# Assessment of needle tip geometry during infusions into a brain phantom gel

## Evaluación de la geometría de la punta de la aguja durante infusiones en gel de agarosa

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Artículo de investigación científica y tecnológica

***Abstract*—Convection-enhanced delivery (CED) is a promising method to deliver therapeutic drugs directly into the brain that has shown limited efficacy, mainly attributed to backflow, in which the infused drug flows back along the needle track rather than forward into tissue. This study evaluates the effect of sharp and blunt needle tips on backflow length under different flow rates via CED. Infusions were performed in a transparent 0.6% (w/v) brain phantom agarose hydrogel. Backflow length was significantly higher using sharp-tip needles for higher flow rates. No significant differences were observed between tip shapes for lower flow rates. In conclusion, sharp-tip needles present limitations for higher flow rates, which are needed to deliver more drug during shortest times.**

***Index Terms* —backflow, brain phantom gel, convection-enhanced delivery, drug infusion, needle insertion.**

***Resumen*— Convection-enhanced delivery es una técnica para suministrar drogas directamente en el cerebro para el tratamiento de enfermedades del sistema nervioso central. Este método ha mostrado una limitada eficacia atribuida principalmente al fenómeno de backflow, en el cual, la sustancia fluye hacia atrás por fuera de la aguja en vez de alcanzar la región del tejido delante de la punta. Este estudio evalúa el efecto de los tipos de punta plana y biselada sobre el fenómeno de backflow bajo diferentes caudales. Las infusiones experimentales se realizaron en gel de agarosa transparente al 0.6% (w/v). La longitud de backflow fue significativamente mayor para infusiones con aguja biselada a caudales mayores. No se observaron diferencias significativas entre ambos tipos de aguja para caudales menores. En conclusión, agujas con punta biselada presentan limitaciones a mayores caudales, las cuales son requeridas para suministrar mayor cantidad de fármaco durante los procedimientos clínicos.**

***Palabras claves*— Backflow, entrega mejorada por convección, gel de agarosa, infusión de drogas, inserción de aguja.**

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## I. Introduction

CONVECTION-ENHANCED delivery (CED) is a novel technique to bypass the blood-brain barrier and deliver therapeutic drugs over localized zones in the brain for the treatment of disorders and tumors [1]–[4]. This promising method generates a positive pressure at the tip of an infusion catheter to distribute molecules directly through the interstitial spaces of the brain tissue. Although several CED experimental studies have reported promising results[5]–[8], some clinical trials[9]–[12] have been largely unsuccessful due to poor drug distribution in target areas, mainly related with an undesirable effect of backflow, where the infused drug preferentially flows thorough an annular zone around the needle, toward the surface of the brain rather than through of the tissue target [13]. Agarose gel has been reported as a suitable brain phantom to perform infusion experiments to evaluate the effect of infusion rate, insertion velocity, and needle size on the backflow length. These experiments are useful to propose improvements for clinical application of CED [14], [15].

Panse et al. [16] reported experiments in a brain phantom gel using needles of different diameters and configurations aimed at reducing the backflow length. This study evaluated the importance of air bubbles on backflow. However, the potential effects of catheter shape on fluid distributions was not considered. Casanova et al. [17] evaluated the influence of needle insertion velocity on backflow on the agarose gel. These experiments showed that faster insertions reduce the backflow length and damage. Nevertheless, one single tip shape was utilized during those experiments.

Conventionally, needles with a blunt tip are used during insertions and infusions since the tissue reveals smaller damage compared to that produced with other needle tip

shapes [18], [19]. For instance, needles with a beveled tip might increase the risk of damaging or infection during the insertion into the brain. However, recent strategies include designing new shape tips as well as multiport catheters [20], [21] to overcome the limitations of drug distribution in the brain.

Recently, an innovative sharp-tip needle that may reduce backflow by generating smaller local damage during insertion has been developed. Hence, the objective of this study was to evaluate whether a needle with a sharp tip reduces the backflow length during infusion into the agarose gel. We performed in vitro infusion experiments to measure the backflow lengths under combinations of two needle-tip shapes (blunt and sharp) and flow rates. From those experiments, we report the obtained distributions and the backflow lengths for each studied needle. The conducted investigation is relevant for the optimization of tip designs, and the new development of needles for CED applications.

## II. METHODS

### A. *Infusions experiments in agarose gel*

Needle insertions and infusions experiments were performed in samples of 0.6 % (w/v) agarose hydrogel (TreviGel 5000, Trevigen Inc., Gaithersburg, MD) cast into 100 ml Pyrex® beakers (internal diameter 45 mm, height 70 mm). The dye infused into the gel was Evans blue albumin (1:2 molar ratio). The infusion system consisted of a syringe pump driving a 100 µl gas-tight syringe (Hamilton, Reno, NV) coupled to 400 mm of minimally compliant tubing (inner diameter 1 mm, outer diameter 1.58 mm) that was connected to the needle (Fig. 1). Two different needles were used: blunt and sharp tip with 0.36 mm outside diameter (50.8 mm length, Hamilton, Reno, NV) (Fig. 2). The needle was carefully driven by hand with a micrometer attached to a stereotaxic frame (Kopf, Tujunga, CA) to a 20 mm depth at 1.2 mm/s. Infusion started immediately after insertion. In all combinations, the infusion volume was 5.0 µl at a flow rate of 0.3, 0.5, 1, and 2 µl/min.

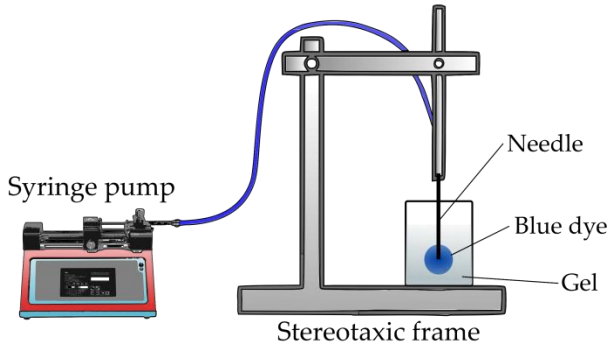


Fig. 1. Schematic of experimental setup for needles testing by CED infusion experiments into agarose gel.

The experiments were repeated ten times for each combination, with 80 measurements in total. Following the infusion, backflow was measured as the length from the needle tip to the point of maximum dye penetration back along the needle track. The measurement was accomplished using the micrometer of the stereotactic frame. In the cases when backflow reached the external surface of the gel, the backflow length was taken to be 20 mm.

### B. *Statistical analysis*

Two-way analysis of variance (ANOVA) was conducted to test whether the means of groups were equal. Means of backflow lengths were compared for the two needle tips (blunt and sharp) and the four flow rates (0.3, 0.5, 1, and 2 µl/min) by using the Tukey's test. Data is shown as mean ± 1 standard deviation and p-values <0.05 were considered significant.

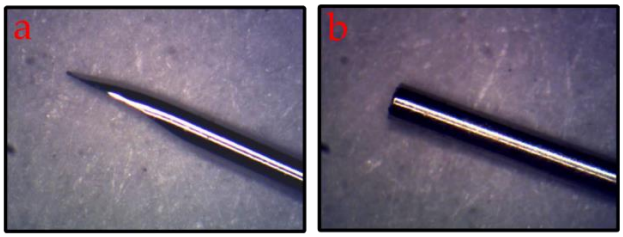


Fig. 2. Needle tips evaluated in the infusion experiments into agarose gel (outside diameter: 0.36 mm). (a) Sharp and (b) blunt tip.

## III. RESULTS

### A. *Backflow length during infusions*

Representative dye distributions were spherical and symmetrical for lower flow rates (0.3 and 0.5 µl/min) and both needle tips. In contrast, infusions with higher flow rates (1 and 2 µl/min) showed irregular dye spreads for both type of needles (Fig. 3).

The ANOVA revealed significant main effects and interaction effects. Backflow length was significantly smaller for the 0.3 µl/min flow rate compared to those for the other three flows (p-values = 0.01, 0.00, and 0.00 for 0.5, 1, and 2 µl/min, respectively.) The average backflow length was 9.7±5.44, and 13.9±6.66 mm for the blunt and sharp tip, respectively. For the flow rates 0.3, 0.5, 1, and 2 µl/min the average backflow length was 5.2±2.3, 11.9±5.5, 14.0±5.5, and 16.0±5.6 mm, respectively.

Simple main effects analysis showed that for the sharp tip needles, the backflow length was significantly greater for higher flow rates, while for the blunt tip needles, only the backflow length for 0.3 µl/min was significantly smaller than that for the 2 µl/min flow rate. (p-value = 0.021). For the 1 µl/min and 2 µl/min flow rates, the backflow length was

significantly higher for sharp tip needles than that for blunt tip and no significant differences with respect to needle tip type were found at the 0.3 and 0.5 µl/min flow rate (Fig. 4).

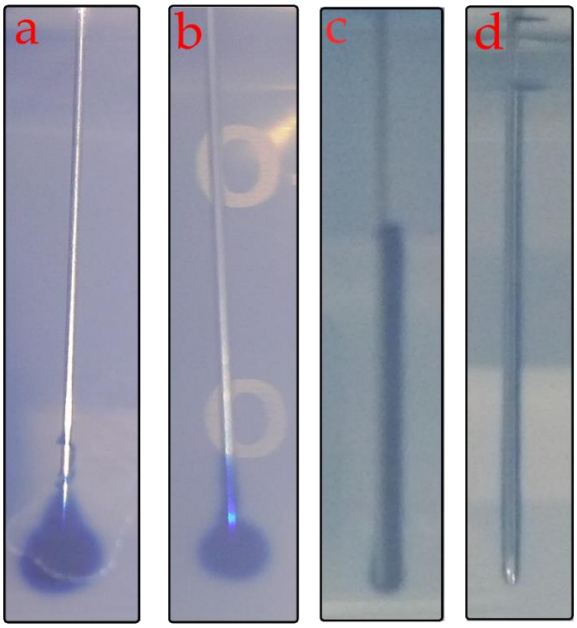


Fig. 3. Typical dye distributions in agarose gel for each needle tip: (a) blunt tip with low flow rate, (b) sharp tip with low flow rate, (c) blunt tip with high flow rate, (d) sharp tip with high flow rate.

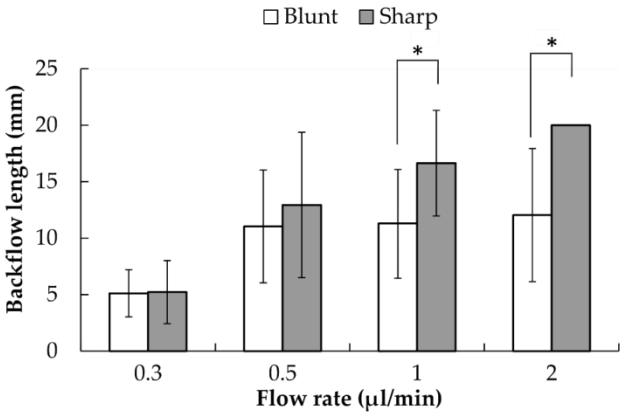


Fig. 4. Average backflow length for each needle tip type at different flow rates with $n = 10$ (* indicates $p$-value < 0.05).

## IV. DISCUSSION

In the present study, we performed infusions in agarose gel with two needle tip types and four different flow rates to determine the effect of each tip on the backflow length. The dye distributions and the backflow lengths were similar for both tips at lower flow rates. The greater backflow produced during the infusions with sharp tip needle might be related to the lack of symmetry of the needle and the local damage generated during the insertion. In this process with sharp tip needle, the agarose gel is mainly compressed on one side and might produce a wider gap between the external surface of the needle and the phantom tissue.

Similar results with both needles were obtained for low flow rate values, however, as the flow rate was increased, backflow was greater for sharp tip needle. In contrast, the increase of flow rate using blunt tip needle did not significantly affect the backflow lengths. This is a relevant result for future clinical applications, since higher flow rates provide high amount of therapeutic and reduce the operation time.

The mechanical response of phantom material during the insertion for each needle tip might explain the differences on fluid distributions. The axial force in the sharp tip could have been higher during penetration into the agarose gel than the blunt tip. Gerwenet al. [18] reported variations in the axial forces for different needle tip shapes during insertion into distinct materials. Based on this, a blunt needle cuts more easily than a sharp one, hence sharp needles tend to create more damage in the material during the insertion. Shergold et al. [22] reported different behavior of the axial force with sharp needle in comparison with blunt needle. In those experiments, they documented that the sharp tipped needle penetrates by the formation and opening of a planar crack, while a blunt needle penetrates by the propagation of a ring crack and subsequent higher deformation of the tissue. These findings might explain why often backflow appears during the infusion with the sharp needle contrasted with the blunt needle, where the fluid is restricted by the radial compressive deformation after insertion.

In conclusion, our results suggest that sharp tip needle is not a suitable catheter for insertions and CED infusions into brain phantom gel for higher flow rates. However, future infusions in animal brain tissue should be carried to determine whether this tip might be appropriate for CED in brain tissue.

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