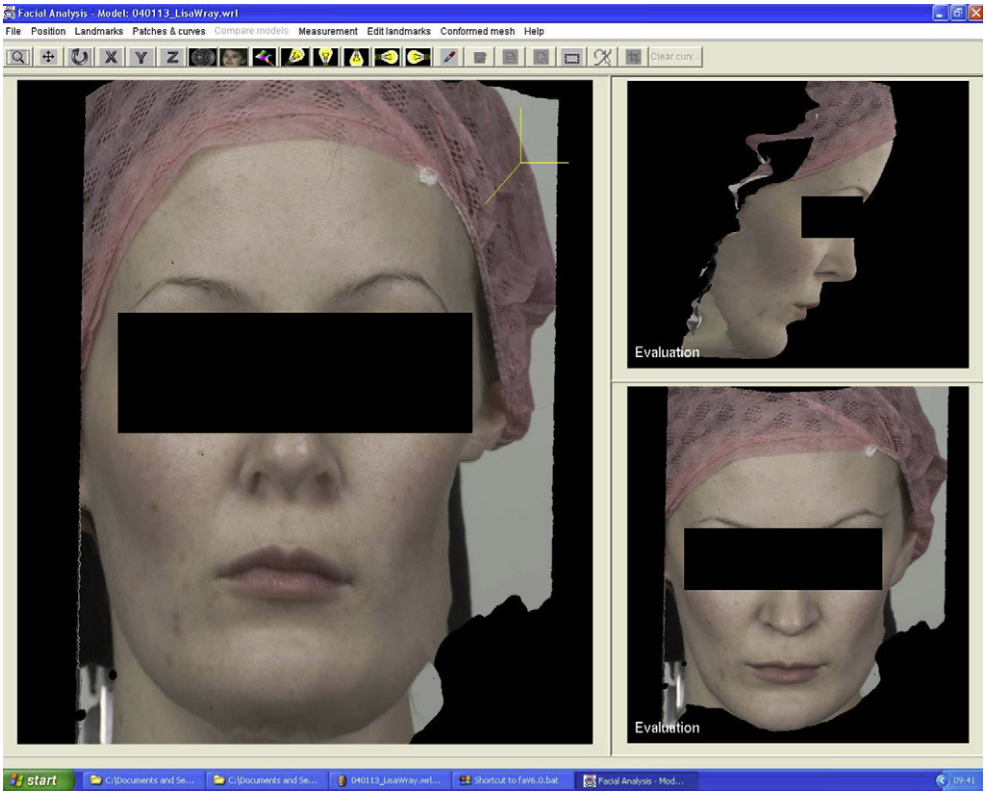

Figure 1 The interface of the facial analysis tool. This programme enables the operator to visualise the 3D model from different directions (x, y, z axes) using the three viewing windows, as well as different manipulation buttons.

Power calculations determined suitable sample sizes based on comparing any two particular groups of interest. Further calculations were performed using the change in volume measurement of the upper lip as the variable of interest. Mean differences of this variable across the groups of interest were assumed to be 0.2 cc. This figure was based on previous validation work using the same capture system. The standard deviation (SD) of the difference in measurements across each treatment population was assumed to be 0.2 cc and the proportion lost to follow-up was assumed to be 0.2. For a power of 0.8, the total sample size across all four groups was 80 patients, with equal allocation rates to each of the four treatment groups (i.e. 1:1:1:1 ratio).

The principal analysis was carried out on an intent-to-treat basis (ITT). Analysis of safety variables was performed on the ITT population, which included all available safety data from patients who received treatment and had at least one safety variable assessed.

For each follow-up period, summary statistics were presented by treatment group, which included the proportions of cases where volume loss and changes in shape were identified from captured 3D images by comparing follow-up images with those taken at baseline, using an algorithm developed by the Computing Science research team. Repeated measures regression models were used to analyse the changes in the response variables of interest (i.e. mean volume change and changes in CKC scale variables) across time and across the treatment groups.[4] Log transformations of lip volume changes were performed due to non-normality and a constant of 0.80 was added to all responses before transformation to account for some zeros and negative numbers in the volume changes. The response variables were also analysed at each time point to clarify the nature of time and treatment effects of interest. The longevity of effectiveness of the four treatments was compared using survival analysis methods to analyse the time after treatment at which facial wrinkles returned to baseline levels, as determined by each CKC scale.

Safety assessments were based on the frequency of adverse events and on the number of laboratory values falling outside of pre-determined ranges. Fisher's Exact Test was used to evaluate any differences in adverse event prevalence across treatment groups.

The Kruskal Wallis Rank Sum test was used to investigate any differences in injectors' opinions between the treatments with regard to ease of injection, pressure required, ease of needle gliding into the skin, ease of judging degree of correction and the degree of immediate post-treatment erythema and swelling. In addition, differences in patients' opinions regarding degree of pain of injection and treatment satisfaction were also assessed. If the Kruskal Wallis test was significant, a multiple comparison test was then performed to determine which pairs of treatments were significantly different.

Results

Seventy-nine patients were enrolled into the study: PRI 1: 19 patients, PRI 2: 19 patients, Perlane®: 23 patients, Zyplast®: 18 patients, one patient dropped out of the study.

According to the 3D assessments of lip volume changes and the assessment of the 2D photographs rated using the CKC Scale, all treatment groups showed a shift towards larger, less wrinkled and more prominent lips (Figure 2), with the effects wearing off during the follow-up period. Patients administered PRI 1, PRI 2 and Zyplast® showed similar upper lip volume gains over baseline, while Perlane® resulted in a significantly higher average upper lip volume gain from baseline to week 1 compared to the other three groups, which persisted throughout the 12-month study period (Figure 3). However, there was no evidence that the four treatment groups differed in terms of the rate of decrease in upper lip volume over time (between group difference $p = 0.19$). A similar pattern was observed with respect to upper lip assessments of 2D images using the CKC scale, with Perlane® showing the largest average changes from baseline throughout the follow-up period ($p < 0.01$), particularly in terms of upper lip size. In general, however, the 3D assessments were more sensitive for detecting between-treatment effect differences.

There was some evidence of treatment effect differences regarding the longevity of effect on the lower vermillion body ($p = 0.007$), with PRI 1 and Perlane® producing longer-lasting effects compared to the other two treatment groups. There was also some evidence for treatment effect differences regarding upper vermillion border ($p = 0.05$), with PRI 1 showing less longevity of effect than Perlane®. None of the other scales demonstrated any between treatment differences.

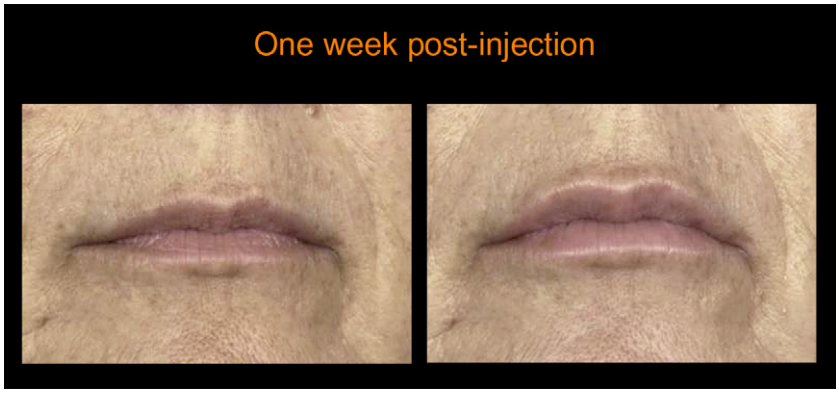

Figure 2 Clinical images at baseline and week 1 demonstrating lip augmentation.

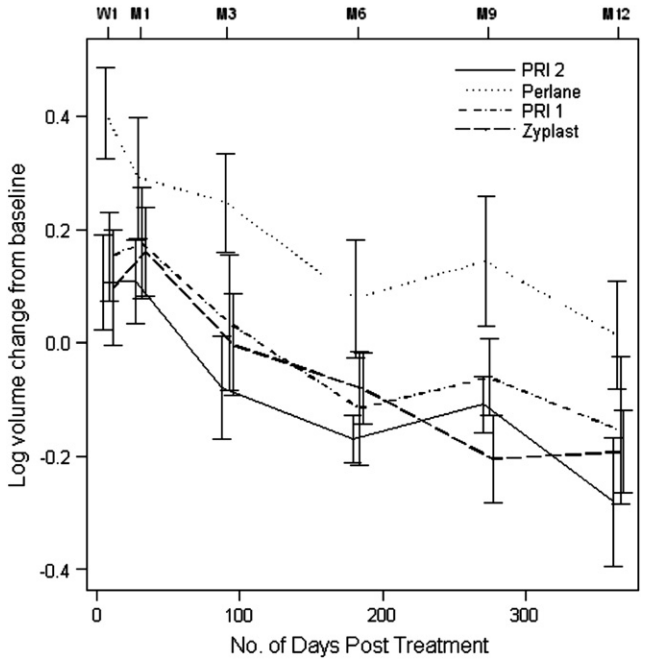

Figure 3 Group means of the log transformed upper lip volume changes over time (95% Confidence intervals).

Injected treatment volumes differed between the groups (PRI 1: 0.90, PRI 2: 0.99, Perlane®: 0.72, Zyplast®: 0.85), with Perlane® having the lowest mean treatment volume (mL) ($p < 0.01$).

The effect of injected volume on lip volume change at week 1 was analysed and it was found that injected volume had no significant effect on volume change at week 1. In general, larger injected volumes were found to be associated with greater upper lip volume changes at 1 week, regardless of treatment group ($p = 0.003$). An average across all time points showed a significant positive effect of injected volume on lip volume change from baseline, but since the group differences in log transformed upper lip volume change were unaffected by this factor, they could not be attributed to discrepancies in injected volume between the groups.

There was evidence to suggest a treatment difference in investigators' opinion regarding ease of application ($p = 0.0047$), with PRI 1 found to be significantly easier to deliver than Zyplast®. None of the other pair wise comparisons were statistically significant, thus providing no evidence of any differences between the treatments. There was evidence of a difference in the degree of pressure required for the injection ($p = 0.0005$), with less pressure being required for administration of Perlane® compared to PRI 1 and Zyplast®. No differences were found between PRI 2 and the other treatments. All four treatments were comparable with respect to the other variables e.g. ease of needle gliding into the skin, ease of judging degree of correction, patient tolerance of injection pain, and degree of immediate post-treatment erythema and swelling.

There were no significant treatment differences regarding patients' subjective opinions of treatment satisfaction and degree of pain of injection. Patients were asked to rate their satisfaction with treatment as 'very satisfied', 'satisfied', 'neither satisfied or dissatisfied', 'dissatisfied' or 'very dissatisfied'. Patient satisfaction scores were fairly similar for all groups at the time of treatment, with a general increase in dissatisfaction over time being evident for all treatments. Patients who were administered PRI 1 and PRI 2 appeared to be more dissatisfied than those who had Perlane® and Zyplast®, and this was most evident at month 9 ($p = 0.052$) (Figure 4).

Twenty-one patients (27%) experienced at least one adverse event (PRI 1: 8 patients, PRI 2: 7 patients, Perlane®: 5 patients, Zyplast®: 1 patient). The most common adverse event was 'cold sore' (14 events) (Table 2). Four patients experienced multiple adverse events (Table 3) and the total number of adverse events recorded during the study was 26. The prevalence of adverse events differed among the treatment groups ($p = 0.032$), with a higher proportion occurring in the PRI 2, Perlane® and PRI 1 treatment groups compared to the Zyplast® group. However, there was no evidence of any difference in the prevalence of adverse events of a specific organ class across treatment groups.

Two patients experienced a Serious Adverse Effect (SAE). One patient was hospitalised for a urinary tract infection (PRI 2 group) and another suffered a miscarriage (Perlane® group), neither of which were considered related to the study treatment.

Discussion

Lips are considered the key aesthetic feature of the lower face,[5] being associated with sensuality, youthfulness and fertility. Plump lips are considered more attractive in both males and females, and lips of both sexes have a comparable upper to lower lip ratio and vermillion height to mouth width.[6–8]

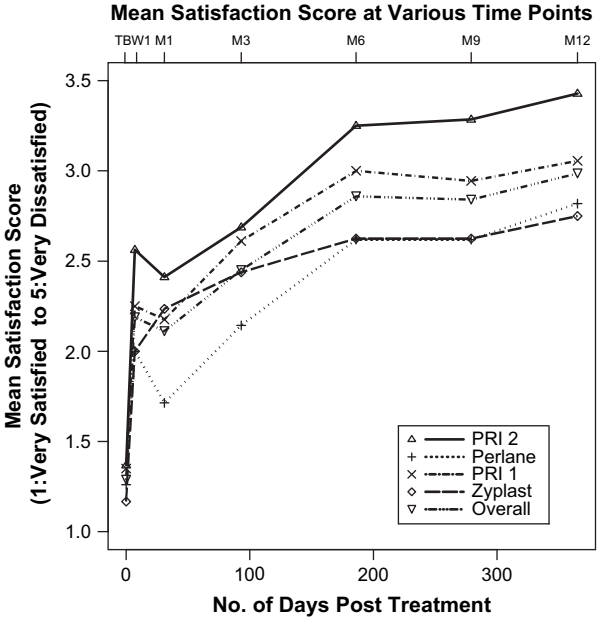

Figure 4 Plot of mean satisfaction scores at various time points for all patients by treatment group.

Table 2 All recorded adverse events (by group)

Number of subjects	Group			
Adverse event	PRI 2	Perlane®	PRI 1	Zyplast®
Allergic reaction	0	0	1	0
Angular chelitis	0	0	1	0
Blistering at injection site	0	0	1	0
Cold sore	4	5	4	1
Dry lips	0	1	0	0
Hyperthyroidism	0	0	1	0
Infection in lip bacterial stomatitis	1	0	0	0
Miscarriage	0	1	0	0
Mouth ulcer	1	0	0	0
Right knee replacement	0	0	1	0
Toothache front tooth	0	0	1	0
Tooth extracted L2	1	0	0	0
Urinary tract infection	1	0	0	0
Total	8	7	10	1

Facial augmentation has increased markedly over the years largely due to the heightened awareness of the availability of non-surgical dermal fillers, which replace lost natural collagen and elevate the wrinkles.[9–11] However, despite the increasing popularity of the use of dermal fillers for lip augmentation, there is little robust clinical data available regarding treatment efficacy, with clinicians largely relying on manufacturers or suppliers to provide evidence of product effectiveness.[12–15] Several wrinkle classification scales are available but are restrictive and not always appropriate. For example, the Lemperle scale is restricted to lines on and above the upper vermillion border but does not include the vermillion or lower lip and cannot be used to assess increase in size of tissues.[16] The Fitzpatrick classification focuses on wrinkling and skin elastosis, with little reference to soft tissue augmentation or the vermillion, and the Glogau's wrinkle classification system is not sufficiently specific to assess the results of lip augmentation.[17,18] Thus, a new classification scale (CKC Scale) which allows assessment of the upper and lower lips in terms of size, vermillion wrinkling and vermillion border lines which could be applied both before and at any stage after treatment was developed and used in this study (Table 1).

Currently, dermal fillers can be divided into two categories: natural and synthetic. All four study treatments were natural and comprised PRI 1 and PRI 2 (two new materials derived from purified porcine [pig] collagen), Zyplast® (purified bovine [cow] collagen) and Perlane® (a cross-linked hyaluronic acid gel, manufactured by bacterial synthesis). However, just as with existing collagen, these injectable forms eventually break down, so ongoing treatments are necessary to maintain the desired results.

Disadvantages associated with bovine collagens (e.g. Zyplast®) are the possibility of an allergic reaction, since approximately 3%–3.5% of patients will demonstrate sensitivity and 1%–5% can develop an allergy during treatment.[19] Also bovine collagen is temporary with the majority of patients requiring touch-up injections every 3–12 months.[5] Perlane® is a clear, transparent and viscous cross-linked hyaluronic acid gel, manufactured by bacterial synthesis. Hyaluronic acid is a natural sugar glycosoaminoglycan found in all organs of the body. It is a large molecule consisting of repeating chains of sugars which provide a 'ground substance' to support the collagen and elastin fibres and it binds water to give the skin its characteristic 'feel'. This characteristic nature of the material may be responsible for the larger volume gain with upper lip injection. The main disadvantage is that treatment with Perlane® is not permanent, with repeat injections being required approximately every 6–12 months.

PRI 1 and PRI 2 are both fine, injectable forms of Permacol™, comprising particulate porcine derived collagen suspended in saline. PRI 2 differs from PRI 1 in having a greater degree of cross–linking. The main advantage of Permacol® is that it produces minimal inflammatory response and minimal risk of immune response, thereby precluding the need for testing for potential allergic reaction. Permacol™ Injection is currently used as a urethral bulking agent in the treatment of urinary stress incontinence and is a modification of Permacol™ collagen sheets (an acellular dermal collagen successfully used for a variety of repair procedures in the fields of ENT, plastic surgery, maxillofacial, urology, gynaecology and general surgery). It is anticipated that both PRI 1 and PRI 2 may be ideal filler substances for skin and soft tissue augmentation by acting as bulking agents for the treatment of soft tissue defects, such as wrinkles, and will reduce the need for additional injections earlier than 6 months.

Table 3 Patients experiencing multiple adverse events

Group	Subject ID	Adverse event	Start date	End date
PRI 1	37	Cold sore	Jan 05	Jan 05
		Hyperthyroidism	Mar 05	Mar 05
		Tooth ache front tooth	Sep 04	Oct 04
Perlane®	74	Cold sore x3 episodes	Jun 04	Aug 04
		Dry lips	Jul 04	Aug 04
		Cold sore	Jun 05	Jun 05
PRI 1	96	Angular chelitis	Jan 05	May 05
		Blistering at injection site	Aug 04	Aug 04
PRI 2	79	Cold sore	Jul 04	Jul 04
		Mouth ulcer	Jan 05	Feb 05

This study used objective, standardised assessment scales, such as 3D facial volume stereophotogrammetry and blinded assessment of repeated 2D images by multiple observers, rather than simplistic 'before and after' photographs which are commonly used. Results from this initial study showed that all treatment groups had a shift towards larger, less wrinkled and more prominent lips. All four fillers were found to be comparable to Zyplast® in terms of producing similar upper lip volume gains. Perlane® treatment resulted in the highest average upper lip volume gain. PRI 1 showed comparability with Perlane® in producing long-lasting effects on the lower vermillion body compared to the other two treatment groups.

Injected volumes were significantly different between groups, however, the design of the study was not compromised. Patients were randomized to each of the four groups which would prevent any selection bias. There is no evidence that the baseline point before injection was different among the groups. No doubt, the variabilities within the groups would reduce the possible differences between the treatments.

An unexpected finding in this investigation was the adverse effects which were recorded. Almost two thirds of those adverse effects were in patients who had either PRI 1 or PRI 2 injections. However, this finding has to be interpreted carefully as the majority of the adverse effects were not relevant to the injected material e.g. knee replacement or extraction of a tooth which happened during the course of the study and have to be recorded according to the protocol of the clinical trial. Interestingly, cold sores were the most common adverse effect that was noted in the study. There is no clear explanation for this complication, apart from the direct trauma caused by the injections which may render the tissue more vulnerable to this viral infection. In all the cases, cold sores disappeared within a few days and did not affect the course of the study. The 3D capture of the face was postponed until the cold sore had subsided.

With respect to investigator handling, PRI 1 was found to be significantly easier to deliver than Zyplast®, with no evidence of any differences between the treatments for any other pair wise comparisons. Analysis of patient satisfaction showed little difference between the treatments, with a general increase in dissatisfaction over time, although at month 9 there was a trend towards greater dissatisfaction being associated with PRI 1 and PRI 2 ($p = 0.052$).

Methodologically, we found estimates of lip volume derived from 3D facial volume stereophotogrammetry to be a more sensitive measurement technique for assessing treatment effect differences than assessments of lip size based on 2D images, though the CKC scale can be used effectively to provide repeated assessments of vermillion body and border over time when multiple blinded observers are used. Furthermore, we found analyses of study outcomes based on repeated measures regression models to provide a more sensitive evaluation of the differences between treatments than Cox proportional hazards models of the longevity of effect.

This study demonstrates interesting initial results, but further methodologically rigorous studies comprising large, long-term, prospective, randomised clinical trials in the cosmetic field are required to establish the performance of these dermal fillers and patient acceptability of treatment over longer periods of follow-up. We feel that 3-D soft tissue modelling will play a key role in the objective assessment of these filler materials over time.

This study demonstrated the usefulness of using 3D imaging for the objective analysis of facial changes secondary to injection of biological fillers. The method is non-invasive, captures the face in 50 milliseconds and does not expose the patient to harmful radiation. Therefore, it is a useful tool for clinical trials and longitudinal epidemiological studies. The system used in this investigation was provided by Di3D Ltd (Dimensional Imaging, Hillington Park, Glasgow, UK); it comprises two professional, high-resolution colour digital cameras (4000 pixels $\times$ 3500 pixels). It is easy to operate and reliable for clinical applications. Over all, stereophotogrammetry is a cost-effective method for facial analysis; it is useful for everyday practice with minimal burden on the patient.

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