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BASIC SCIENCE

Needle-free jet injection-induced small-droplet aerosol formation during intralesional bleomycin therapy

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Abstract

Objectives: Needle-free jet injectors are frequently used in dermatological practice. Injection-generated small-droplet aerosols could be harmful upon inhalation when chemotherapeutics, like bleomycin, are used. Here, we aim to explore jet injector-induced small-droplet aerosol formation of bleomycin in relation to air ventilation and to provide safety measures for clinical practice.

Materials and Methods: With a professional particle sensor, we measured airborne aerosol particles (0.2–10.0 μm) after electronic pneumatic injection (EPI), spring-loaded jet injection (SLI), and needle injection (NI) of bleomycin and saline (100 μl) on ex vivo human skin. Three levels of air ventilation were explored: no ventilation, room ventilation, and room ventilation with an additional smoke evacuator.

Results: EPI and SLI induced significant small-droplet aerosol formation compared with none after NI (0.2–1.0 μm; no ventilation). The largest bleomycin aerosol generation was observed for the smallest particles (0.2–1.0 μm) with 673.170 (528.802–789.453) aerosol particles/liter air (EPI; no ventilation). Room ventilation and smoke evacuation led to a reduction of ≥99% and 100% of measured aerosols, respectively.

Conclusion: Jet injectors generate a high number of small-droplet aerosols, potentially introducing harmful effects to patients and healthcare personnel. Room ventilation and smoke evacuation are effective safety measures when chemotherapeutics are used in clinical practice.

KEYWORDS

aerosol, bleomycin, chemotherapy, dermatology, droplet, drug delivery, injection, jet injection, pneumatic, ventilation

INTRODUCTION

Needle-free jet injectors have been used for over 75 years in dermatological practice and vaccination of large populations.[1–3] Jet injectors generate high-velocity jet streams to effectively deliver liquid drugs into the skin.[4] Advantages of jet injectors include the avoidance of needle-stick injuries, low risk of contamination, usage in needle-phobic patients, less painful drug delivery, swift operation, and high patient comfort. However, jet injectors are also associated with some disadvantages, such as a spill of medication and relatively unpredictable delivery within the dermal or subcutaneous layer depending on the device used.[5] Currently, the two most commonly used jet injectors are spring-loaded injectors (SLI) that generate high-velocity jet streams with fixed volume and

pressure settings, and gas- or air-powered injectors, such as electronic pneumatic injectors (EPI), that operate with tuneable settings to offer more tailored treatments.[2]

In dermatological practice, jet injectors are used for intralesional delivery of triamcinolone acetonide for the treatment of hypertrophic scars, keloids, and alopecia areata.[6–9] Off-label intralesional chemotherapy with jet injectors, however, have also shown efficacy, such as 5-fluorouracil for the treatment of keloids and hypertrophic scars, methotrexate for non-melanoma skin cancer, and bleomycin (BLM) for recalcitrant warts.[10–15] Of these chemotherapeutics, lung toxicity has been reported after high cumulative dosages of intravenous BLM (400 U) resulting in lung fibrosis.[16,17] The working mechanism of BLM, an antineoplastic antibiotic, entails its ability to break DNA-strands after binding via electrostatic attraction.[18,19] BLM is broken down by the enzyme bleomycin hydrolase, additionally to renal clearance, but shows low activity in lung and skin tissue.[20,21] For dermatological treatments, lung toxicity in patients is not reported because of the use of low dosages (2–4 U), which are administered with needle injections (NI) directly in the target area.[13]

Although jet injectors aim to deliver complete dosages in the skin, large droplets, or spills, can be observed directly after injection on the skin surface.[4,22] In addition, direct splashback, which occurs during the injection phase, consists of small droplets (≤5.0 μm) that can become airborne aerosols and potentially expose healthcare professionals and patients to lung toxicity risks when chemotherapeutics such as BLM are used.[21] To date, however, no studies have reported on the formation of jet injector-induced aerosols, and the risk of lung toxicity due to small-droplet inhalation. In addition, no guidelines are available that can advise physicians on safety measures during intralesional chemotherapy using needle-free jet injectors.

Here, we aim to explore the extent of needle-free jet injector-induced small-droplet BLM aerosol formation in relation to air ventilation and to provide safety measures for clinical practice.

MATERIALS AND METHODS

Study design

In this experimental ex vivo human skin study, small-droplet aerosol formation generated by needle-free jet injections was measured using a professional particle sensor at different levels of ventilation (Table 1; Figure 1). Dermal injections of BLM, saline (SAL), and distilled water (H_2O) were performed using EPI, SLI, and NI on ex vivo human skin in a closed container without ventilation. Experiments with EPI and SAL were repeated in an office-like clinical setting with mechanical room ventilation, and with additional capturing of airborne particles via a high-powered smoke evacuator.

Skin preparation

Human skin samples were anonymously collected after elective abdominoplasty (Department of Plastic Surgery, OLVG Hospital), and bulk subcutaneous fat was reduced before storage at −20°C for a maximum of 8 weeks. The skin sample was thawed at room temperature before the start of the experiments and fixed on a substrate under light tension.

Injection techniques

EPI was performed perpendicularly on the skin surface with an electronically-controllable pneumatic jet injector (EnerJet 2.0; PerfAction Technologies Ltd.) at a pressure of 4 bar and an injection volume of 100 μl (device range: 2–6 bar, 50–130 μl, maximum jet stream velocity ≤ 150 m/s).[23]

TABLE 1 Overview of interventions

Jet injection				Air ventilation			
Interventions				Without ventilation, n = 3		With ventilation, n = 3	
Description	BLM	SAL	H_2O	Perpendicular injection	Angled injection[a]	Room ventilation	Smoke evacuator[b]
EPI	+	−	−	+	−	−	−
	−	+	−	+	+	+	+
	−	−	+	+	−	−	−
SLI	−	+	−	+	+	−	−
NI	−	+	−	−	+	−	−
				Total without ventilation, n = 21		Total with ventilation, n = 6	

Abbreviations: +, experiment was performed; −, experiment was not performed; BLM, bleomycin; EPI, electronic pneumatic injection; H_2O, distilled water; NI, needle injection; SAL, saline; SLI, spring-loaded jet injection.

[a]Injection at a 35–40° angled positioning to the skin.

[b]Additional capturing of airborne particles with a smoke evacuator at ≤5 cm distance from jet injector tip.

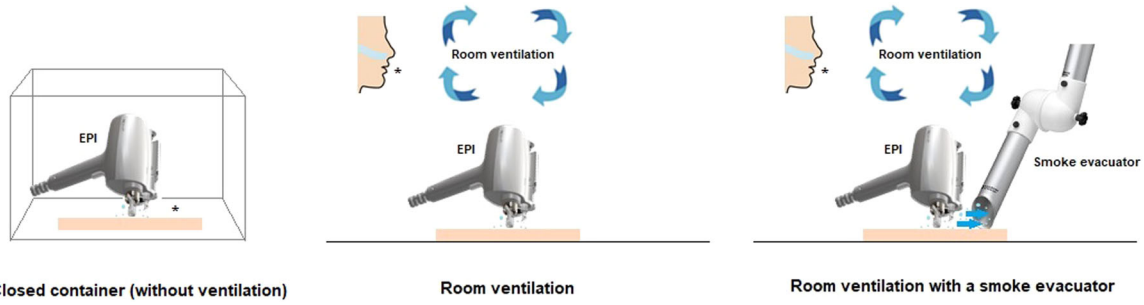

FIGURE 1 A schematic illustration of the study design including measurements of jet injection-induced small-droplet aerosols with a particle counter (*) at different levels of air ventilation.
EPI, electronic pneumatic injection

The selected EPI setting resulted in the highest intradermal drug delivery in a previous study.[24] Injection fluids included a bleomycin 1 U/ml in saline solution ($n = 3$; Bleocell; STADApharm GmbH), SAL ($n = 3$) and H_2O ($n = 3$). A spring-loaded jet injector (Dermojet; AKRA) with an injection volume of 100 µl of SAL ($n = 3$) was used for SLI. The jet injectors were placed perpendicular to the skin during injections, under light pressure. The experiments were repeated with an angled positioning of the jet injector (35–40°), leaving a small space between the tip and the skin surface to evaluate the effect of incorrect placement in clinic practice.

As a control, we performed an intradermal NI of 100 µl of SAL with a 0.5 mL insulin syringe and 29G needle ($n = 3$, BD Micro-Fine, 324892; Becton Dickinson).

Small-droplet aerosol measurements without ventilation

Airborne particles of 0.2–10.0 µm were measured using a particle counter (Handheld 2016; Lighthouse) with a flow rate of 0.017 cubic feet per interval of 10 seconds. This method of quantification of aerosol concentration was validated by Somsen et al.[25] Every experiment consisted of particle counting for 16.5 minutes, divided into three phases: (i) baseline (5 minutes), (ii) injection phase of 10 injections (1.5 minute, (iii) rest phase (10 minutes). In the no ventilation set-up, the particle counter was placed in close proximity to the jet injector and the skin sample inside a closed plastic container without risk of inhalation for the operator (Figure 1).

Small-droplet aerosol measurements with ventilation

To mimic an office-like clinical set-up, the particle counter was placed at the inhalation level of the operator (vertical distance of 39 cm from the injection site) in a closed consultation room with a mechanical ventilation system of 8 air changes per hour (Figure 1). EPI (4 bar, 100 µl) with SAL was performed on the ex vivo skin tissue while minimizing any movements in the room ($n = 3$). SAL was selected as injection fluid due to the potential risk of inhalation for the operator in this open room set-up and because aerosol formation of SAL was most similar to BLM compared with H_2O (particles of 1.0–5.0 µm/L air: 21.168 [BLM], 11.140 [SAL], and 2.454 [H_2O]; Table 2). The experiment was repeated with a high-powered smoke evacuator (TBH LN 100 series) with its maximum flow rate of 610 L per 10 seconds, and an extraction arm (ø5.5 cm) placed within a 5 cm distance of the EPI nozzle tip ($n = 3$).

Data analysis

The maximal aerosol formation per intervention was calculated according to the formula below.

$$\text{Maximal aerosol formation} = \text{Median}([AP^{\text{highest}}, AP^{\text{highest}-1}, AP^{\text{highest}-2}]_n - \text{Baseline}_n) \times 2.$$

For n = experiments 1, 2, and 3; AP = aerosol production, and volume conversion from 0.017 cubic feet to liter (×2). Data were presented as the median and interquartile range (Q1–Q3). Mann–Whitney U test was used to assess differences in aerosol concentration in different levels of air ventilation. An alpha level of $p \leq 0.05$ was considered statistically significant. Analyses were performed with SPSS version 25 (IBM Corporation) and Microsoft Excel version 2016 (Microsoft).

RESULTS

Small-droplet aerosol production by needle-free jet injection systems

The maximal aerosol formation after EPI, SLI, and NI with SAL in a closed container without ventilation are

TABLE 2 Maximal aerosol production per intervention at different levels of ventilation

Intervention		Maximal aerosol production, median (IQR)							
		Without ventilation					With ventilation		
Injection technique/ Aerosol size		BLM	SAL	SAL angled[a]	H_2O	*p* value[b]	Room ventilation	Smoke evacuator[c]	*p* value[d]
EPI	0.2–1.0 µm	673.170 (528.802–789.453)	331.810 (239.241–510.980)	500.944 (369.034–595.827)	208.518 (172.741–245.573)	0.007	2.634 (1.471–18.078)	1.620 (−70 to 2.036)	0.038
	1.0–5.0 µm	21.168 (13.947–22.991)	11.140 (4.549–39.653)	63.602 (51.595–85.632)	2.454 (1.526–2.869)	0.691	64 (18–243)	28 (7–39)	0.093
	5.0–10.0 µm	116 (48–165)	78 (50–2.509)	20.160 (4511–35.283)	212 (57–700)	0.691	0 (0–4)	0 (0–2)	0.362
SLI	0.2–1.0 µm	–	274.308 (140.852–322.271)	374.894 (316.337–438.815)	–		–	–	
	1.0–5.0 µm	–	15.216 (8.975–18.660)	39.930 (28.048–47.630)	–		–	–	
	5.0–10.0 µm	–	538 (39–8.208)	6.994 (2.995–9.256)	–		–	–	
NI	0.2–1.0 µm	–	−326 (−1.230–−57)	–	–		–	–	
	1.0–5.0 µm	–	−2 (−3–−2)	–	–		–	–	
	5.0–10.0 µm	–	2 (0–4)	–	–		–	–	

Note: Data presented as aerosol particles per liter air.

Abbreviations: BLM, bleomycin; EPI, electronic pneumatic injection; H_2O, distilled water; IQR, interquartile range (Q1–Q3); NI, needle injection; SAL, saline; SLI, spring-loaded jet injection.

[a]Jet injector tip at a 35–40° angled positioning to the skin during injection.

[b]EPI with bleomycin compared with EPI with saline.

[c]Additional capturing of airborne particles with a smoke evacuator at ≤5 cm distance from jet injector tip.

[d]Room ventilation alone compared with room ventilation with additional extraction of aerosols via a smoke evacuator.

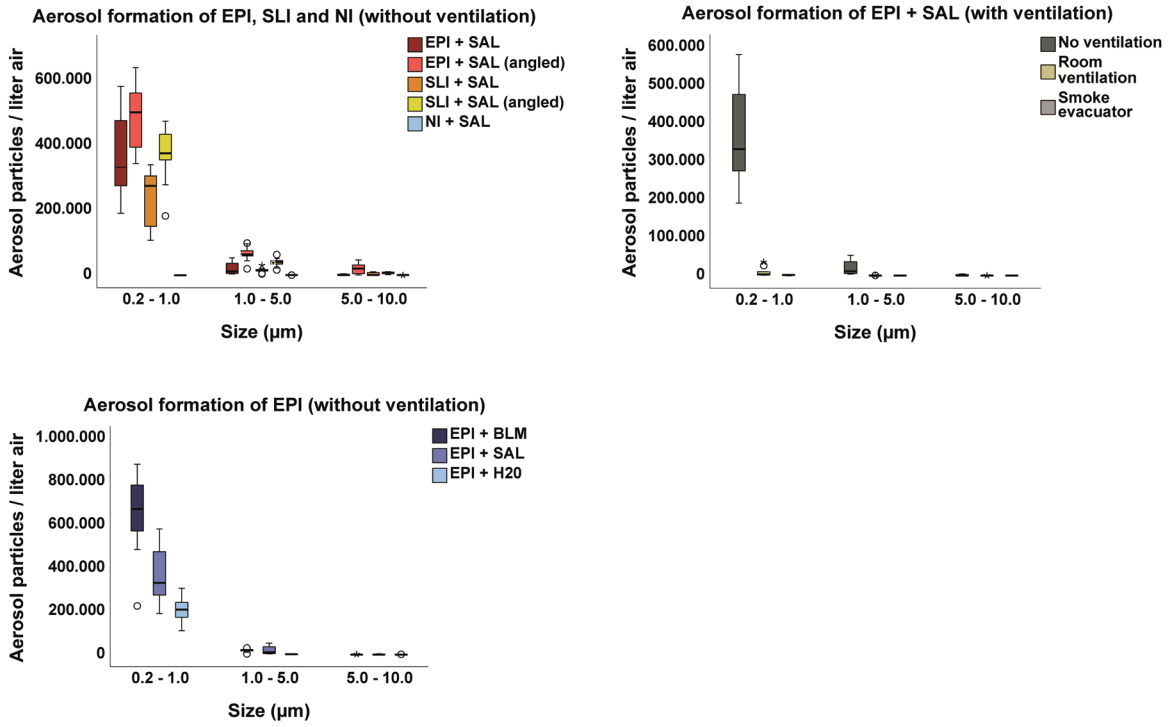

FIGURE 2 Box plots with min-max whiskers of aerosol production during needle-free jet injection in a closed container without ventilation or in a closed consultation room with ventilation. BLM, bleomycin 1 U/ml diluted in saline; EPI, electronic pneumatic injection; H_2O, distilled water; NI, needle injection; SAL, saline; SLI, spring-loaded jet injection

shown in Figure 2 and Table 2. Both jet injector systems induced significant numbers of the smallest droplet aerosols (0.2–1.0 µm) with 331.810 (239.241–510.980) and 274.308 (140.852–322.271) aerosol particles/liter air for EPI and SLI, respectively ($p = 0.145$). Angled positioning (35–40°) of the injector tip resulted in a significant increase of aerosol production compared with perpendicular positioning ($p = 0.038$, $p = 0.007$, EPI and SLI respectively; Figure 2). In contrast to the jet injectors, NI induced no small-droplet aerosols (0.2–5.0 µm; $p < 0.001$).

In general, we observed that the majority of the injection fluid was delivered in the skin and only a small amount of residual surface fluid was visible after each injection.

Small-droplet aerosol production after EPI with bleomycin, saline, and H_2O

The maximal aerosol production after EPI with BLM, SAL, and H_2O are presented in Table 2 and Figure 2. EPI with BLM resulted in a maximal aerosol production of 673.170 (528.802–789.453) aerosol particles/liter air of 0.2–1.0 µm, 21.168 (13.947–22.991) aerosol particles/liter air of 1.0–5.0 µm and 116 (48–165) aerosol particles/liter air of 5.0–10.0 µm. Of the aqueous solutions, EPI-induced aerosol production with SAL was most similar to BLM ($p = 0.007$–0.691, Table 2).

Jet injector-induced small-droplet aerosols in relation to air ventilation

The maximal aerosol production after EPI in relation to air ventilation is shown in Figure 2. Compared with no ventilation, EPI with normal room ventilation resulted in a ≥99% reduction of measured aerosols at the inhalation level of the operator ($p < 0.001$; 0.2–10.0 µm). Additional capturing of airborne aerosols using a smoke evacuator resulted in a complete reduction of 100% of aerosols ($p = 0.038$; 0.2–1.0 µm). The greatest benefit of the smoke evacuator was observed for particles of 0.2–1.0 µm. No large aerosol particles of 5.0–10.0 µm were detected during EPI with air ventilation.

DISCUSSION

To our knowledge, this is the first *ex vivo* human skin study that explored pneumatic jet injector-induced small-droplet aerosol formation after intradermal drug delivery of bleomycin in relation to mechanical room ventilation and fume evacuation. We showed that pneumatic jet injection is a aerosols generating procedure, specifically of small-droplet aerosols that could penetrate deep into the lungs.[26] In a clinical setting, safety measures with room ventilation and a smoke evacuator are of paramount importance for capturing generated aerosols.

In this study, we measured a high number of 0.2–1.0 µm aerosol particles after spring-loaded and gas-powered jet injections compared with no aerosol formation during needle injections (no ventilation). Jet injectors propel liquids via high-powered jet streams to penetrate the skin and cause some degree of splashback during the initial jet-skin contact creating small and large droplets.[4,27] To protect the surroundings from contamination with large droplets, a plastic cylinder is installed at the injector tip creating a chamber on the skin during treatment, when placed perpendicularly. When performing multiple injections, however, the device is lifted between each injection, enabling the spread of small-droplet airborne aerosols. We showed that angled positioning of the injector tip (35–40°) creates a direct airflow passage, and increases the maximal aerosol production significantly. When comparing the two jet injector systems, we found that the EPI generated the highest number of small-droplet aerosols. This could be explained by different jet stream characteristics of EPI compared with SLI.

Following the dispersion into air, a number of processes may influence the airborne time and spreading distance of droplets, including gravitational deposition (large droplets), shrinkage by evaporation, fusion with other airborne particles, and deposition on the surface.[28,29] Droplets of ≤100 µm usually evaporate in less than 1 s before reaching the ground surface, however, the droplet residue remains in the air. For SAL, evaporation of water causes formation of solid salt crystals with a smaller-droplet diameter and thereby extending the airborne travel time. Under standardized conditions, the time for a water droplet to drop 1 meter varies between 0.3 s for a droplet of 1000 µm compared with 30.000 s for a droplet of 1 µm.[28] After vaporization of the BLM solution, solid BLM crystals are formed in addition to salt crystals, which is reflected in a higher number of small-droplet aerosols (0.2–0.1 µm), compared with SAL alone. The aerosol diameter is relevant for the potential deposition location within the respiratory tract after inhalation and the extent of pulmonary toxicity. Aerosols of ≤3 µm are deeply inhaled into the lungs, reaching the alveoli, while bigger particles will be deposited in the large bronchioles or up to the pharyngeal or nasal cavity depending on the particle size.[26,30]

Of the large amount of jet injector-induced aerosols, only a fraction was measured at inhalation level when the procedure was performed with standard mechanical room ventilation. However, this may depend on characteristics of the room ventilation, such as the air refreshment rate and airstream of the specific room in which the procedure is performed in. The additional use of a high-powered smoke evacuator in close proximity (≤5 cm) to the injector tip led to an almost undetectable formation of small-droplet aerosols. Besides protection of direct inhalation, incorporating a powerful smoke-evacuator during jet injector treatments reduces the risk of environmental contamination with small and large droplets containing BLM residue. From other aerosol-generating procedures, we have learned that a high-powered smoke evacuator is an important tool to protect physicians from the transmission of airborne pathogens.[31] For this reason, Mohs surgeons are advised to use personal protective measures and a smoke evacuator when treating the oral or nasal mucosa.[32] In addition, laser surgeons use a smoke evacuator to capture laser-induced fume, containing hazardous substances including toxic, carcinogenic, and viral pathogens, such as HPV when treating warts.[33]

Limitations of this study include the use of SAL to mimic BLM aerosol formation in the room ventilation experiments. Formed SAL aerosols may be an underestimation of the produced BLM aerosols, which emphasizes the use of a high-powered evacuator system to capture airborne aerosols as a safety measure in clinical practice. In addition, this is an ex vivo study with healthy human skin while aerosol formation may differ during BLM administration by jet injectors in in vivo cutaneous pathologies. Skin tissues with higher surface tension and consistency, such as fibrotic keloid scars, could potentially lead to a higher aerosol production compared with healthy tissue. Moreover, jet-specific settings such as pressure, injection volume, nozzle size, and operating mechanism could also influence the extent of aerosol production.

Recommendations for clinical practice

At our tertiary academic hospital, we frequently treat patients with recalcitrant common warts, keloids, and hypertrophic scars with intralesional BLM using SLI.[13,15] Due to the cumulative risk of lung toxicity after repeated exposure to small amounts of BLM, it is necessary to prevent lung exposure of procedure-generated aerosols for healthcare workers and patients. This is also highly relevant for treatments with other chemotherapeutics such as 5-fluorouracil or methotrexate.[26] In addition, physicians should be aware that jet injectors can also produce bioaerosols containing blood, viruses or bacteria, and are, therefore, a risk for airborne transmission of infection.[34,35] Here, we demonstrated that jet injector-produced aerosols are adequately captured when mechanical room ventilation is combined with a high-powered smoke evacuator. To ensure safe intralesional chemotherapy, we advised to use the following safety precautions: disposable gloves, safety goggles, a smoke evacuator (≤5 cm distance of the jet injector tip), and a surgical mask or FFP-2 mask, the latter in case of absence of a smoke evacuator, for the physician and patient. Importantly, avoid angled positioning of the jet injector tip on the skin surface to prevent a further increase in aerosol formation.

CONCLUSION

In this ex vivo human skin study, we demonstrate that after intralesional chemotherapy using needle-free jet injectors a large number of small-droplet aerosol particles is produced. To prevent deep lung inhalation of potentially toxic aerosols, the use of mechanical room ventilation combined with a high-powered smoke evacuator is of paramount importance when using jet injectors in clinical practice.

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CONFLICT OF INTERESTS

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