Backflow reduction in local injection therapy with gelatin formulations

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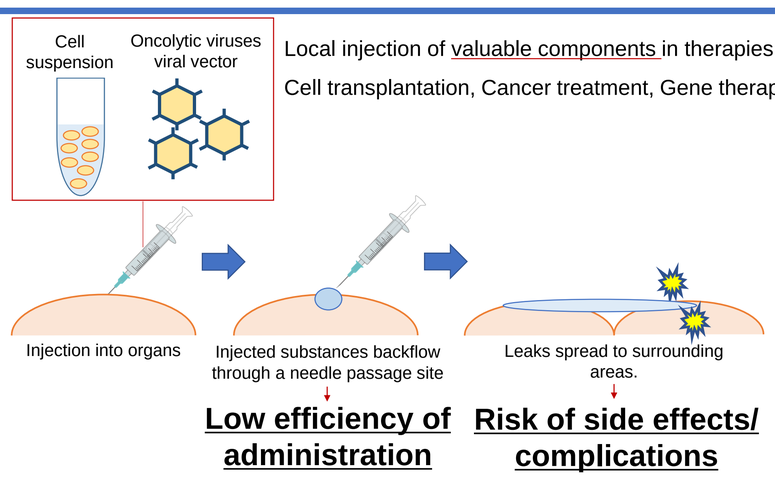
Introduction

The local injection of therapeutic drugs, including cells, oncolytic viruses and viral vectors, into different organs is an administrative route used to achieve high drug exposure at the site of action.

However, after local injection, material backflow and side effect reactions can occur. Hence, this study was carried out to investigate the effect of gelatin on backflow reduction in local injection.

We injected gelatin particles (GPs) and hydrolyzed gelatin (HG) into tissue models with the aim of preventing leakage after local injection.

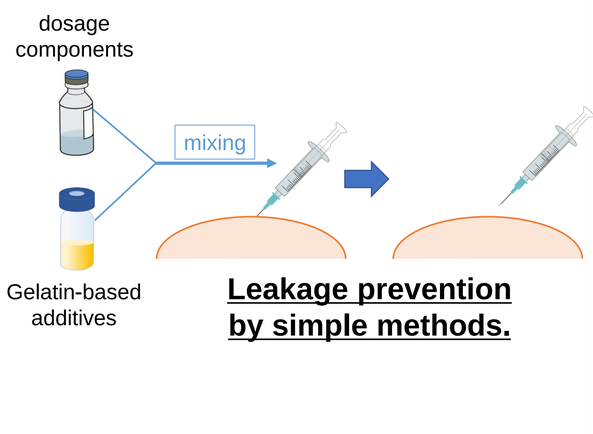


Local injection of valuable components in therapies

Cell transplantation, Cancer treatment, Gene therapy, etc.

Low efficiency of administration

Risk of side effects/ complications

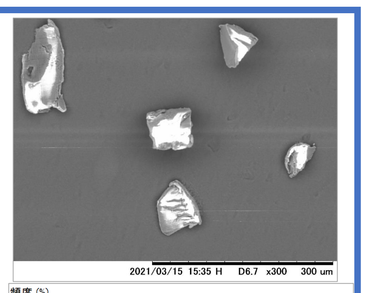


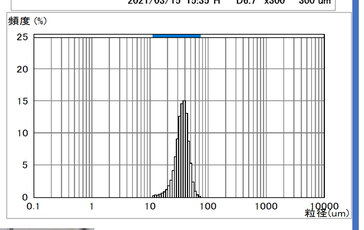
Leakage prevention by simple methods.

Materials

■ Gelatin particles (GPs)

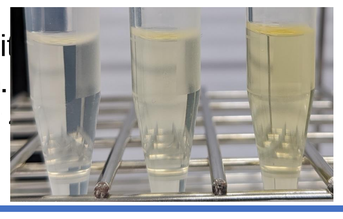
- Raw material: alkali-treated gelatin
- Method of production
  Gelatin is crushed, classified on a sieve and then thermally dehydrated and cross-linked at 150° C for 24 hours. This is dispersed at a concentration of 1-5%.
- Particle size distribution
  Average 35 micrometres, as shown on the right.





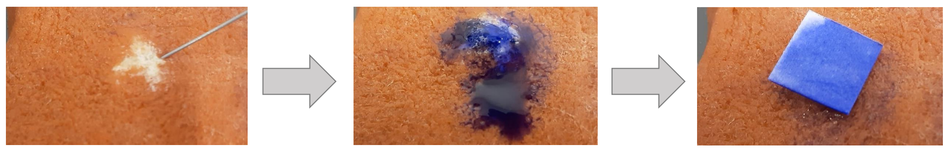
■ Hydrolyzed gelatin (HG)

- Raw material: alkali-treated gelatin
- Method of production
  Gelatin was autoclaved under acidic conditions to reduce i
  weight. This is then dissolved at a concentration of 5-40%.
- Molecular weight: Weight average molecular weight about



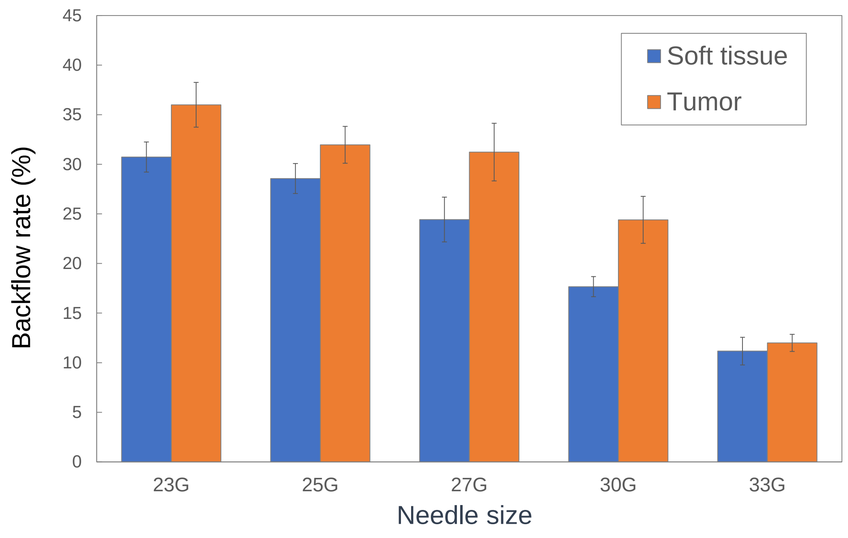
Method

The tissue models was versatile training tissue (VTT) which are simulated organs for medical training whose touch, strength and elasticity are similar to those of human tissue. (manufactured by KOTOBUKI, Medical, Inc., Japan.)



Injection procedure with VTT mock tissue and dye liquid (PBS colored with bromophenol blue for photography). The backflow was collected with filter paper immediately after needle removal.

Result 1 Leakage after injection into VTT



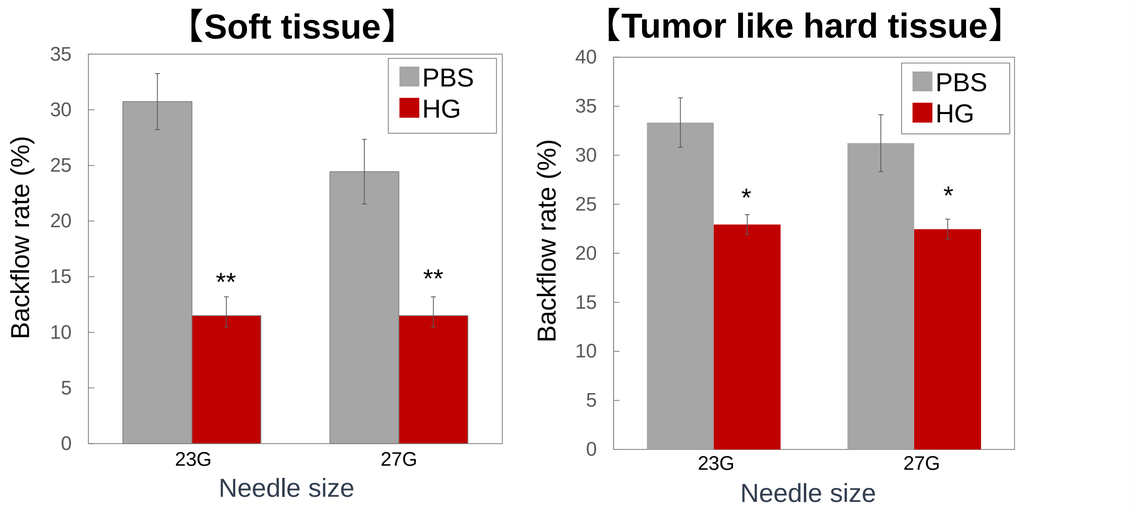
Needle size	Outer diameter (mm)
23G	0.66
25G	0.51
27G	0.41
30G	0.31
33G	0.20

Backflow rate (%) formula
{Weight of liquid absorbed by filter paper (mg)/200} x 100

n=3 (Means ± S.E.)

- Leakage was lower when a needle with a smaller outer diameter was used.
- A tendency for leakage to occur more easily in tumor area than in soft tissue was observed.
- As the two trends are similar to those for injections into living tissue, the experiment using VTT was considered to have a certain reasonable validity.

Result 2 Leakage control effect of HG

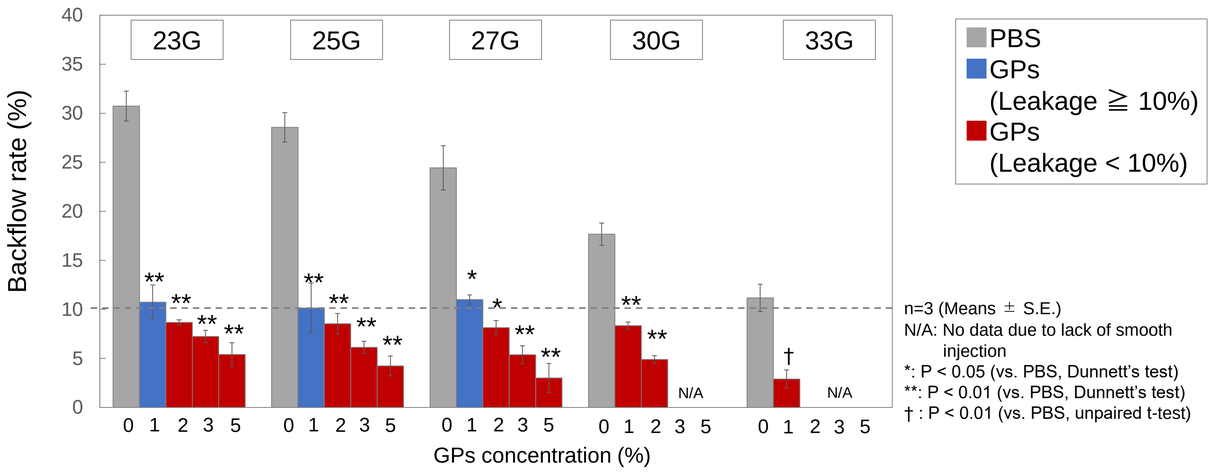


n=3 (Means ± S.E.), *: P < 0.05 (vs. PBS, unpaired t-test), **: P < 0.01 (vs. PBS, unpaired t-test)

- The HG solution inhibited leakage after injection into soft tissues.
- Injection into hard tissues had a limited effect on leakage inhibition.
- The HG concentrations at which leakage was lowest differed depending on the needle: at 23G, leakage was most inhibited at 40% and at 27G, at 20% solution.

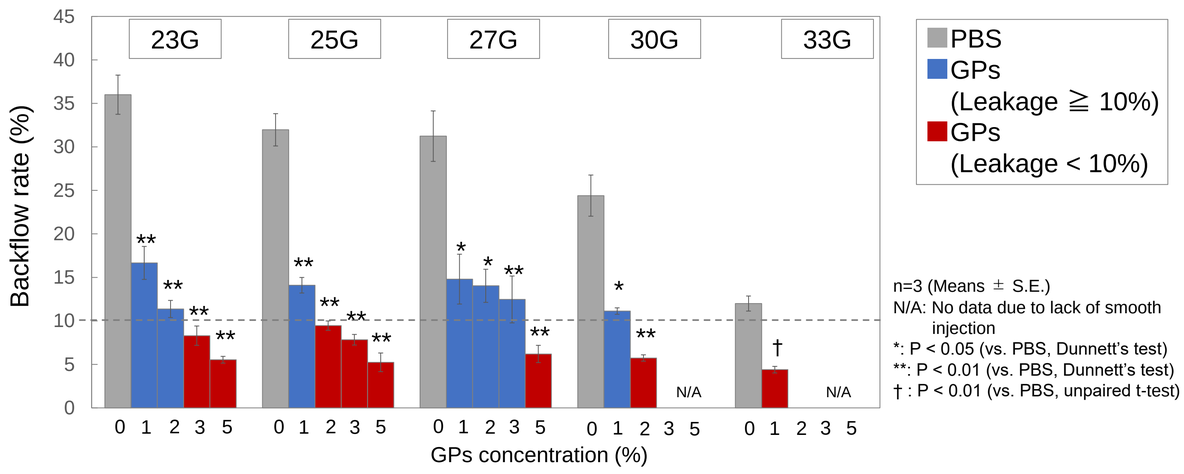
Result 3 Leakage control effect of GPs

【Soft tissue】



n=3 (Means ± S.E.)
N/A: No data due to lack of smooth injection
*: P < 0.05 (vs. PBS, Dunnett's test)
**: P < 0.01 (vs. PBS, Dunnett's test)
† : P < 0.01 (vs. PBS, unpaired t-test)

【Tumor like hard tissue】



n=3 (Means ± S.E.)
N/A: No data due to lack of smooth injection
*: P < 0.05 (vs. PBS, Dunnett's test)
**: P < 0.01 (vs. PBS, Dunnett's test)
† : P < 0.01 (vs. PBS, unpaired t-test)

- A tendency was observed for hard tumour-like areas to be more difficult to control leakage than soft tissue.
- In both cases, leakage after injection could be significantly reduced by adjusting the fines concentration to the extent that ease of administration was not compromised.

Conclusion

- An optimal concentration of GPs or HG can prevent material backflow in local injection.
- Further studies with active drugs are necessary to investigate the applicability in tumor and organ injections.

In fields such as cell transplantation, where leakage after local injection is an issue, mixing gelatin is expected to improve yield in a simple and safe method.

	Gelatin Particle	Hydrolyzed gelatin
Property	Water-insoluble fine powder Average size 35 μm	Non-gelation Dissolvable at room temperature
How to use	Dispersed in the dosing solution at a concentration of 1-5 %.	Dissolve in dosing solution to a concentration of 5-40 %.
Leakage reduction in soft tissues	○ Large decrease	○ Large decrease
Leakage reduction in hard tissues	○ Large decrease	△ Significant but not large decrease
syringeability	○ Available with fine injection needles up to 33G.	◎ Smooth administration even with an ophthalmic 38G cannula
Interaction with cells	Cells will adhere to gelatin particles.	Promotes cell adhesion Inhibits cell-cell aggregation

Articles information

1. More details
Kotani, K., et al. (2024). Backflow reduction in local injection therapy with gelatin formulations. Drug Delivery, 31(1), 2329100.

2. Application example
Kitahata, S., et al. (2024). Investigation of the effectiveness of gelatin hydrolysate in human iPS-RPE cell suspension transplantation. Regenerative Therapy, 25, 238-249.