

# Needle-free Mental Incisive Nerve Block: *In vitro*, Cadaveric, and Pilot Clinical Studies<sup>☆</sup>

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## ABSTRACT

The present study aimed to optimize Needle-Free Liquid Jet Injection (NFLJI) for Mental Incisive Nerve Blocks (MINB) and evaluate its clinical safety and feasibility. A MINB protocol was developed and optimized by series of NFLJI experiments in soft tissue phantoms and cadavers, then validated in two pilot Randomized Controlled Trials (RCT). The NFLJI penetration depth was found to be directly proportional to the supply pressure and volume. High-pressure NFLJIs (620 kPa or above) created maximum force and total work significantly greater than needle injections. Low-pressure NFLJIs (413 kPa), however, produced results similar to those of needle injections. Additionally, high-pressure NFLJIs created jet impingement pressure and maximum jet penetration pressure higher than low-pressure NFLJIs. Pilot RCTs revealed that high-pressure NFLJI caused a high risk of discomfort (60%) and paresthesia (20%); meanwhile, low-pressure NFLJI was less likely to cause complications (0%). The preliminary success rates of MINB from cadavers using NFLJIs and needles were 83.3% and 87.5%. In comparison, those from RCTs are 60% and 70%, respectively. To conclude, NFLJI supply pressure can be adjusted to achieve effective MINB with minimal complications. Furthermore, the cadaver study and pilot RCTs confirmed the feasibility for further non-inferiority RCT.

## 1. Introduction

Needle fear and phobia may deter patients from receiving necessary treatment, worsening their oral health conditions (Baier et al., 2004; Majstorovic and Veerkamp, 2004; Orenius et al., 2018; Sokolowski et al., 2010). Needle-Free Liquid Jet Injection (NFLJI) systems could solve this problem. These systems are powered by gas (Gao et al., 2021), laser (Rohilla and Marston, 2020), or spring (Schoubben et al., 2015) pressure to create thin (usually 76–360  $\mu\text{m}$  in diameter) and high-

velocity (typically  $> 100 \text{ m s}^{-1}$ ) liquid jets. The liquid jets can deliver therapeutic fluid across the skin into the subcutaneous or intramuscular region (Mitragotri, 2006). In addition, the use of NFLJI eliminates the risk of needle fracture during injection (Malamed et al., 2010) and disease transmission via re-used needles (Mitragotri, 2006).

Dental anesthesia is mainly achieved by two different techniques: infiltration and nerve blocks. Infiltration anesthesia is achieved by penetrating through a thin layer of mucosa (3–5 mm thick) overlying the rigid alveolar bone and depositing anesthetics near the small nerve

**Abbreviations:** NFLJI, Needle-Free Liquid Jet Injection; RCT, Randomized Controlled Trial.

<sup>☆</sup> This study has been registered online with the title needle-free dental anesthesia (NCT04493528), <https://clinicaltrials.gov/ct2/show/NCT04493528>.

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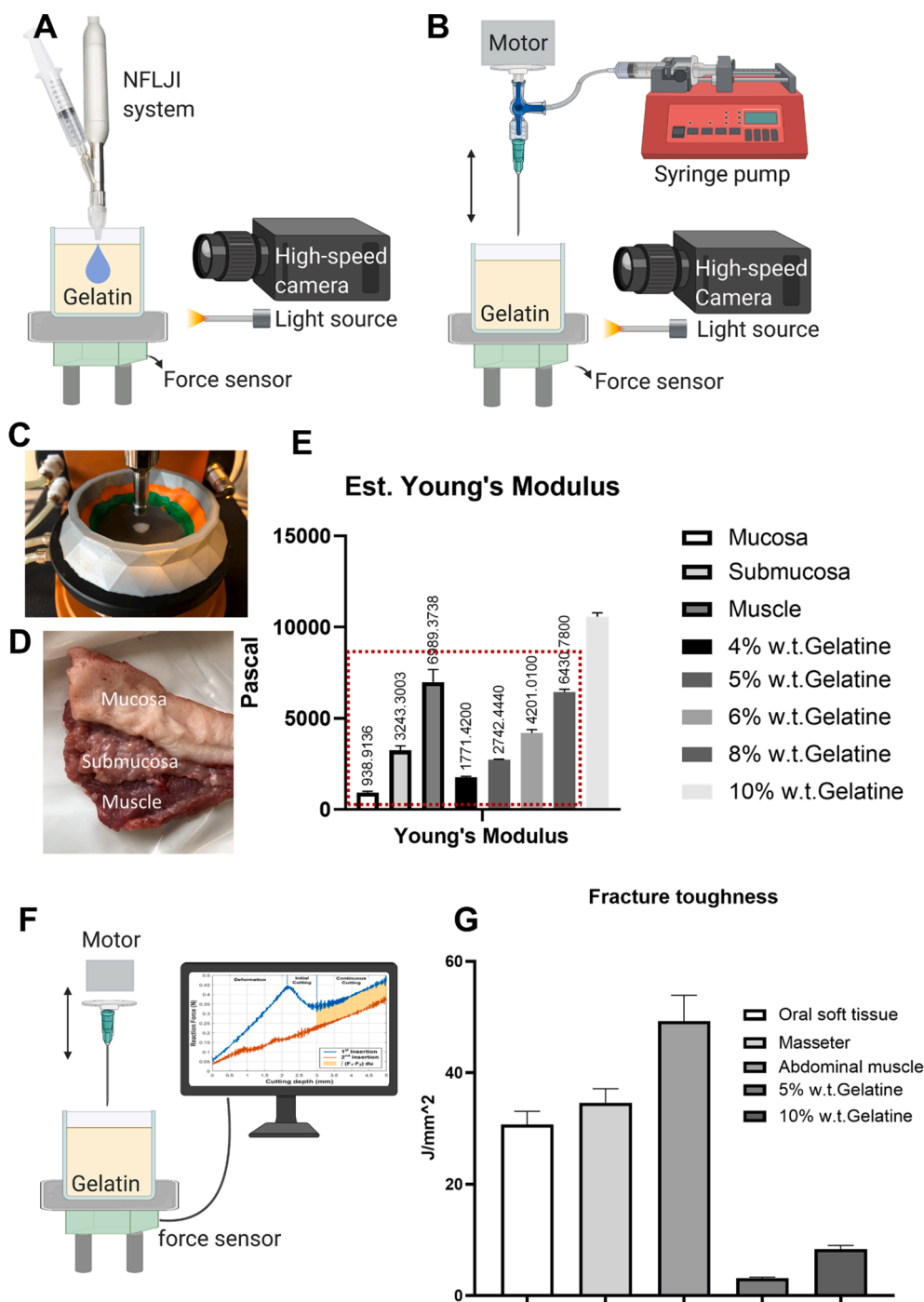
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terminals of the tooth apices and the surrounding soft tissue (Malamed, 2014). These anatomical characteristics pose a challenge to NFLJI. Although a high-speed jet can easily penetrate the mucosa, it can rebound off the hard tissues resulting in significant liquid regurgitation and tissue laceration. Recently, our group demonstrated that these problems could be mitigated using the oblique impact angle, which helps achieve adequate infiltration anesthesia with minimal complications (Gao et al., 2021).

Although infiltration anesthesia can adequately anesthetize the maxillary and mandibular anterior teeth, it cannot anesthetize the

mandibular posterior teeth because their small nerve endings are embedded deep in partially impermeable bone (Malamed, 2014). For the latter, nerve block anesthesia is needed. Dental nerve blocks deliver anesthetics to desensitize major nerve branches that control downstream teeth and soft tissues; Unlike infiltration anesthesia, nerve blocks require deeper injections able to penetrate deep enough (5–20 mm) to reach the major nerves (Malamed, 2014). The nerve block technique poses different challenges compared to infiltration anesthesia due to the anatomical structure. Moreover, the risk of high-speed liquid jets directly impacting main nerve branches remains unclear. However, to



**Fig. 1.** (A) Experimental set up for *in vitro* needle injection and (B) NFLJI. (C) Measurement of Young's modulus for (D) oral soft tissue and phantom materials, 4–10% wt. gelatin. (E) Young's modulus of 5% gelatin is within the range of oral soft tissue, while 10% gelatin is stiffer than oral soft tissue. (F) Concept of fracture toughness measurement using needle piecing method. (G) Fracture toughness of oral soft tissue is higher than that of 5% gelatin. A, B, and F were created with BioRender.

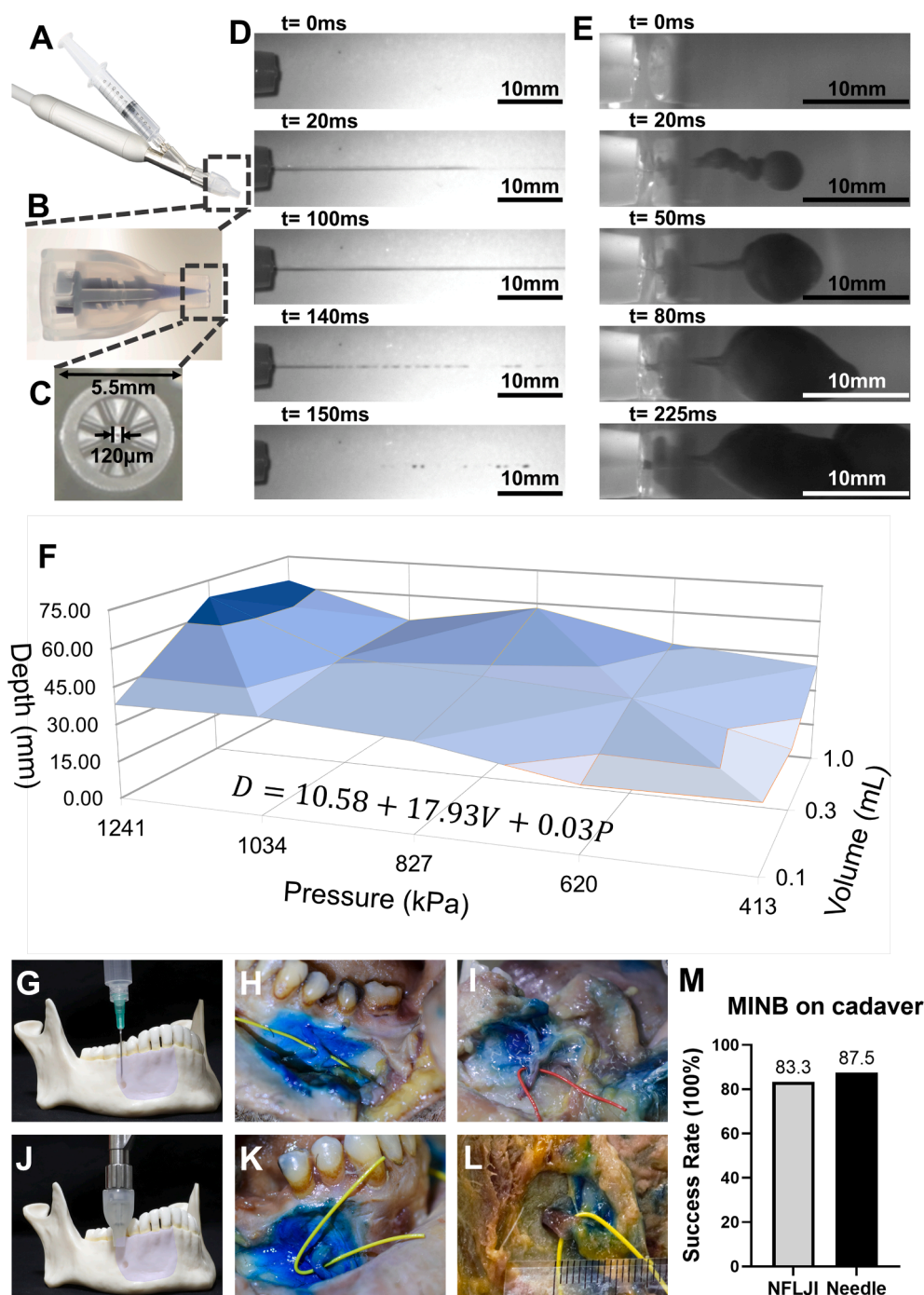
the best of our knowledge, NFLJI has not been investigated in depth for nerve block applications.

The mental incisive nerve block (MINB) is a technique used to anesthetize mandibular premolars by injection anesthetic solution near the mental foramen to block the mental incisive nerve (Aggarwal et al., 2016; Batista da Silva et al., 2010; Ghabraei et al., 2019). MINB requires a relatively simple penetration depth of 5–6 mm (Reed et al., 2012) and thus was selected for this study.

Three factors influence NFLJI penetration and dispersion: the injector and operative parameters (Mitragotri, 2006; Rohilla et al., 2020; Schramm-Baxter and Mitragotri, 2004), the tissue properties

(Baxter and Mitragotri, 2005), and the injected fluid (Baxter and Mitragotri, 2006; Mohizin and Kim, 2018; Seok et al., 2016). Among these factors, only the injector parameters may be adjusted to optimize the outcome. Poor selection of injector parameters can cause undesirable side effects, such as tissue damage and nerve paresthesia. Therefore, appropriate parameters are the most critical consideration for safe NFLJIs before translating the NFLJI to clinical practice.

This study aimed to investigate the NFLJI technique for MINB and to evaluate its clinical safety and feasibility. We hypothesized that the NFLJI penetration depth and potential tissue damage are correlated with the supply pressure; and that an optimal supply pressure could achieve



**Fig. 2.** (A) Needle-free liquid jet injection system in this study, view from (B) side and nozzle tip (C). The injection dispersion in (D) air and in (E) 10% gelatin. (F) The penetration depth increased with supply pressure and injected volume. (G) The MINB using needle, example of (H) successful and (I) failed injection result after dissection. (J) The MINB using NFLJI, examples of (K) successful and (L) failed injection result. (M) The simulated success rate of MINB on cadaver.

successful MINB with minimal complications.

## 2. Methods

The pneumatic NFLJI system (Medical International Technologies Inc, Montreal, Canada) used in this study has an orifice diameter of 120  $\mu\text{m}$ , adjustable volume of 0.1–1.8 mL, and adjustable supply pressure of 413–1400 kPa (Fig. 2 A–C). Note that the supply pressure determines the acceleration of the free piston inside the system and does not necessarily correspond to the pressure immediately upstream of the nozzle. The fluid exiting velocity and driving pressure were presented in the previous paper (Gao et al., 2021). Based on experimental data (Fig S5), the discharge coefficient varies from 0.6 to 0.9 depending on the injector parameters (Fig S4).

### 2.1. Characterization of phantoms for *in vitro* NFLJI experiments

To develop an appropriate phantom for *in vitro* NFLJI experiments, first, the Young's modulus and fracture toughness of oral soft tissue was quantified using tissue samples harvested from fresh porcine heads within 24 h post-mortem. Young's modulus is the elasticity of a material measured by a rheometer assessing how it withstands the compression or elongation with respect to its length. Fracture toughness is the ability of a material to resist fracture. Both serve as a basis for material comparison, selection, and quality assurance (ASTM, 2001). The fracture toughness of many materials is determined by a shear test or a single-edged notch test with coupon-type specimens. These methods are not applicable for oral soft tissue due to size limitations. Oral soft tissue toughness can alternatively be determined using scissor-cutting tests (Pereira et al., 1997) or needle-insertion tests (Gokgol et al., 2012). The latter method was selected in this study due to its similarity to needle injection.

To measure Young's modulus, cylindrical porcine oral mucosa samples with a 10-mm diameter and 2-mm thickness were prepared and preserved in a PBS bath (Fig. 1 C&D). Gelatin phantom samples (Sigma-Aldrich, Merck KGaA, US) with similar dimensions were prepared with a concentration ranging from 2 wt% to 10 wt% (Cronin and Falzon, 2011) using a mold. The Young's modulus was inferred from the shear modulus, assuming that the tested material is isotropic, homogeneous, and incompressible. Shear tests were performed using a torsional rheometer (DHR2, TA instrument, USA), with a test head diameter of 10 mm, at frequencies from 1 to 100 Hz (Fig. 1 C).

To measure the fracture toughness, oral soft tissue was harvested from three fresh porcine heads. Rectangular samples with dimension  $2 \times 4 \times 1$  cm were prepared using dissection tools and mounted within 5% gelatin inside a  $4 \times 4 \times 4$ -cm glass container (Fig. 1F). A 25-gauge needle driven by a motorized linear transverse stepper (SPN7338, Velmex Inc, US) at a velocity of 5 mm/s was inserted into the sample to a 15-mm depth. The needle was retracted and inserted a second time at the same location to evaluate friction forces. A force transducer (GS0500, transducer technique, USA) located underneath the glass container recorded the vertical force-time history during needle insertion (Fig. 1F). LabVIEW (LabView 2019, National Instruments, US) was used to program the needle movement and record the force data. The fracture toughness of porcine masseter muscles and abdominal muscles, as well as the gelatin of 5 wt% and 10 wt% were also quantified using the same method for oral mucosa. The fracture toughness was calculated using the relation (Azar and Hayward, 2008):

$$\int_{x_2}^{x_1} (F - F') dx = J_{IC} a dx \quad (1)$$

where  $x_1$  and  $x_2$  are the beginning and end positions of the needle insertion,  $F$  is the dynamic force during the first insertion (friction + fracture),  $F'$  is the dynamic force during the second co-located insertion (friction alone),  $a$  is the cross-sectional area of the needle, and  $dx$  is the

dynamic change of needle position. The fracture toughness,  $J_{IC}$ , could be calculated from Eq (1) (Azar and Hayward, 2008).

### 2.2. Laboratory investigation of NFLJI safety

According to the test results and a previous study (Rohilla and Marston, 2019), 5 wt% gelatin can best represent Young's modulus of oral soft tissue. Hence 5 wt% gelatin was prepared in customized optical clear glass containers of  $W 4 \times L 4 \times H (4-15)$  cm dimension for further NFLJI test. To investigate how NFLJI parameters affect injection in oral soft tissue, NFLJI experiments were conducted in gelatin phantom using a range of supply pressure (413–1240 kPa) and delivery volume (0.1–1 mL). The jet travel in the air was also recorded using a high-speed camera (Fastcam MC2, Photron, Japan) (Moradiafrapoli et al., 2017) to estimate the initial liquid jet velocity. The NFLJI nozzle tip was 2 mm from the phantom surface to maintain a visible jet trajectory for high-speed camera analysis. The NFLJI impact angle is  $90^\circ$  to the phantom surface to maintain sufficient phantom thickness.

A laboratory test bench was designed to simultaneously measure the force-time history during injection using a force sensor and the jet dispersion-time history using a high-speed camera (Fig. 1A) to investigate the relationship between injector parameters and tissue damage. Afterward, this setup was modified to simulate clinical needle injection by adding a linear stage (SPN7338, Velmex Inc, US) and a syringe pump (NE-1000, New Era pump system Inc) (Fig. 1B) to measure the dynamic force during needle injection.

High-speed videos were recorded at 10,000 frames per second (fps) and analyzed frame by frame to plot the penetration depth-time history and match with synchronously acquired force-time history. Force data were processed using MATLAB (The MathWorks, Inc, USA). Figures were refined using Prism8 (GraphPad Software, USA). The maximum force (Fig. 3A) was determined as the highest force value during the NFLJI or needle injections, as shown in Fig. 3 A, B.

The total work of NFLJI was calculated as the integral of dynamic force ( $F$ ) and dynamic penetration depth of the jet leading edge ( $x$ ) versus time from the beginning ( $x_1$ ) to the end position point ( $x_2$ ), i.e.

$$W = \int_{x_2}^{x_1} F dx \quad (2)$$

The total work of needle injection was the sum of the calculated work for needle insertion ( $W_{injection}$ ) and the estimated work for the injection of 1-mL fluid ( $W_{injection}$ ). The needle insertion work was calculated as the integral of dynamic force ( $dF$ ) multiplied by needle travel ( $dx$ ) at each sampling interval. The estimated work of injection was calculated as the product of injection volume ( $V$ ), the minor loss coefficient for the flow through the needle ( $K$ ,  $K = 1$  in this case), the density of water at  $20^\circ\text{C}$  ( $\rho$ ), and average velocity of fluid flow ( $\bar{U}$ ), which is based on Euler's equation for the kinetic energy of fluid (Pritchard and Mitchell, 2016). The average velocity of fluid flow ( $\bar{U}$ ) was calculated as volumetric flow rate ( $Q$ ) divided by the internal area of the needle ( $A_{needle}$ ). The mathematical expressions used are:

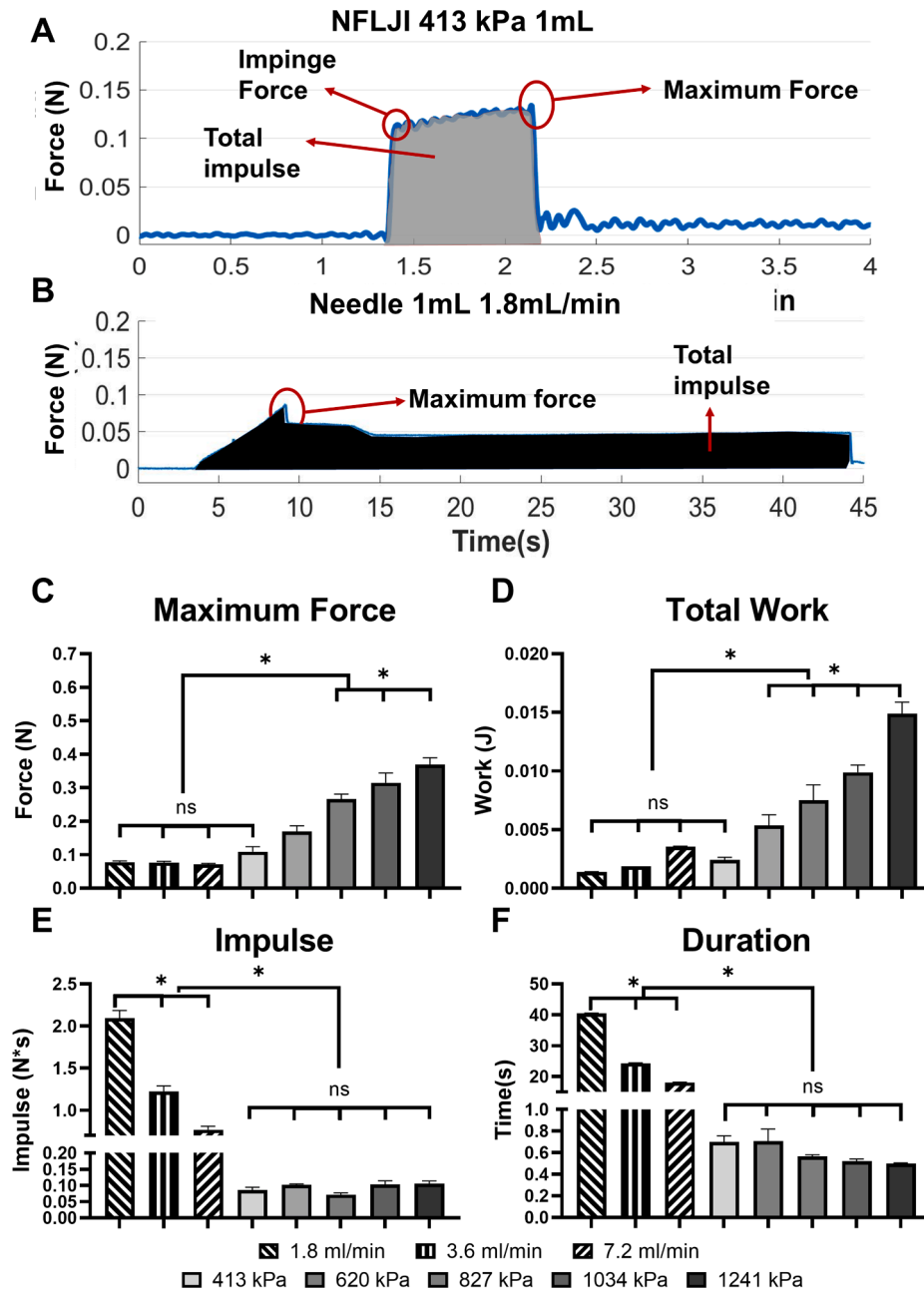
$$W = W_{injection} + W_{injection} \quad (3)$$

$$W_{injection} = \int_{x_2}^{x_1} F \cdot dx \quad (4)$$

$$W_{injection} = V \cdot K \cdot \frac{1}{2} \rho \bar{U}^2 \quad (5)$$

$$\text{and } \bar{U} = \frac{Q}{A_{needle}} \quad (6)$$

The impulses of NFLJI (Fig. 3A) and needle injection (Fig. 3B) were calculated as the integral of dynamic force ( $F$ ) versus time ( $t$ ) as



**Fig. 3.** (A) The force signal versus time of NFLJI using 413 kPa and 1 mL. (B) The force signal of needle injection using 1 mL with insertion speed of 5 mm/s and injection flow rate of 1.8 mL/min. (C–F) The maximum force, total work, impulse, and duration of injections using needle with 1.8, 3.6, and 7.2 mL/min flow rate and using NFLJI with 413–1241 kPa supply pressure.

$$I = \int_{t_2}^{t_1} F \cdot dt \quad (7)$$

The duration of NFLJI was the difference between the beginning and ending points of injection in the high-speed video. The duration of needle injection was the difference between the beginning and ending points of the needle movement.

The jet central core velocity was calculated as:

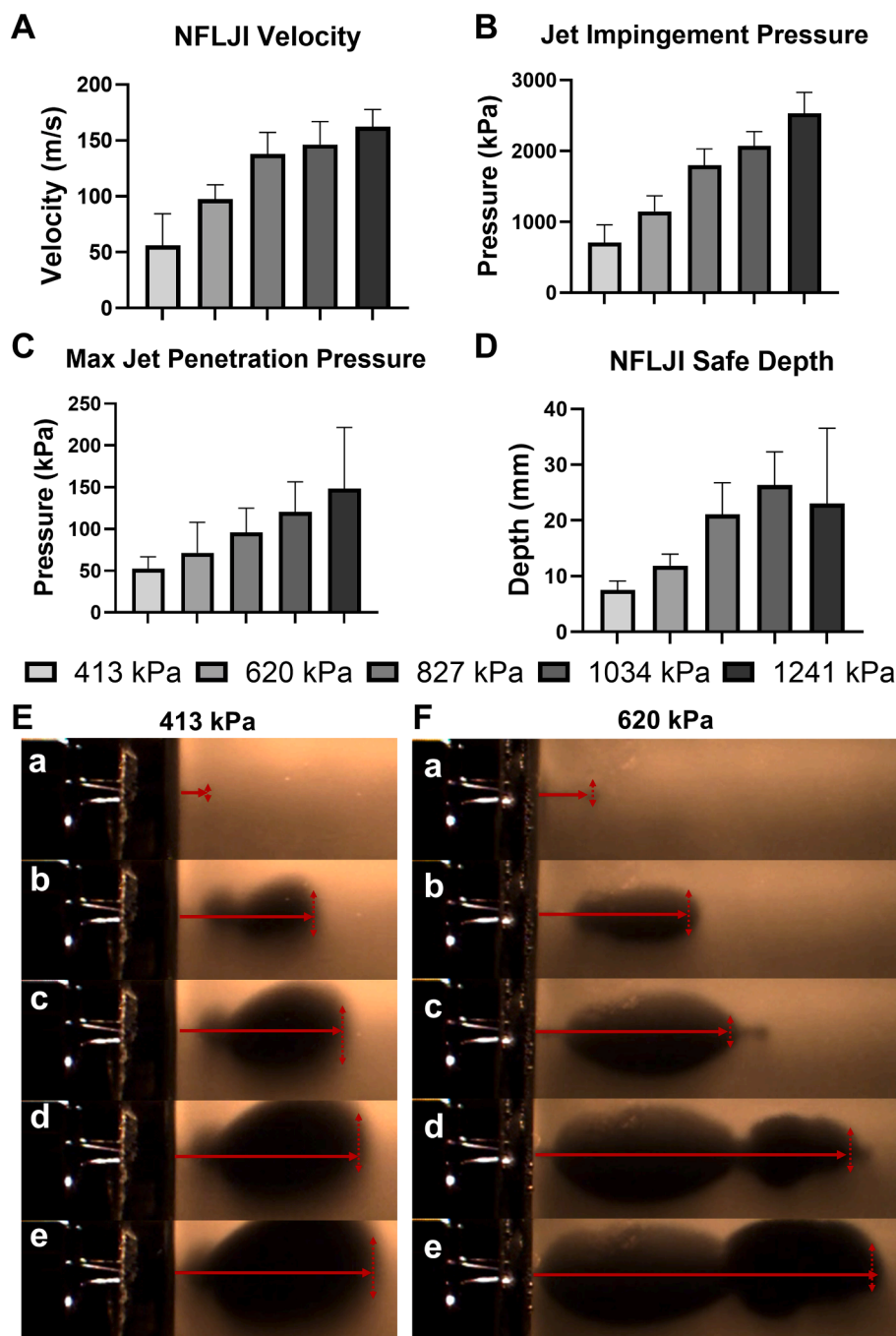
$$v = \frac{\bar{F} \cdot \Delta t}{\rho \cdot V} \quad (8)$$

where  $\bar{F}$  is the mean force during jet penetration,  $\Delta t$  is the duration of jet injection,  $\rho$  is the density of water,  $V$  is the volume of injected liquid.

Further analysis was done after matching the force-time history (Fig. 3A) and dispersion-time history (Fig. 4E). First, the jet

impingement force was defined as the force when the jet starts to impinge the phantom surface. The estimated jet impingement pressure was calculated as jet impingement force divided by the skin hole area; the latter was calculated using a nozzle/skin wound diameter ratio of 0.3 based on a previous study (Baxter and Mitragotri, 2005). Since the jet penetration pressure is highest at the surface and decreases with depth, the estimated jet maximum penetration pressure was calculated as the force when the jet pieces through the tissue phantom (Fig. 3Aa) divided by the jet dispersion area calculated from the first frame where jet penetration is visible in the high-speed camera video (Fig. 4 Ea) (Table S1). In contrast, the maximum force of needle injection occurs at the end of insertion (Fig. 3B); hence the maximum pressure of needle injection is calculated by the maximum force when the needle penetrates the tissue phantom divided by the area of a 25-gauge needle.

A previous study has determined that the safe pressure for nerve



**Fig. 4.** (A-D) Analysis of NFLJI (1 mL) based on the force - time history and depth- time history. (E-F) the high-speed video record showed that jet penetration depth versus time.

damage is 80 kPa (Marcol et al., 2012). Accordingly, the safe depth of NFLJI was defined as the depth beyond which the jet pressure inside the tissue phantom drops below 80 kPa.

### 2.3. Cadaveric evaluation for the efficacy of NFLJI mental nerve block

A total of ten cadavers were used. Two cadavers were used to validate the NFLJI parameters for MINB. Eight cadavers were used for a randomized cross-over split-mouth study to compare the anesthesia efficacy between NFLJI and needle. Methylene blue (0.2%) was used to visualize the injection outcome (Guay and Grabs, 2011) using a volume of 0.3 mL (Seok et al., 2016).

Needle injection MINBs were performed following standard

procedures (Malamed, 2014) (Fig. 2G). Needle-free MINBs were performed by placing the nozzle of the NFLJI device in the mucobuccal fold of the mandibular vestibule using a mean loading force of 0.3 N at the premolar region and depositing the local anesthetic around the mental foramen (Fig. 2J). After each injection, the site was dissected by an independent anatomist (G.N.) and photographed.

In cadaveric studies, the typical evaluation for the success of nerve blocks is based on staining patterns. Unfortunately, this evaluation is subjective and inaccurate. To address this issue, we added additional objective criteria: the mental nerve was adequately stained (Kampitak et al., 2018), the mental foramen was in the center of the stained area (Eichenberger et al., 2006), and four blinded assessors agreed on the judgment (Fig. 2 H&I, K&L). In addition, the four blinded assessors had

to be experienced dentists or anatomists.

#### 2.4. Clinical validation of high-pressure NFLJI

A pilot RCT with a split-mouth cross-over design was conducted at the McGill Student and Staff dental clinic over September 1-20, 2019, to evaluate the feasibility and safety of high-pressure NFLJI for MINB. This study was approved by the McGill Research Ethics Board (A09-M36-18A) and retrospectively registered online (NCT04493528). Ethical approval for the clinical and cadaver studies was obtained under the same ethical protocol because experiments were considered two stages of the same study. The clinical investigation performed in this study followed a similar methodology to our previous work regarding the inclusion and exclusion criteria, endpoint, allocation, randomization, blinding, and follow-up (Gao et al., 2021). However, the six participants enrolled are different from the previous study.

Each participant received two MINBs on the left and right lower premolar regions, one site with needle injection and another with NFLJI. The injection techniques were the same as described in the cadaveric study. The NFLJI supply pressure was 620 kPa. As justified previously, the anesthetic was 1 mL of 2 % Lidocaine with 1:100,000 epinephrine (Gao et al., 2021).

The primary outcomes were feasibility and safety: the feasibility depended on recruitment time and rate, withdrawal rate, participants' concerns, and problems during operation, while the safety of NFLJI was determined by complications such as bleeding, laceration, hematoma, and nerve paresthesia. The secondary outcomes were recorded in three categories: (a) the success rate of MINB, confirmed by electric pulp test (EPT) on canine, premolars, and first molar (Malamed, 2014); (b) the effect of MINB, including the time to initial anesthesia, the onset, and the duration; (c) side effects after injections, including pain score assessed using the numeric rating scale (Hawker et al., 2011) and taste score measured using the 9-point hedonic scale (Wichchukit and O'Mahony, 2015) (Fig. S1 A).

#### 2.5. Clinical safety and feasibility of low-pressure NFLJI

The first pilot RCT was stopped due to one case of paresthesia; the *in vitro* experiment suggested that reducing the supply pressure could reduce complications by minimizing the total work, force and pressure applied on the soft tissue. For these reasons, a second pilot clinical trial was conducted to validate the safety of the refined NFLJI technique using a lower supply pressure of 413 kPa. Another 6 participants were recruited, and the clinical trial was conducted from January 6 to March 12, 2020, at the McGill Student and Staff Dental Clinic. The study design, primary outcomes, and secondary outcomes were the same as the first pilot RCT (Fig. S1 B). In addition, a visual analog scale (VAS) for anxiety was added to assess the anxiety levels before and during the injections; the pain numeric rating scale (NRS) was replaced by a pain VAS to provide a more sensitive measurement (Thong et al., 2018).

#### 2.6. Statistical analysis

Descriptive analysis was performed using SPSS21.0 (IBM, SPSS statistics) and Prism8 (GraphPad Software, San Diego, California, USA). Categorical variables, such as complication rates and success rates, were presented as count and percentage. Continuous variables, such as durations and scores, were presented as median and inter-quartile range (IQR).

### 3. Results

#### 3.1. NFLJI penetration depth and its parameters

Gelatin of 5 wt% was selected for *in vitro* experiments as its Young's modulus is similar to that of porcine oral soft tissue (Fig. 1E), even

though gelatin's fracture toughness is significantly lower than that of oral soft tissue (Fig. 1G).

The time histories of the liquid jet dispersion in air and gelatin are shown in Fig. 2 D&E. Upon impingement on the soft tissue phantom surface, the jet penetrates the surface and then creates an initial conical region of high velocity. Over time, flow recirculation accumulates at the end of the conical tunnel to create a pocket-like region with increased width. This process would be repeated within the initial pocket-like region resulting in a secondary conical tunnel and pocket-like propagation (Fig. 2E). Higher shear between the injected liquid and the solid substrate causes fractures and breakages of the substrate into a slurry. Vorticity accumulation at the end of the conical tunnel results in large-scale flow recirculation. The recirculated flow region acts as a drill, carving more profound into the substrate over time. Eventually, momentum decreases, and shear is reduced so that the injected drug diffuses into the solid substrate with no visible fracture.

*In vitro* assessment of NFLJI revealed that the penetration depth ( $D$ ) is directly proportional to the delivery volume ( $V$ ) and supply pressure ( $P$ ) (Fig. 2 F) according to the relation:

$$D = 10.58 + 17.93V + 0.03P \quad (9)$$

(This equation is only valid for the following threshold  $413 \text{ kPa} < P < 1241 \text{ kPa}$ ,  $0.1 \text{ mL} < V < 1 \text{ mL}$ ).

where  $V$  is the volume (mL),  $P$  is the pressure (kPa),  $D$  is the depth (mm), and the coefficient of determination for this linear model is 75 % ( $r^2 = 0.75$ ).

#### 3.2. *In vitro* analysis of NFLJIs

The maximum force of NFLJI and total work were measured and calculated, and they were found to be directly proportional to the supply pressure (Fig. 3 C D). For NFLJIs employing supply pressure from 413 kPa to 1241 kPa and volume of 1 mL, the mean (SD) maximum force was 0.11 (0.034) N to 0.37 (0.036) N (Fig. 3C), total work was 0.0024 (0.00048) J to 0.015 (0.0017) J (Fig. 3D). For NFLJIs employing 1 mL and pressure from 413 to 1241 kPa, the mean (SD) duration was found to be 0.70 (0.16) s to 0.50 (0.02) s, and this duration showed a reducing trend when the pressure increases (Fig. 3F). Based on the force-time history and Eq (7), the mean (SD) impulses were from 0.072 (0.010) N·s to 0.11 (0.014) N·s (Fig. 3 E).

Further analysis was done by matching the force-time history from the sensor and depth-time history from the high-speed camera. For supply pressures from 413 kPa to 1241 kPa and volume of 1 mL, the NFLJI mean (SD) central stream velocity increases from 55.9 (28.4) m/s to 162.5 (15.3) m/s (Fig. 4A), the estimated jet impingement pressure increased from 706.4 (250.8) kPa to 2530.0 (296.5) kPa (Fig. 4B). The estimated maximum jet penetration pressure was from 52.5 (14.1) kPa to 148.1 (73.4) kPa (Fig. 4C). These three variables were found to be directly related to the supply pressure. The mean (SD) estimated safe depths were 7.5 (1.6) mm to 23.1(13.5) mm (Fig. 4D). An example of pressure estimation is shown in Table S1.

#### 3.3. *In vitro* analysis of needle injections

For delivery flow rates of 1.8, 3.6, 7.2 mL/min and volume of 1 mL, the needle injections created a mean (SD) maximum force of 0.078 (0.0085) N, 0.077 (0.0083) N, and 0.071(0.0068) N, respectively (Fig. 3C). Since the needle insertion speed is 5 mm/s, there is no significant difference among the maximum force of needle injections. The total work of needle injection were 0.0014 (0.00011) J, 0.0019 (0.00007) J, and 0.0036 (0.00008) J, respectively, for the three different flow rates (Fig. 3 D). As for the duration, needle injections of 1 mL fluid using flow rates of 1.8, 3.6, 7.2 mL/min showed respective mean (SD) durations of 40.5 (0.17) s, 24.3 (0.26) s, and 18.1 (0.26) s. Based on the force and time history, the respective impulse for needle injection with

the above-mentioned flow rates were 2.1 (0.24) *-s*, 1.2 (0.16) *N-s*, and 0.77 (0.07) *N-s*. The maximum force of needle injection occurs at the end of insertion (Fig. 3B), leading to a mean (SD) estimated maximum penetration pressure of 527.2 (56.1) kPa.

### 3.4. In vitro comparison between NFLJIs using high or low pressure, and needle injections

High-pressure NFLJI (620 kPa or above) resulted in maximum force and total work values significantly higher than the values of needle injections. Low-pressure NFLJIs (413 kPa), however, featured total work and maximum force similar to those of needle injections (Fig. 3 C&D). Needle injections conversely induced impulse and duration significantly higher than those of NFLJIs (Fig. 3E&F) since the impulse value is directly proportional to the duration.

Upon impinging the soft tissue phantom, low-pressure NFLJI (413 kPa) created a mean (SD) jet impingement force of 0.089 N (0.031), resulting in a mean NFLJI impingement pressure of 706.4 (224) kPa, while the high-pressure NFLJI (620 kPa) created a mean jet impingement force of 0.14 (0.027) N and therefore a mean jet impingement pressure of 1149.8 (194.7) kPa (Fig. 4B). Besides, once the jet penetrated through the phantom surface and started to travel inside, the low-pressure NFLJI resulted in a maximum penetration pressure of 52.46 (14.09) kPa, which is always below 80 kPa; While the high-pressure NFLJI created a maximum penetration pressure of 71.25 (36.66) kPa, indicating a higher risk of nerve damage (Fig. 4 B, C). Needle injections created a maximum penetration pressure of 527.2 (56.1) kPa, which was lower than the jet impingement pressure [706.4 (250.8) to 2530.0 (296.5) kPa], but higher than the maximum jet penetration pressure [52.5 (14.1) to 148.1 (73.4) kPa].

Low-pressure NFLJI had a mean safe depth less than 7.5 (SD 1.4) mm, while high-pressure NFLJI had a mean safe depth above 11.9 (SD 1.9) mm (Fig. 4D). Since there is always a risk of needle tip piercing the nerve for needle injections, there is no safe depth for needle injections.

### 3.5. MINB using NFLJI on cadavers

A total of twenty MINBs were performed on ten cadavers. Twelve injections were performed using NFLJIs (0.3 mL, 120 psi), and eight injections were performed using needles. The simulated success rates of MINB were 83.3% in the needle group and 87.5% in the NFLJI group. No significant difference was found between the two methods regarding the efficacy of MINB (Table 1) (Fig. 2 M&N).

### 3.6. Clinical safety issues of high-pressure NFLJI

A total of five participants (2 males and 3 females) with a median age of 23 (IQR 23–28) were included to evaluate the safety and feasibility of using NFLJI for MINB. This trial was stopped at five instead of six participants because one participant presented temporary nerve paresthesia following NFLJI anesthesia, creating a safety issue.

The recruitment took three weeks with a recruitment rate of 100%, as the study was advertised on social media (Gao et al., 2021). No participants withdrew or reported concerns. Both NFLJI and needle MINB procedures were easily performed intraorally.

High-pressure NFLJIs achieved a preliminary success rate of 60%,

**Table 1**

The success rate of MINB using needle or NFLJI on cadavers.

Interventions	Outcome			
	Success, n (%)	Failure, n (%)	Odds Ratio	p
Needle MINB	7(87.5)	1(12.5)	1	0.79
NFLJI MINB	10(83.3)	2(16.7)	1.40(95% CI, 0.11–18.6)	

whereas needle injections achieved 100%. As for the clinical anesthesia effect (Table 2), the NFLJI group had a median (IQR) time to initial anesthesia of 1.4 (1.2–1.9) min, onset time of 3.5 (2.9–5.5) min, and duration of 252 (198–276) min, whereas the needle group had 1.4 (0.6–2.2) min time to initial anesthesia, 6.0 (4.8–6.5) min onset time, and 182 (146–252) min duration. High-pressure NFLJIs resulted in median (IQR) pain scores of 3.0 (1.5–4.3) and taste scores of 4.0 (3.3–5.0), while the needle group showed median pain scores of 2.0 (1.0–4.0) and taste scores of 5.0 (5.0–5.0) (Fig. 5 C–H).

In terms of complications (Fig. 5 I–M), needle injections caused 2 (40%) cases of bleeding, 0 (0%) cases of laceration, 2 (40%) cases of hematoma, 1 (20%) case of discomfort, and 0 (0%) cases of paresthesia. Meanwhile, high-pressure NFLJIs caused 0 (0%) cases of bleeding, 1 (20%) case of laceration, 2 (40%) cases of hematoma, and most importantly, 3 (60%) cases of discomfort, and 1 (20%) case of paresthesia. Among the 3 participants who had post-procedure discomfort, one had a hematoma (Fig. 5B), followed by nerve paresthesia at the left corner of the lower lip that lasted for two weeks; the other two had mild to moderate pain for three days when pressing the injection sites. Therefore, the pilot study was stopped.

### 3.7. Clinical safety and feasibility of low-pressure NFLJI

The laboratory investigation revealed that low-pressure NFLJI (413 kPa) could achieve similar injection outcomes as high-pressure NFLJI (620 kPa) but with less risk of nerve damage since it created lower total work and maximum force on the soft tissue. Accordingly, another six participants (1 male and 5 females) were recruited for a second pilot RCT to evaluate the safety and feasibility of low-pressure NFLJI. Recruitment time and rate, and the withdrawal rate were the same as previous pilot RCT; no participants reported concerns. One participant was excluded before the procedure because of an unreported root canal treatment on the second premolar in the lower-left region. A total of five participants (1 male, 4 female) with a median age of 23 (IQR 23–28) were included for analysis (Table 3).

MINBs using low-pressure NFLJI achieved a preliminary success rate of 60%, while MINBs using needle injections achieved a rate of 40%. Low-pressure NFLJIs showed a median (IQR) time to initial anesthesia of 0.8 (0.4–1.1) min, onset time of 4.2 (2.5–5.1) min, and duration of 171 (131–195) min, whereas needle injections had a median (IQR) time to initial anesthesia of 1.0 (0.5–1.4) min, onset time of 4.5 (3.7–4.9) min, and duration of 174 (126–219) (Fig. 6A–D). As for the side effects, participants reported a median pain score of 0.8 (0.6–2.6), anxiety score of 0.9 (0.3–3.6), and taste score of 4.0 (3.5–5.0) with NFLJIs, and a median pain score of 1.8 (1.0–2.0), anxiety score of 0.7 (0.0–2.3) and taste score of 5.0 (5.0–5.0) with needle injections (Fig. 6 E–G).

Regarding the complications, the low-pressure NFLJIs induced 1 case

**Table 2**

Demographic and clinical outcomes for the first pilot randomized clinical trial assessing the feasibility and safety of high-pressure NFLJI (620 kPa), and needle injections. Both interventions used 2 % Lidocaine with 1:100,000 epinephrine.

Demographic Outcomes		
Gender (Male/Total), n (%)	2 (40%)	
Age (year), median (IQR)	23 (23–28)	
Clinical Outcomes	<b>NFLJI (n = 5)</b>	<b>Needle (n = 5)</b>
MINB preliminary success rate, n (%)	3 (60%)	5 (100%)
Duration (min), median (IQR)	252 (198–276)	182 (146–252)
Time to initial anesthesia (min), median (IQR)	1.4 (1.2–1.9)	1.4 (0.6–2.2)
Onset of anesthesia (min), median (IQR)	3.5 (2.9–5.5)	6.0 (4.8–6.5)
Pain NRS difference, median (IQR)	3.0 (1.5–4.3)	2.0 (1.0–4.0)
Taste score difference, median (IQR)	4.0 (3.3–5.0)	5.0 (5.0–5.0)
Bleeding, n (%)	0 (0%)	2 (40%)
Laceration, n (%)	1 (20%)	0 (0%)
Hematoma, n (%)	2 (40%)	2 (40%)
Post-procedure discomfort, n (%)	3 (60%)	1 (20%)
Paresthesia, n (%)	1 (20%)	0 (0%)

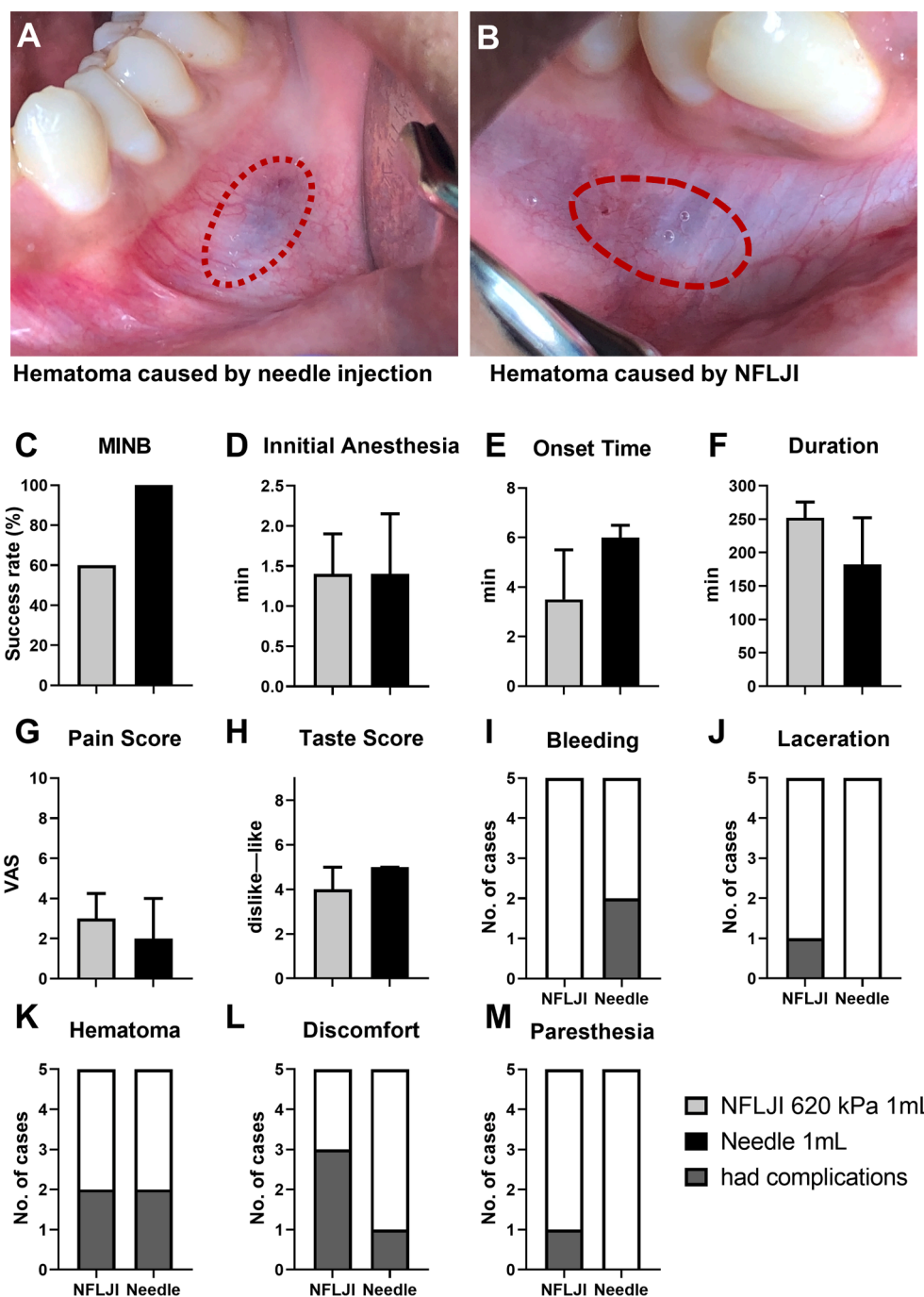


Fig. 5. Cases of hematoma cause by (A) needle insertion and (B) NFLJI. (C-M). Clinical outcome of first pilot study comparing MINB using needle or NFLJI.

of bleeding (20%), 1 case of laceration (20%), 1 case of hematoma (20%), 0 cases of discomfort and paresthesia (0%). The needle injections induced 0 cases of bleeding (0%) and laceration (0%), 1 case of hematoma (20%), 0 case of discomfort (0%) and paresthesia (0%) (Fig. 6 H-L). At the end of the trial, participants were asked to choose their preference between the two techniques. Two participants preferred low-pressure NFLJI because the injection was fast and less painful. The other three participants preferred needle injection as they felt anxious about the novel NFLJI or disliked the noise of NFLJI.

#### 4. Discussion

This study advanced the understanding of how NFLJI parameters affect its penetration in soft tissues and the risks associated with tissue

damage. In addition, an optimal NFLJI technique was developed for MINBs based on *in vitro*, *ex vivo*, and clinical studies. The optimized low-pressure NFLJI technique achieved effective anesthesia while reducing the risk of tissue damage.

##### 4.1. The liquid jet momentum

Our *in vitro* experiments showed that the NFLJI total work and maximum force were directly proportional to NFLJI supply pressure. The increased supply pressure resulted in increased total linear momentum of the liquid jet. This momentum could determine both the penetration depth and the risk of tissue damage. Consequently, the estimated jet pressure upon impingement and penetration is directly proportional to NFLJI supply pressure. This finding can explain why

**Table 3**

Demographic and clinical outcomes for the second pilot randomized clinical trial comparing the low-pressure NFLJI (413 kPa 1 mL) with the needle injection (1 mL). Both interventions used 2 % Lidocaine with 1:100,000 epinephrine.

Outcomes	Low-pressure NFLJI (n = 5)	Needle (n = 5)
<b>Demographic Outcomes</b>		
Gender (Male/Total), n (%)	1 (20%)	
Age, median (IQR)	23 (20–24)	
<b>Clinical Outcomes</b>		
MINB preliminary success rate, n (%)	3 (60%)	2 (40%)
Duration (min), median (IQR)	171 (131–195)	174 (126–219)
Time to initial anesthesia(min), median (IQR)	0.8 (0.4–1.1)	1.0 (0.5–1.4)
Onset of anesthesia(min), median (IQR)	4.2 (2.5–5.1)	4.5 (3.7–4.9)
Pain VAS difference, median (IQR)	0.8 (0.6–2.6)	1.8 (1.0–2.0)
Anxiety VAS difference, median (IQR)	0.9 (0.3–3.6)	0.7 (0.0–2.3)
Taste score, median (IQR)	4.0 (3.5–5.0)	5.0 (5.0–5.0)
Bleeding, n (%)	1 (20%)	0 (0%)
Laceration, n (%)	1 (20%)	0 (0%)
Hematoma, n (%)	1 (20%)	1 (20%)
Post-procedure discomfort, n (%)	0 (0%)	0 (0%)
Paresthesia, n (%)	0 (0%)	0 (0%)

high-pressure NFLJIs showed a high risk of post-operative discomfort and nerve injury while low-pressure NFLJIs had none of these cases.

#### 4.2. A predictive model for penetration depth

Previous studies indicated that NFLJI dispersion and penetration depend on the injector parameters, such as supply pressure, volume, and orifice diameter (Schramm-Baxter and Mitragotri, 2004); operative parameters, such as standoff distance and loading pressure (Rohilla et al., 2020); Young's modulus of tissue (Baxter and Mitragotri, 2005); and the viscosity and density of the injected fluid (Seok et al., 2016). Among these factors, the property of fluid and tissue of the injection site cannot be changed; the operative parameters of NFLJI are predefined using minimal standoff distance and a loading force of 0.3 N for our clinical trial. Therefore, only the injector parameters can be adjusted to optimize the injection outcome. Our study found that NFLJI penetration depth is directly correlated to pressure and volume. These observations are in agreement with previous studies conducted on ballistic gelatin (10% w. t) (Grant et al., 2015) and cadaver skin (Seok et al., 2016), using NFLJI with a volume ranging from 0.2 to 2.5 mL and with a supply pressure ranging from 600 kPa to 20 MPa (Grant et al., 2015; Seok et al., 2016).

In a previous study (Baxter and Mitragotri, 2005), a predictive model was created based on the liquid jet velocity, the nozzle diameter, the tissue's Young's modulus, and the fluid density in the scenario with or without backflow. This model assumed that the flow behaved as a confined jet in a closed tube, implying that the jet center-line velocity decreases approximately linearly with distance. However, the jet velocity reduction was not linear based on the high-speed video of jet penetration and time history (Fig. S2A). The observed jet flow is an impulsive jet with a vortex head. The observations are not consistent with the hypothesis of a confined jet flow.

Nevertheless, this model Eq (2) (Baxter and Mitragotri, 2005) was used with our data to predict the penetration depth based on the jet velocity measured from the high-speed video and compare it with the measured penetration depth, i.e.

$$\frac{v_m}{v_0} = m \left( \frac{x}{D_0} \right) + b \quad (10)$$

where  $v_m$  is the critical center-line velocity required to induce failure,  $v_0$  is jet exit velocity,  $x$  is the jet travel distance, and  $D_0$  is the nozzle diameter. The  $m$  and  $b$  were calculated by attempting a linear regression of the data, which obeyed a non-linear trend.

The predicted penetration depth compared to the real penetration depth showed a high root-mean-square deviation (RSMD) of 54.2 mm (Baldi and Moore, 2013), calculated as:

$$RSMD = \sqrt{\frac{\sum (\hat{y} - y)^2}{n}} \quad (11)$$

Where the  $\hat{y}$  is the estimated depth, and  $y$  is the actual depth obtained from *in vitro* experiment.

The previous model (Baxter and Mitragotri, 2005), which assumes a linear reduction of jet velocity, could only fit 7.8–20.5% of the observed data (Table S2, Fig. S2B). Therefore, a better model assuming non-linear jet velocity reduction in the tissue is desirable to obtain an accurate depth prediction.

#### 4.3. Mental incisive nerve blocks

In our cadaver and clinical studies, MINB anesthesia with NFLJIs had a similar success rate to that achieved with needle injections. This study is the first conducted to assess the use of NFLJI for MINB in either cadavers or clinical practices.

The previous literature on MINB was limited to needle injections only and reported success rates ranging from 50% to 93.8% with lidocaine (Table 4) (Aggarwal et al., 2016; da Silva et al., 2010; Ghabraei et al., 2019; Jaber et al., 2013; Joyce and Donnelly, 1993; Whitworth et al., 2007). This range falls within the success rates obtained with NFLJI and needle injection in cadavers and clinical trials.

The success rate of MINB could be improved by increasing the volume (Brunetto et al., 2008) or the potency of the anesthetic (da Silva et al., 2010; Malamed, 2014). However, high potency is also correlated with high tissue toxicity and a higher risk of nerve paresthesia, especially for mandibular nerve blocks (Garisto et al., 2010). Hence, 2% lidocaine is recommended for patients' safety.

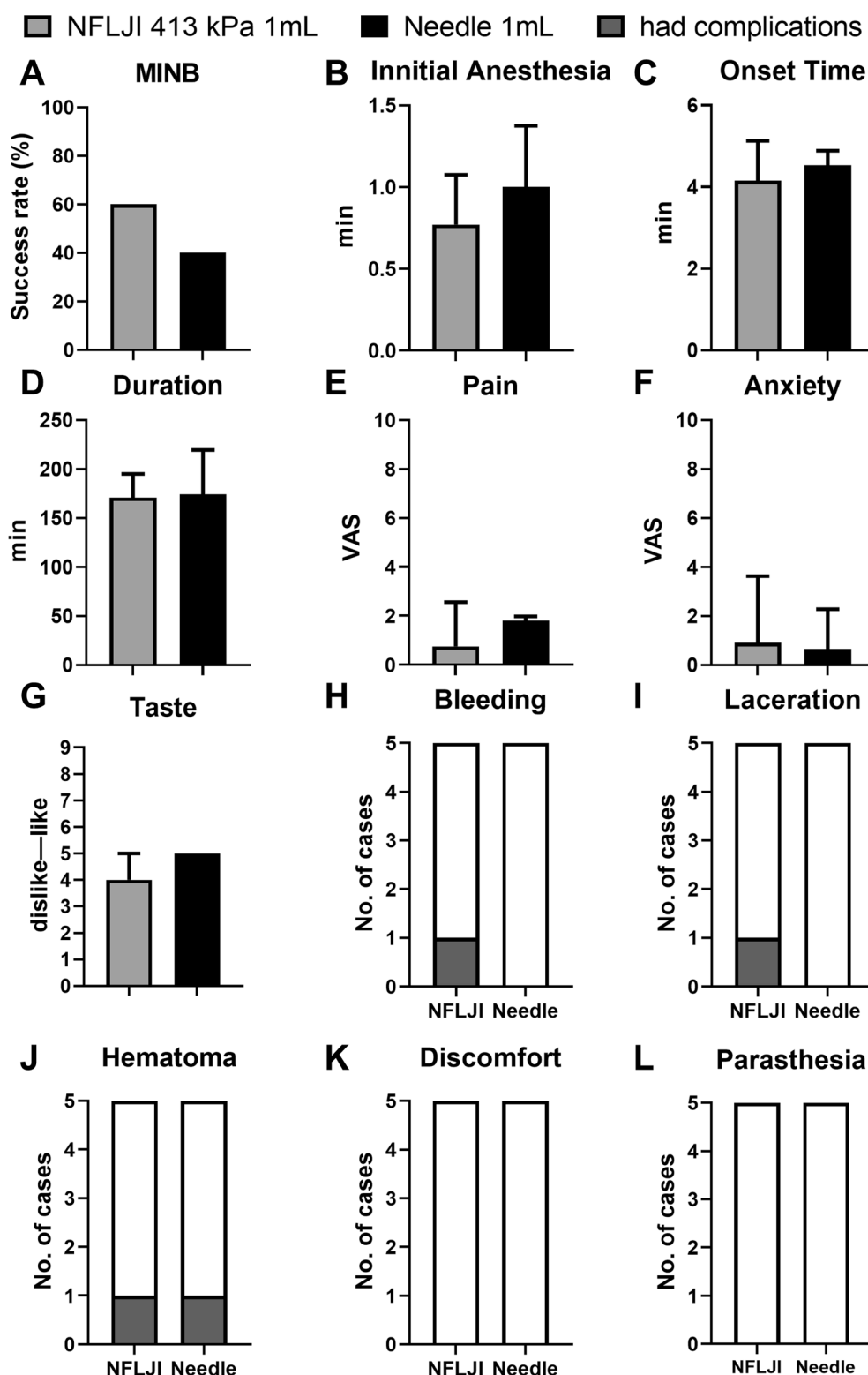
#### 4.4. Complications of NFLJI nerve blocks

In our study, the pressure created by both NFLJIs and needle injections had the potential to injure nerves or blood vessels, leading to paresthesia, hematoma, or discomfort. However, high-pressure NFLJI was more likely to cause these damages because it induced a significantly higher estimated jet impingement pressure and maximum jet penetration pressure compared to those of low-pressure NFLJI and needle injection (Fig. 4 B, C).

One case of mental nerve paresthesia was reported during the first pilot trial using high-pressure NFLJI (620 kPa). Paresthesia is a common complication in which patients present persistent anesthesia or altered sensation beyond the expected duration of anesthesia that can last from days to months (Malamed, 2014). It is usually caused by trauma to the mental nerve or by the pressure from bleeding and hematoma (Malamed, 2014). In our study, the patient first presented a significant hematoma (Fig. 4B) at the mental foramen region after injection before reporting the paresthesia.

Besides a case of paresthesia, high-pressure (620 kPa) NFLJI caused more hematoma (40%) and discomfort (60%) than low-pressure NFLJI, indicating more tissue damage. The low-pressure NFLJI (413 kPa) group caused no discomfort or paresthesia and resulted in only one incident of hematoma (20%). Our *in vitro* experiment shows that this result is probably because low-pressure NFLJIs produce less total work and maximum force in the tissue than high-pressure NFLJIs, causing minor tissue damage.

In addition, one case of laceration was reported with both high- and low-pressure NFLJIs (Fig. S3 E). Our group has previously shown that lacerations were probably caused by jet regurgitation and backflow when the jet impacts hard tissue during perpendicular injection (Fig. S3 F), which can be minimized by employing an oblique injection technique (Gao et al., 2021). Even though the oblique technique was used,



**Fig. 6.** The second pilot RCT to validate the safety of refined NFLJI (n = 5). There was a significant improvement of post-procedure discomfort in the refined NFLJI group compared to the first pilot study, and no parasthesia occurred.

there was still a risk of laceration (Gao et al., 2021). Further studies are therefore needed to eliminate the laceration risk. Other reasons for laceration could be patients' head movement and operators' hand movements during the injection, as reported in our previous study (Gao et al., 2021), or a sharp edge at the nozzle tip.

#### 4.5. The estimated pressure during injection

To explain why lower-pressure NFLJI is safer than high-pressure NFLJI, we need to understand the jet pressure when penetrating soft tissue. For example, the required pressure for a liquid jet to pierce through human skin is 690 kPa (Neal and Burke, 1991), whereas the

**Table 4**

The clinical efficacy of MINB in previous clinical trials.

Reference	Anesthetic	Injection volume	Success cases	Sample size	Efficacy
(Ghabraei et al., 2019)	4% articaine with 1:100,000 epinephrine	1.8 mL	30	32	93.8%
(da Silva et al., 2010)	4% articaine with 1:100,000 epinephrine	0.6 mL	32	40	80%
	2% lidocaine with 1:100,000 epinephrine	0.6 mL	28	40	70%
(Aggarwal et al., 2016)	2% lidocaine with 1:200,000 epinephrine	2.0 mL	27	51	53%
(Jaber et al., 2013)	2% lidocaine with 1:80,000 epinephrine	2.2 mL	33	38	86.8%
(Joyce and Donnelly, 1993)	2% lidocaine with 1:100,000 epinephrine	0.9 mL	30	41	73%
(Whitworth et al., 2007)	2% lidocaine with 1:80,000 epinephrine	2 mL	30	38	78.9%
Total events	4% articaine with	<1 mL	32	40	80%
		>1 mL	30	32	93.8%
	epinephrine	All	62	72	86.1%
	2% lidocaine with	<1 mL	58	81	71.6%
		>1 mL	90	127	70.8%
	epinephrine	All	148	208	71.2%

pressure at which the nerve damage occurs is 80 kPa (Marcol et al., 2012). Therefore, jet pressure must initially be high enough to pierce the skin while delivering drugs within the tissue at a low pressure to prevent nerve damage.

The NFLJI system uses pneumatic pressure to drive a that impacts the liquid to create the jet. The supply pressure of the system, the pressure when the liquid jet exits the nozzle, and the pressure when the jet travels inside the tissue are different due to the energy loss and area difference between the nozzle orifice and wound. Therefore, the pressure generated by the jet when it travels inside soft tissue should be estimated by dividing the instantaneous force measured using the force transducer by the instantaneous area of the jet measured using the high-speed video record.

Our study discovered that both high- and low-pressure NFLJI created imping pressure higher than 690 kPa (Neal and Burke, 1991) to pierce through the skin. However, low-pressure NFLJI can keep a penetration pressure beneath 80 kPa (Marcol et al., 2012) to avoid nerve damage. In contrast, the high-pressure NFLJIs could create a penetration pressure higher than 80 kPa, which increases the risk of nerve damage when jet traveling inside soft tissue.

This observation would explain the nerve paresthesia case that occurred with high-pressure NFLJI in the pilot RCT. It also provided clinical guidance to dentists for selecting proper injector parameters to minimize complications while maintaining the anesthesia outcome.

#### 4.6. Injection pain and pressure

The low-pressure NFLJIs showed a trend of lower pain scores than those of the high-pressure NFLJI group. This trend is presumably because the low-pressure NFLJI caused lower maximum force, total work (Fig. 3 C&D), and maximum penetration pressure (Fig. 4C), hence less mechanical pain stimulus on soft tissue. The relationship between NFLJI pressure and pain feelings warrants further investigation.

Two clinical studies investigating needle injection speed and pain feeling can support this mechanical pain stimulus theory. Slow injections (2 mL/min) create significantly lower pain scores than rapid injection (8 mL/min) on patients receiving mandibular nerve blocks

(Kanaa et al., 2006) or MINBs (Whitworth et al., 2007). Similarly, our *in vitro* experiment for needles demonstrated that slow injection (1.8 mL/min) created lower total work than rapid injection (7.2 mL/min) (Fig. 3D), hence less mechanical pain stimulus on soft tissue.

In our study, a slow-speed needle injection (1.8 mL/min) was used for the needle injection group for patients' comfort. This slow injection gave a relatively lower pain score in the study, making it more challenging to see the difference in pain score between the NFLJIs and the needle injections.

#### 4.7. Strengths, limitations, and future directions

Gelatin (5 wt%) is an acceptable phantom for injection experiments because it has Young's modulus similar to that of oral soft tissue. However, its fracture toughness is significantly lower than that of soft tissue. In addition, when dispersing in gelatin, the vortex jet flow creates a crack by shear force since gelatin is a non-porous material. Meanwhile, the jet diffuses through the porous structure instead of creating a crack when dispersing in soft tissue. This results in smaller wound size and lower regurgitation volume. Therefore, a porous phantom material with more real properties would be desirable for future research.

Our study presented a jet central core velocity based on the momentum force and time and the volume and fluid dentistry; this velocity cannot represent the jet velocity when it exits the orifice. A few methods could calculate jet exiting velocity; for example, the piston speed can be related to the volumetric average jet speed (McKeage et al., 2018), the momentum force, fluid density, and area of the orifice can provide the jet speed when jet impinging on a force sensor (McKeage et al., 2018; Shergold et al., 2006). Though this paper focused on the supply pressure of NFLJI and the correlated risk, further studies are needed to make a link between the NFLJI parameter, jet dynamic velocity, and outcomes.

Our study showed that it is feasible to conduct an RCT with relative safety using low-pressure NFLJI. In addition, the recruitment rate was high if social media was used. Future trials should consider recruiting patients who visit the dental clinic for tooth extraction or filling to get more samples.

Safety is the biggest concern before conducting a formal RCT using NFLJI. Our study presented a pressure estimation to assess the risk of nerve injury and reduced the risk of nerve paresthesia by reducing the injector's supply pressure. However, the injection force was measured using a force transducer, consisting of a net force including the jet penetration or needle injection force, the gravity force of the liquid, and the friction from tissue phantoms. Therefore, the estimated injection pressure might be slightly overestimated than the actual value. A further force calculation considering the type of forces mentioned above would be desirable. In addition, more studies are still needed to minimize the other complications of NFLJI, such as mucosa laceration. As volume and potency influence the anesthesia efficacy, future studies should consider increasing the volume from 1 mL to 1.8 mL since 2% lidocaine has lower potency and efficacy than other anesthetics.

Cadaver experiments and pilot RCTs both indicated that the efficacy of NFLJI is comparable to that of needle injection for MINB. However, with only a total of ten cadavers and ten human subjects in this study, the limited sample size could not ensure strong statistical power to claim non-inferiority in the efficacy of NFLJIs compared to needle injections. A non-inferiority randomized controlled trial using a cross-over design could have sufficient power with 160–492 participants based on statistical simulation ( $\alpha = 0.05$ ,  $\beta = 0.2$ ) (Lui and Chang, 2012). Future studies should report the efficacy of NFLJI and needle anesthesia, the odds ratio, and the frequencies of concordant-discordant results per group. They should run the statistical analysis using a mixed model logistic regression.

## 5. Conclusion

Pneumatic NFLJI penetrates the oral soft tissue deep enough to

deliver anesthetic around the mental nerve foramen effectively. Low-pressure NFLJI is relatively safer than high-pressure NFLJI because the former showed the lower value of maximum force and total work similar to those of needle injection and lower value of estimated jet impingement pressure and maximum jet penetration pressure. Therefore, reducing NFLJI supply pressure can help minimize its complications while still achieving clinical outcomes comparable to needle injections.

On cadavers, the simulated success rates of MINB were 83.3% in the NFLJI group and 87.5% in the needle group. The preliminary clinical success rates of MINB were 60% in NFLJI and 70% in the needle group.

#### CRediT authorship contribution statement

**Qiman Gao:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Anna Henley:** Formal analysis, Investigation, Data curation, Writing – review & editing. **Geoffroy Noël:** Conceptualization, Methodology, Investigation, Writing – review & editing. **Zovinar Der Khatchadourian:** Conceptualization, Methodology, Investigation, Resources, Writing – review & editing. **Doaa Taqi:** Validation, Investigation, Data curation, Writing – review & editing. **Mohammad Abusamak:** Validation, Investigation, Data curation, Writing – review & editing. **Zixin He:** Methodology, Validation, Investigation, Formal analysis, Data curation. **Swen Grøn:** Methodology, Validation. **Rani Taher:** Methodology, Validation. **Karim Menassa:** Methodology, Validation, Investigation. **Ana Velly:** Conceptualization, Methodology, Formal analysis, Writing – review & editing. **Elham Emami:** Conceptualization, Methodology, Writing – review & editing. **Luc Mongeau:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Faleh Tamimi:** Conceptualization, Methodology, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition.

#### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. Mr. Karim Mennasa is the founder of Medial International Technology Canada Inc. and invented the needle-free liquid jet injection system in this study. He has no financial contribution to the study.

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#### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijpharm.2021.121197>.

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