Clinical endpoints of needle-free jet injector treatment: An in depth understanding of immediate skin responses

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Abstract
Objectives: Needle-free jet injectors have been used in dermatological practice for many years. However, predefined clinical endpoints that guide physicians to choose optimal device settings have not been clearly defined. Here, we evaluate immediate skin responses as clinical endpoints for needle-free jet injector treatments.

Methods: We injected methylene blue in ex vivo human skin using an electronically-controllable pneumatic injector (EPI; 3–6 bar, 50–130 µl; n = 63), and a spring-loaded jet injector (SLI) with fixed settings (100 µl; n = 9). We measured the immediate skin papule (3D-camera), residual surface fluid (pipette), dermal dye distribution by estimating depth and width, and subcutaneous dye deposition.

Results: EPI with 4 bar and 100 µl resulted in the largest skin papule of 48.7 mm³ (35.4–62.6 mm³) and widest dermal distribution of 8.0 mm (5.5–9.0 mm) compared to EPI with 6 bar and 100 µl (p < 0.001, p = 0.018, respectively). The skin papule volume showed a significant moderate to high positive correlation with the width and depth of dye distribution in the dermis (rs = 0.63, rs = 0.58, respectively; p < 0.001 for both correlations). SLI showed high variability for all outcome measures. Finally, a trend was observed that a small skin papule (≤7 mm) and little residual surface fluid (≤10% of injection volume) were warning signs for subcutaneous deposition.

Conclusions: The immediate skin papule and residual surface fluid correspond with dermal drug deposition and are relevant clinical endpoints for needle-free jet injector treatments in dermatological practice.

KEYWORDS
dermatology, drug delivery, injection, intralesional, jet injection, needle-free injection, pneumatic injection

INTRODUCTION

Needle-free jet injectors have been used for over 75 years for the transdermal delivery of vaccines, insulin and for the treatment of dermatological indications such as hypertrophic scars, keloids, and warts.1 By producing a high-powered jet stream of fluids, jet injectors are able to penetrate the epidermis providing dermal drug delivery without the use of (painful) needles. Advantages of jet injectors include the fast-working mechanism, standardized injections, absent risk of
needle-stick injuries, and nearly pain-free delivery of fluids into the skin. Disadvantages of jet injector systems might include clogging of the nozzle, splash back, need for sterilization of the device after each patient, and non-adjustable settings. Since the introduction of the first jet injector in the 1960s, novel (electronically powered) jet injector systems have been developed to overcome most of these drawbacks.

Jet-injectors can mainly be classified into two groups: (a) spring-loaded jet injectors (SLI) and (b) gas/air-powered jet injectors. Traditional SLI operate with a spring mechanism, which is manually charged for every injection, and released by triggering the device which induces a jet-stream. Device settings are usually fixed and non-tuneable. Electronically-controlled pneumatic jet injectors (EPI) are novel air-powered jet injectors that, in contrast to SLI, operate with tuneable pressure and injection volume settings to create tailor made treatments for dermal drug delivery.

Needle-free jet injectors induce immediate skin responses that are directly visible after each injection. This jet-tissue interaction, such as skin elevation and residual surface fluid, are potential clinical endpoints that may serve as indicators of dermal drug delivery. Close observation of the clinical endpoints can be a useful tool for selecting optimal device settings for each patient and/or anatomical location. To date, however, predefined clinical endpoints that relate to dermal drug delivery of jet injectors have not been defined. Therefore, we aimed to evaluate immediate skin responses as clinical endpoints for spring- and air-powered needle-free jet injector treatments.

**MATERIALS AND METHODS**

**Study design**

In this ex vivo human skin study, jet injector induced immediate skin responses including skin papule formation, postinjection residual surface fluid and dermal dye distribution, were explored using two types of jet injectors. Needle injections were included for comparison. Skin papule dimensions were captured with a 3D camera system, and postinjection residual surface fluid was extracted and measured using a pipette. Dermal distribution dimensions were analysed by estimating depth and width of the dye staining following excision of skin tissue.

The Ethics Board Committee of Amsterdam UMC concluded that this study with ex vivo human tissue was exempted from formal approval because of no risk to participants and the use of anonymous tissue.

**Skin preparation**

Freshly excised human skin was anonymously obtained from three patients during elective abdominoplasty (Department of Plastic Surgery; OLVG Hospital). Excessive adipose tissue was removed until a skin thickness (including subcutaneous layer) of 2 cm remained, and the specimen was subsequently stored at −20°C up to 8 weeks. Before start, the tissue was thawed at room temperature, fixated under light tension, and marked with 2 × 2 cm test zones.

**Interventions and sample collection**

EPI was performed with an electronically-controlled pneumatic jet injector (EnerJet2.0; PerfAction Technologies Ltd.) at 3, 4, 5, and 6 bar, (100 µl; n = 36), and injection volumes of 50, 100, and 130 µl (4 bar; n = 27). The EPI nozzle tip (Ø 0.2 mm) has a 5 mm distance to the skin surface, determined by the spacer. A spring loaded jet-injector (Dermojet; AKRA) with a fixed pressure of 98 bar and injection volume of 100 µl was selected for SLI (n = 9). One researcher (MW) delivered a constant intradermal bolus of 100 µl by conventional needle injection with a 0.5 ml syringe with 29 G needle (n = 9, BD Micro-Fine, 324892; Becton Dickinson). All injections with normal saline containing 0.1% of methylene blue (C.I. 52015; Merck Millipore) were divided over three different human tissue specimens and performed in triplicate to minimize bias due to variation in physical skin properties. Undelivered liquid on the skin was defined as residual surface fluid, and collected and measured using a lab pipette (0.5–10 µl; 10–100 µl). The skin papule border was manually contoured using a black marker for 3D analyses. Photographs were captured by digital camera (D5300; Nikon), and a 3D camera system (Antera 3D® CS; Miravex Limited) under standardized conditions including normal room lighting, fixed distance and perpendicular angle. Each skin papule was linearly incised directly at the entry point of injection, removed (2 cm × 1 cm), and mounted under slight pressure between two microscopic slides with the injection site facing upwards. A ruler was used for measurements of the immediate cutaneous distribution by two trained assessors (AM & AW) who measured the maximum dermal width and depth (dermis only), and the presence of dye deposition into the subcutaneous layer.

**3D-system assessment of the skin papule**

Antera 3D® CS (Miravex Limited) operates by multi-directional illumination of LEDs at different wavelengths, and was used to capture the skin papule immediately after each injection. The contour of the skin papule was selected as field of interest for assessment of the skin papule volume (mm³) and diameter (mm) in the corresponding software (Mode: elevation, Filter: extra-large).
Statistics

Descriptive data were presented as median and interquartile ranges (IQR; Q1–Q3). Outliers were included after comparing groups with and without outliers using Mann-Whitney $U$ test ($p > 0.05$). The correlation coefficient between the skin papule volume and dermal distribution was measured with Spearman’s rho for nonparametric correlations. Equality of EPI subgroups in papule volume, dermal distribution and residual surface fluid was explored using Kruskal–Wallis test. Since all tested outcome measures showed inequality ($p < 0.05$), additional comparisons using Mann–Whitney $U$ test were performed. Comparisons were limited to two EPI subgroups with the highest numerical differences for pressure and injection volume. Formal correction for multiple testing was therefore not required. The $\chi^2$ test was used for comparison of the risk of subcutaneous dye deposition following jet injection. An $\alpha$ level of 5% was applied. Analyses were performed in SPSS version 25 (IBM Corporation).

RESULTS

Jet injection induced skin papule

The skin papule formation was evaluated immediately after injection for all interventions by 3D-camera (Figures 1 and 2; Table 1). For EPI, we compared different pressures while using a constant injection volume of 100 µl. EPI with 4 bar resulted in the largest skin papule with a volume of 48.7 mm$^3$ (35.4–62.6 mm$^3$) and a diameter of 9.8 mm (8.8–11.2 mm), compared to the smallest skin papule for EPI with 6 bar with a volume of 11.9 mm$^3$ (4.6–26.9 mm$^3$; $p < 0.001$) and diameter of 6.1 mm (5.1–8.1 mm; $p = 0.018$). When comparing different injection volumes while using a constant pressure of 4 bar, EPI with 100 µl resulted in the largest skin papule with a volume of 48.7 mm$^3$ (35.4–62.6 mm$^3$) and diameter of 9.8 mm (8.8–11.2 mm), compared to 50 µl with a small papule volume of 12.8 mm$^3$ (5.5–21.0 mm$^3$; $p < 0.001$) and diameter of 6.5 mm (6.1–8.1 mm; $p = 0.020$). For SLI, we observed a large variation.
Jet injection induced residual fluid on skin surface

Directly after injection, residual fluid on the skin surface was observed for all interventions and collected using a pipette (Figures 1 and 3; Table 1). EPI with 5 bar and 100 µl resulted in the lowest residual surface fluid volume of 9.5 µl (7.7–15.7 µl), compared to EPI with 3 bar and 100 µl with a residual surface volume of 18.7 µl (11.7–30.8 µl; \( p = 0.053 \)). When comparing the different injection volumes of EPI, injections with 130 µl left a residual surface fluid volume of 12.6 µl (9.9–19.8 µl), corresponding to 9.3% of its injection volume. Smaller injection volumes of 100–50 µl led to an increase in the residual fluid percentage. SLI with 100 µl resulted in a residual fluid volume of 16.0 µl (6.2–26.5 µl; 16.0%). Needle injections with 100 µl resulted in a limited residual fluid volume of only 0.6 µl (0.5–1.5 µl; 0.6%).

Jet injection induced dermal dye distribution

The immediate dermal dye distribution dimensions are shown in Figures 1 and 4A,B, and in Table 1. EPI with 4 bar and 100 µl resulted in the largest dermal distribution dimensions with a dermal width of 8.0 mm (5.5–9.0 mm) and dermal depth of 5.0 mm (4.0–6.0 mm), compared to EPI with 6 bar and 100 µl with the smallest dimensions with a dermal width of 5.0 mm (3.5–6.0 mm; \( p = 0.018 \)) and dermal depth of 3.0 mm (2.5–5.0 mm; \( p = 0.059 \)). Comparing different injection volumes, EPI with 4 bar and 100 µl resulted in the largest dermal distribution (dimensions stated above), compared to EPI with 4 bar and 50 µl with a small dermal width of 4.5 mm (3.0–6.0 mm; \( p = 0.009 \)) and dermal depth of 3.0 mm (1.8–4.5 mm; \( p = 0.147 \)). SLI resulted in small dermal distribution, and high inter-injection variance, with a dermal width of 4.0 mm (2.5–8.0 mm), and a dermal depth of 4.0 mm (2.5–5.5 mm). For needle injections, we observed a dermal distribution with a width of 6.0 mm (5.0–6.0 mm) and a depth of 3.0 mm (2.0–4.0 mm). Dermal thickness of the three skin samples was 5.0 mm (4.0–5.0 mm) measured before intervention, similar as reported in previous studies, and differ not significantly from each other.3 Measured dermal depth distribution of >5.0 mm was caused by swelling/expansion of the dermis by the injected fluid volume.

Overall, a significant moderate to high positive correlation was observed for the skin papule volume and the dermal distribution in width (\( \rho = 0.63; \ p < 0.001 \)), and papule volume and dermal distribution in depth (\( \rho = 0.58; \ p < 0.001 \)).

Jet injection induced subcutaneous deposition

After excision, deep dye distribution reaching the subcutaneous tissue was observed for a subset of the skin samples for all interventions (Table 1). For EPI with 5 bar and 100 µl, subcutaneous dye deposition was
| Injection technique | Skin papule | Residual surface fluid | Dermal dye distribution | Subcutaneous deposition |
|---------------------|-------------|------------------------|------------------------|------------------------|
|                     | Volume in mm\(^3\), (Q1–Q3) | Diameter in mm, (Q1–Q3) | Volume in µl, (Q1–Q3) | % of injection volume | Width in mm, (Q1–Q3) | Depth in mm, (Q1–Q3) | Number of samples, (%)\(^a\) |
| **EPI**             |             |                        |                        |                        |                        |                        |                        |
| 100 µl/3 bar\(^b,c\) | 31.9 (21.8–47.7) | 9.8 (8.1–11.2) | 18.5 (11.7–30.8) | 18.9% | 6.0 (5.0–7.0) | 3.0 (2.5–4.0) | 1 (11%) |
| 100 µl/4 bar        | 48.7 (35.4–62.6) | 9.8 (8.8–11.2) | 15.2 (13.2–20.3) | 15.2% | 8.0 (5.5–9.0) | 5.0 (4.0–6.0) | 2 (22%) |
| 100 µl/5 bar        | 23.9 (13.7–41.3) | 7.0 (7.0–8.8) | 9.5 (7.7–15.7) | 9.5% | 6.0 (5.0–7.3) | 4.0 (3.5–5.0) | 9 (100%) |
| 100 µl/6 bar        | 11.9 (4.6–26.9) | 6.1 (5.1–8.1) | 10.8 (7.9–13.4) | 10.8% | 5.0 (3.5–6.0) | 3.0 (2.5–5.0) | 8 (89%) |
| 50 µl/4 bar         | 12.8 (5.5–21.0) | 6.5 (6.1–8.1) | 9.8 (7.5–13.3) | 19.6% | 4.5 (3.0–6.0) | 3.0 (1.8–4.5) | 2 (22%) |
| 130 µl/4 bar        | 48.7 (35.4–62.6) | 9.8 (8.8–11.2) | 15.2 (13.2–20.3) | 15.2% | 8.0 (5.5–9.0) | 5.0 (4.0–6.0) | 2 (22%) |
| SLI                 |             |                        |                        |                        |                        |                        |                        |
| 100 µl              | 19.2 (4.1–60.4) | 7.0 (6.7–12.8) | 16.0 (6.2–26.5) | 16.0% | 4.0 (2.5–8.0) | 4.0 (2.5–5.5) | 5 (56%) |
| NI                  |             |                        |                        |                        |                        |                        |                        |
| 100 µl              | 48.7 (36.6–56.3) | 10.7 (10.7–11.7) | 0.6 (0.5–1.5) | 0.6% | 6.0 (5.0–6.0) | 3.0 (2.0–4.0) | 2 (22%) |

Note: EPI with 4 bar and 100 µl is presented in duplicate.

Abbreviations: EPI, electronic pneumatic injection; NI, needle injection; SLI, spring-loaded jet injection.

\(^a\)Total per group; \(N = 9\).

\(^b\)Injection volume.

\(^c\)Driving pressure.
observed in all samples (100%), while this was only observed in one sample for EPI with 3 bar and 100 µl (11%; \( p < 0.001 \)). Moreover, a trend was observed for subcutaneous dye deposition when using a high injection volume of 130 µl (56%), compared to a low injection volume of 50 µl (22%, \( p = 0.147 \)). For SLI, subcutaneous deposition was observed in 54% of the injections. For needle injections, only 22% of the injections resulted in subcutaneous dye deposition, which was similar to EPI with a low pressure level (4 bar).

**DISCUSSION**

In this ex vivo human skin study, the clinical endpoints of spring- and air-powered needle-free jet injector systems were assessed by evaluating their immediate skin responses. Our results suggest that the immediate skin papule and residual surface fluid on the skin surface are useful clinical endpoints, which closely correspond with the intradermal spatial dye distribution. A relatively small skin papule and little residual surface fluid, however, could act as warning sign for deep distribution into subcutaneous tissue. Of all tested EPI settings, 4 bar and 100 µl resulted in the highest intradermal dye deposition. For SLI, we observed intradermal drug deposition with high variability between single injections.

In dermatological practice, immediate clinical endpoints are commonly used to indicate therapeutic response or risk for complications.\(^4\) Well-known examples in laser dermatology are the whitening response from Q-switched lasers and the purpura from pulsed dye lasers. With jet injectors, such endpoints have not been investigated systematically. In this study, we found that the immediate formation of a skin papule is a good clinical endpoint that indicates delivery of the fluid into the dermis. Moreover, EPI with 4 bar and 100 µl resulted in the largest skin papule volume and most extensive dermal deposition in width and in depth. Both higher and lower EPI pressure settings, or SLI with fixed settings, resulted in a smaller skin papule size, and corresponding decreased dermal deposition. We previously reported a similar relation between the papule size and dermal dispersion, however, with no difference between EPI at 4 or 6 bar pressure, in ex vivo pig skin.\(^5\) This could be explained by the small injection volume of 50 µl that was injected in thicker and more resilient pig skin tissue in the previous study. Erlendsson et al. investigated the dermal dispersion pattern of EPI, using the same jet injector system as in our study, at 3.1, 3.9, and 4.6 bar pressure and 80 µl injection volume in ex vivo pig skin, and found that dermal depth was influenced by the pressure level, while the dermal width increased by stacking of single injections.\(^6\) However, they did not measure the skin papule dimensions or volume of residual surface fluid on the skin. Simmons et al quantified skin reactions after SLI in ex vivo guinea pig skin, and reported a positive correlation between the dye dispersion diameter from a transsectional side-view and the injection volume.\(^7\)

Besides the skin papule, the residual fluid on the skin surface also appears to be a relevant clinical endpoint, especially for the risk of infiltration into the subcutaneous tissue when aiming for a dermal target. We found that a combination of a relatively small residual surface fluid (≤10% of injected volume) and a small papule (≤7 mm in diameter) relates to a high risk of subcutaneous infiltration, mostly seen after EPI at higher pressures (5 and 6 bar) and SLI (98 bar). The sole use of residual surface fluid as clinical endpoint for subcutaneous deposition is insufficient. We assume that beyond a certain pressure level, the kinetic energy of the fluid is high enough to cross the dermis and deliver fluid primarily into the subcutaneous tissue. The injection volume was also found to be an important factor for the location of drug deposition; EPI with a larger volume of 130 µl resulted more frequently in subcutaneous infiltration. In addition, residual fluid is likely to spread to other skin areas due to the skin elasticity. This study suggests that the residual skin papule and residual surface fluid together can be used as clinical endpoints for jet injector treatment.
fluid on the skin surface is also relevant for environmental drug contamination and the cumulative drug dosage, especially when chemotherapeutic agents are being used. Besides, it is important to realize that the physical properties of the skin vary with dermal thickness, age, body mass index, ethnicity, gender, and anatomical location, which may all influence the drug distribution. Therefore, based on clinical endpoints, optimal jet injector settings should be adjusted for every individual patient, skin condition and anatomical location.8,9

Since the introduction of the first jet injector in the early twentieth century, spring- and gas-/air-powered jet injectors were developed to deliver substances into the skin. Advantages of SLI devices include their compactness, low cost and high durability, while disadvantages include fixed settings, need of sterilization between patients, and higher risk of (unwanted) subcutaneous drug deposition.1 EPI devices have the advantage of a reliable injection force, greater flexibility in device settings, and disposable nozzle tips to provide continuation of patients care. Their disadvantages include the use of an exhaustible gas source (for gas-powered jet injectors operating with gas [usually CO₂] cartridges), and higher cost.

In clinical practice, jet injectors are mainly used for intradermal drug administration of topical corticosteroids in keloids, hypertrophic scars and inflammatory disorders. A growing, but unregulated grey area, is the jet injection of hyaluronic acid for skin rejuvenation by

**FIGURE 4** (A, B) Boxplots presenting the median and interquartile ranges with min/max whiskers of needle-free jet injector induced dermal dye distribution in width (A) and depth (B) for all interventions. EPI with 4 bar and 100 µl resulted in the largest dermal distribution. SLI showed high variability for intradermal dye distribution in depth and width. Needle injection served as control. The boxplot includes outliers and EPI with 4 bar and 100 µl is presented in duplicate. EPI, electronic pneumatic injection; NI, needle injection; SLI, spring-loaded jet injection.
non-physicians. Other, more specialized indications are the delivery of bleomycin in common warts, anaesthetics for local pain management, botulinum toxin for hyperhidrosis, and 5-aminolevulinic acid for photodynamic therapy. Jet injectors can also be directed to target the subcutaneous tissue, for example, for administration of biologics, vaccines, insulin, and nicotine. The parameters of the currently available jet injector systems, however, needs to be optimized to adequately deliver larger volumes.

Limitations of this study include the use of an ex vivo human skin model to mimic an in vivo clinical setting. Although we expect that the correlation between jet injector settings on the clinical endpoints and dermal distribution in ex vivo skin will most likely be the similar to an in vivo setting, a formal evaluation of clinical endpoints in in vivo skin has yet to be performed. In addition, the use of abdominal skin from three ose patients that was partially affected by stretch marks potentially altering the distribution patterns. However, by performing all measurements in triplicate for each of the three patients, we could minimize the effect of outliers. In addition, only two of many available jet injectors were evaluated, and fluids with a different viscosity may lead to different results. Lastly, the residual surface fluid was measured with a lab pipette, which is unpractical in clinical practice. The researcher, however, were able to visually distinguish low and high residual surface fluid volumes during the course of the study (Figure 4). We suggest operators to first gain experience with the device settings and visually distinguishing surface fluid volumes to correctly use this clinical endpoint, in combination with the skin papule, in daily clinical practice.

For future research, we suggest to investigate the effect of jet injection induced skin responses at different anatomical sites, differences in age of the patient and skin lesions with other mechanical properties like various forms of scar tissue.

CONCLUSION

In conclusion, our results suggest that the immediate skin papule and residual fluid on the skin surface are relevant clinical endpoints for spring- and air-powered needle-free jet injector systems in normal human skin. These endpoints are indispensable for the successful and safe treatment with needle-free jet injector systems in clinical practice.

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CONFLICT OF INTERESTS

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