



Use of Injectable Alginate-Based Hydrogel in Head and Neck Submucosal Hydrodissection: A Feasibility Study

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Introduction

Biocompatible injectable solutions have become advantageous in medical procedures requiring separation of tissue via injection hydrodissection (IH). This technique employs a pressurized injection of fluid to divide tissue or separate adhesions less traumatically than ordinary sharp dissection. IH is of particular importance in oncologic resection, where clear delineation between tumor and healthy tissue prior to excision is required for optimal patient outcomes. For example, IH has been effectively utilized in polypectomy and endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) of gastrointestinal (GI) neoplasms.^{1,2} In EMR and ESD, IH materials create a separation between surface mucosa and muscle or deeper tissue layers, enabling conservative, precise excisions and thorough en bloc resections, facilitating adequate tumor margins and reducing risk of local recurrence. Additionally, IH can help minimize intraoperative complications through elevation of target lesion away from critical neurovascular structures, reducing risk of thermal injury, hemorrhage or other tissue damage. Due to the myriad of important tissue and neurovascular structures in close proximity within the confined anatomy of the head and neck, IH carries great potential application to EMR/ESD of oropharyngeal head and neck cancers (HANC).

Many different solutions and materials have been used in submucosal injection and evaluated for height and duration of tissue separation. These materials each carry limitations including cost, short duration of tissue separation, limited tissue elevation, or high viscosity compromising injectability. Aleo BME Inc. has developed a series of shear-thinning fluid gel compositions (Tisseparation solution; **Figure 1**), mainly comprised of sodium alginate as the gelling component and calcium ion as the crosslinker, to facilitate the safe and efficient removal of lesions via EMR/ESD. While Tisseparation solutions have shown success in GI neoplasm management, their performance in oral and oropharyngeal cancer has not yet been evaluated.³ Thus, this feasibility study sought to determine if such hydrogels could be applied in the HANC setting using an ex-vivo porcine model.



Figure 1: Tisseparation Solution. X-high, High, Medium, Low and X-low viscosity Tisseparation solutions in 10mL syringes used for injection.

Methods

To determine injectability and tissue elevation properties of Tisseparation solution, the investigators conducted initial investigation in an ex-vivo porcine model. Tisseparation solutions at 5 different viscosity range (X-High, High, Medium, Low, X-Low) were prepared by varying the concentrations of alginate and crosslinkers, and all solutions displayed shear-thinning properties (**Figure 2**). To identify suitable Tisseparation solution viscosity for tissue injection, 1mL subcutaneous injections were performed using an 18-gauge needle and 10mL syringe. Using suitably viscous solution, injections were then attempted across head and neck anatomic subsites potentially amenable to hydrodissection, including tongue, floor of mouth (FOM), buccal mucosa, tonsil, and vallecula to identify anatomic regions most suitable for further testing. Successful injections were measured for dimensions of tissue spread and elevation 15 minutes after injection. Finally, injections were performed in quadruplicate across 7 anatomic subsites (3 tongue, 1 FOM, 1 vallecula, 1 tonsil, 1 buccal mucosa) in coronally bisected porcine models. Tissue elevation was measured for each injection to assess site-specific efficacy.

Shear-Thinning Behavior of Tisseparation Solution

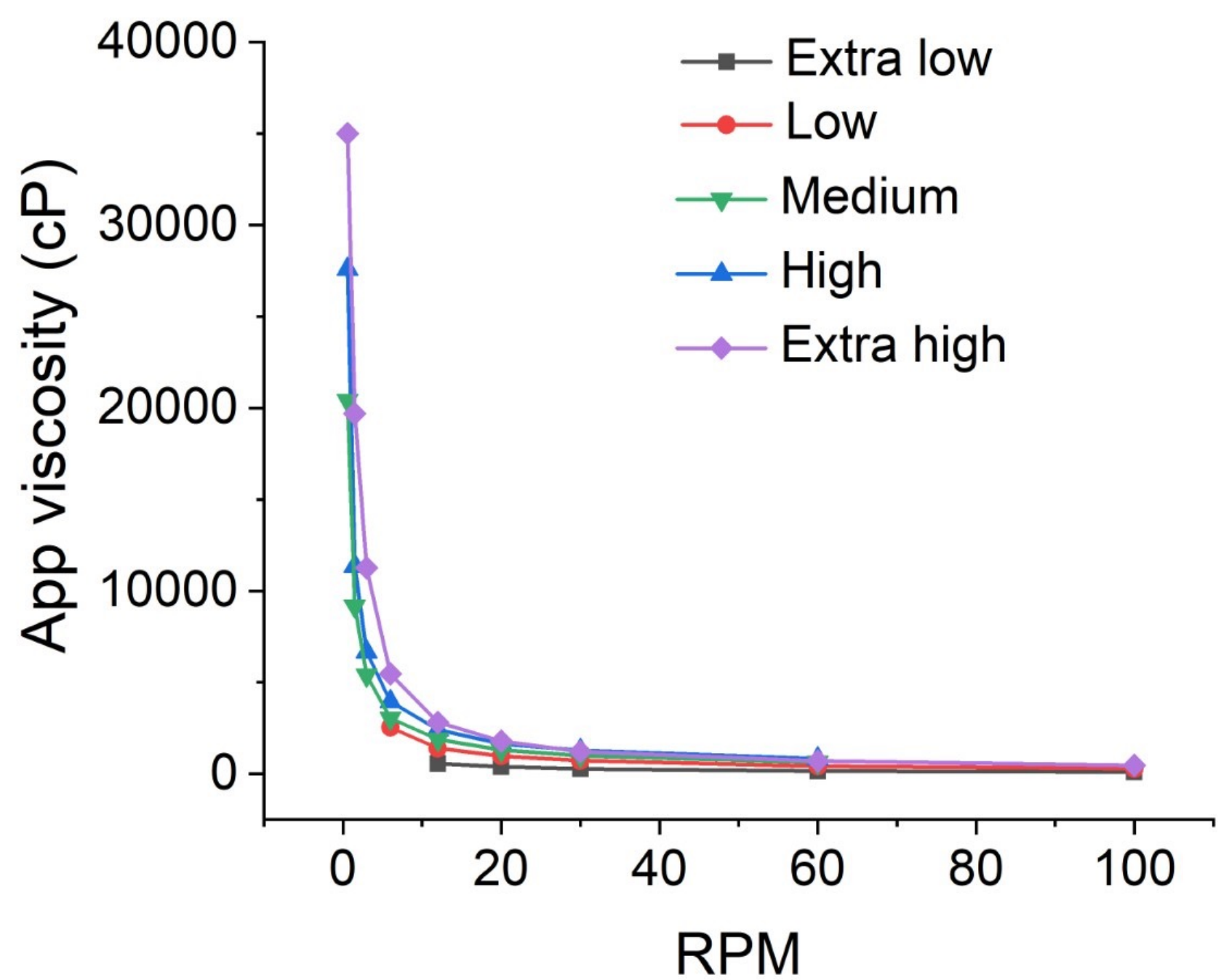


Figure 2: Shear-Thinning Behavior of Tisseparation Solution. Shown at 5 different viscosity range (X-High, High, Medium, Low, X-Low).

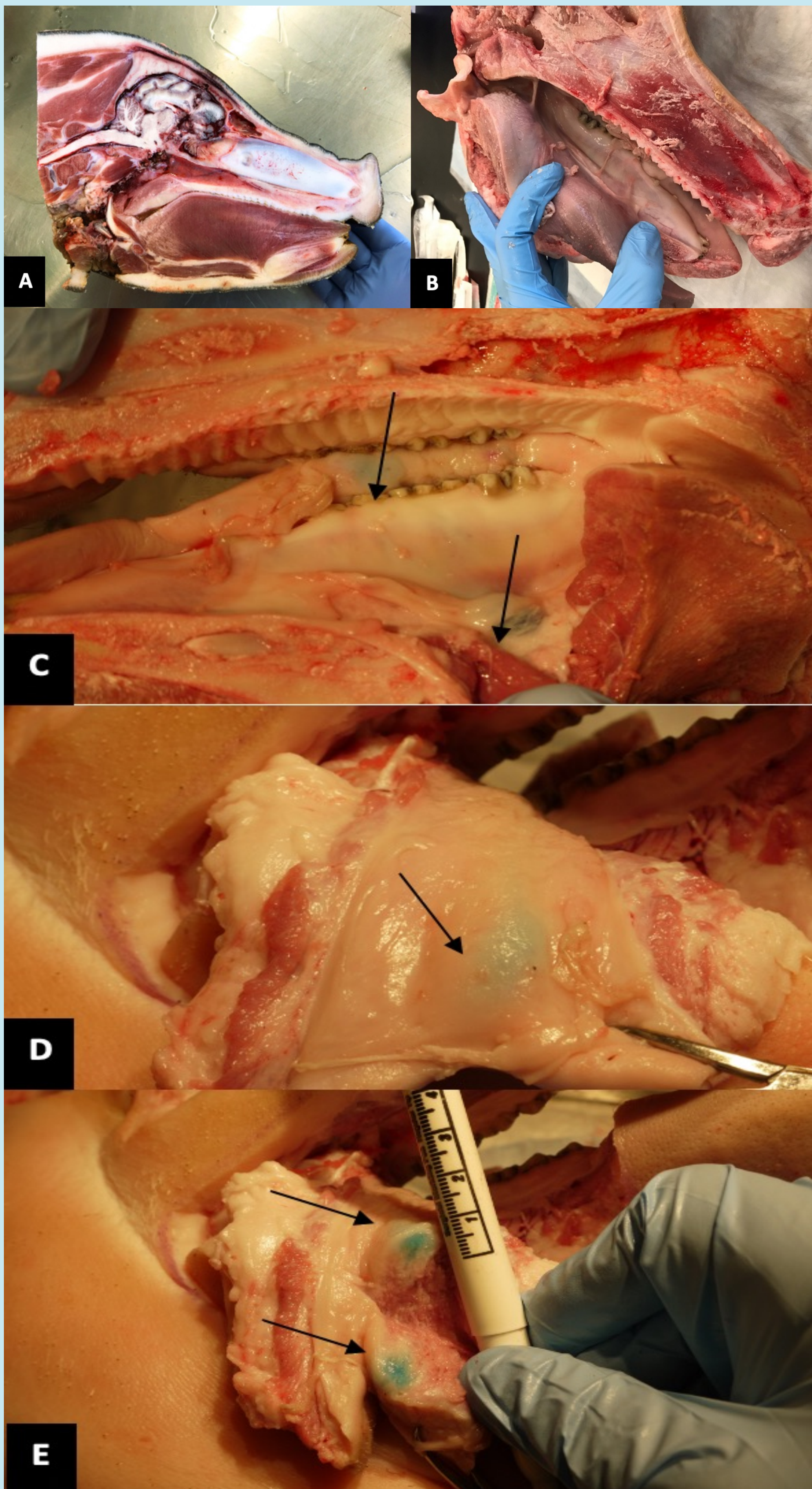


Figure 3: Porcine Ex-Vivo Injection Model. Coronally bisected porcine head used for injection testing with visible anatomic subsites of interest. **A:** Lateral view showing tongue (1), nasopharynx (2), oropharynx (3) and epiglottis (4). **B:** Visible buccal mucosa (5) and anterior tonsillar pillar (6). **C:** Submucosal Tisseparation injection of buccal mucosa and floor of mouth (arrows). **D:** Buccal mucosa submucosal elevation retained after 15 minutes (arrow). **E:** Bisected of Tisseparation injection demonstrating significant submucosal elevation from deeper tissue (arrows).
Figure 3A image from Sauropod Vertebra Picture of The Week <https://svpow.com/2018/12/04/what-half-a-pig-head-looks-like/>

Results

At 12rpm, apparent viscosities of the X-High through X-low Tisseparation solutions were 2815cP, 2415cP, 1890cP, 1400cP and 555cP, respectively (**Figure 2**). Preliminary testing demonstrated “X-low” and “Low” viscosity solutions extravasated from porcine tissue without obtaining sufficient submucosal elevation, while “High” viscosity solution obtained the best tissue elevation without significant extravasation or compromising its ease of injectability.

Injections were then attempted using high viscosity solution in a variety of head and neck potential subsites to identify appropriate oral and oropharyngeal anatomic subsites for potential Tisseparation hydrodissection application. Successful injections were measured for dimensions of tissue spread and elevation. These injections showed best planar spread and elevation in the FOM (24 x 17x6mm, 30x18x4mm) and peritonsillar (23mm x 13mm x 4mm) subsites.

Repeated injections performed in quadruplicate across 7 anatomic subsites (**Figure 4**) showed mean IH tissue elevation of 6.4mm across all anatomic subsites (range 4.0 - 9.3mm). Greatest mean elevation was seen in FOM (9.3mm), vallecula (8mm), buccal mucosa (7mm) and tonsil (6.5mm).

Mean Tissue Elevation of Tisseparation Solution Injection By Anatomic Subsite

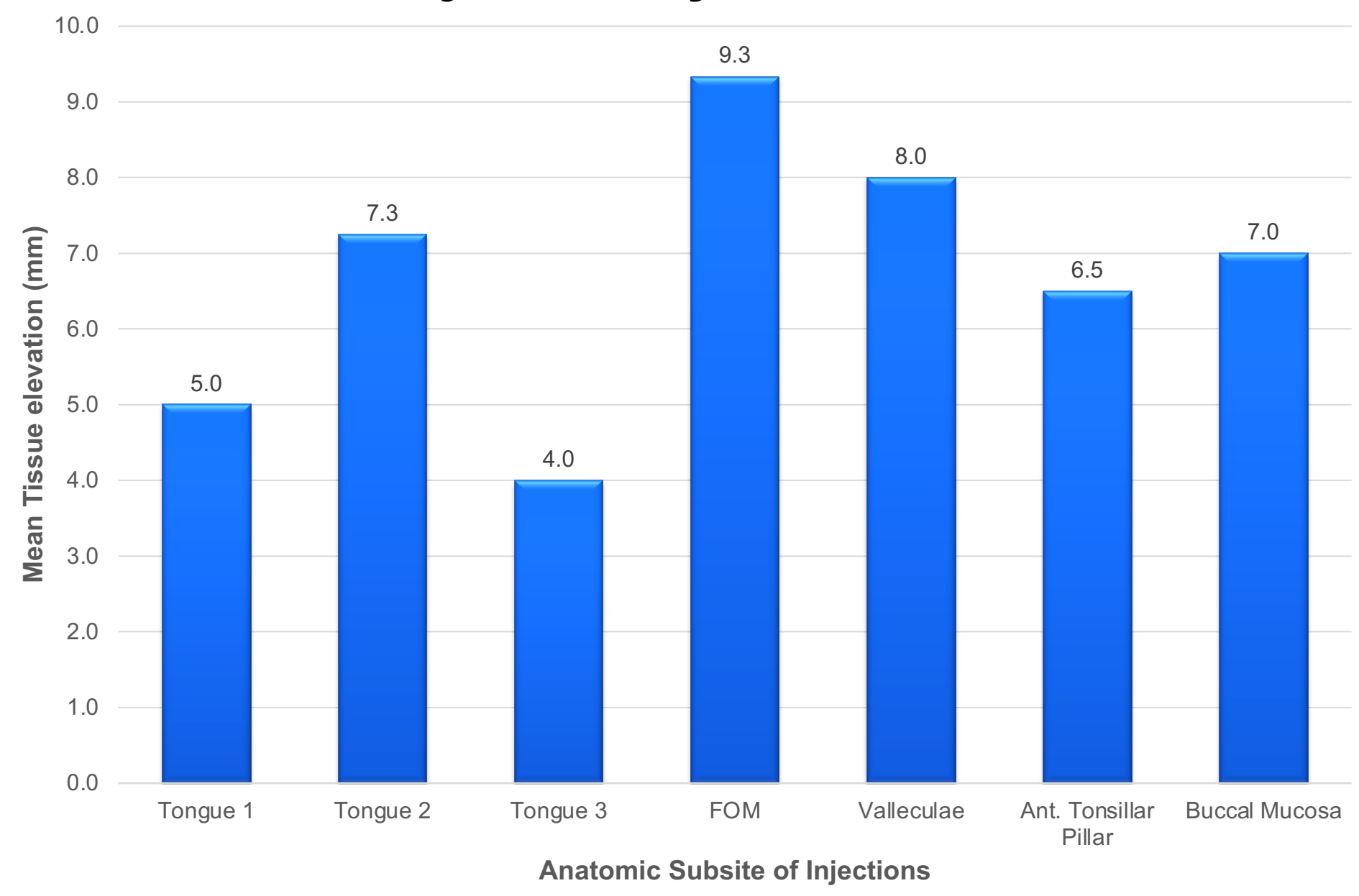


Figure 4: Mean Tissue Elevation of Injected Tisseparation Solution by Anatomic Subsite. Mean tissue elevation (mm) shown for quadruplicate injections across multiple tongue sites, floor of mouth, vallecula, anterior tonsillar pillar and buccal mucosa.

Discussion

One area of great potential application of IH is in EMR and ESD of superficial oral, oropharyngeal and hypopharyngeal carcinomas. While oropharyngeal disease may be detected at advanced disease stage requiring extensive surgical resection and/or chemoradiation for curative treatment, improvements in endoscopic imaging have increased detection of early-stage pharyngeal cancers, providing the option of minimally invasive endoscopic surgical resection.^{4,5} As with GI and esophageal neoplasms, successful en bloc resection of oral and oropharyngeal cancer can prevent positive surgical margins and local recurrence. Though IH has shown benefit in head and neck procedures such as septoplasty and tonsillectomy, it has not yet been explored in HANC.^{6,7} Our results demonstrate that Tisseparation solution may carry utility for en bloc cancer resection due to effective and long-lasting tissue elevation across a variety of head and neck anatomic subsites. It represents a novel tool in assisting surgical resection of HANC.

Conclusion

This feasibility study demonstrates the potential utility of injectable alginate-based Tisseparation solution toward head and neck tissue hydrodissection. Greatest applicability was shown in anatomic subsites with higher tissue flexibility including FOM, tonsil, and buccal mucosa. Future directions include additional ex vivo porcine experimentation with head and neck tissue hydrodissection and in vivo animal testing toward clinical application in OPSCC.

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