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Does endoscopic balloon dilatation improve intranasal drug delivery to the olfactory cleft? A pre-clinical cadaver feasibility study

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Main Article

Mr S Leong takes responsibility for the integrity of the content of the paper

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Abstract

Background. Although systemic steroids have been shown to improve olfactory function, topical steroids have not demonstrated the same efficacy. This could a result of limited drug delivery to the narrow, superiorly placed olfactory cleft. This study aimed to examine the penetration of intranasal drugs to the olfactory cleft following endonasal balloon dilatation.

Methods. Balloon dilatation was performed in 12 thawed, fresh-frozen cadaver specimens. In the Mygind position, nasal drops mixed with blue food dye were administered into the nostril before and after the dilatation procedure. Endoscopic videos were recorded to assess dye staining of the olfactory cleft and osteo-meatal complex using a 4-point Likert scale.

Results. Prior to balloon dilatation, the mean penetration of nasal drops into the olfactory cleft was 1.34, which improved significantly ($p < 0.05$) to 2.66 following the procedure. There was no change in dye penetration into the osteo-meatal complex after balloon dilatation.

Conclusion. The results of this exploratory study suggest that balloon dilatation may improve the delivery of nasal drops to the olfactory cleft area. The clinical applicability and impact on olfactory function will require further assessment.

Introduction

During the process of smelling, odorant molecules enter the nose and cause stimulation of the olfactory sensory neurons at the olfactory epithelia, located mostly at the olfactory cleft. The olfactory cleft is a narrow space (1–2 mm wide) located at the nasal roof, between the cribriform plate superiorly, the superior nasal septum medially, and the superior part of the medial aspect of the middle turbinate and superior turbinate laterally.[1,2]

Olfaction impairment is common, affecting 18–20 per cent of the general population, reaching up to 25 per cent in subjects aged over 50 years.[3,4] A prevalent cause of olfaction impairment is sinonasal disease (chronic rhinosinusitis with or without nasal polyposis), which constitutes 72 per cent of cases.[5] Steroids, with their anti-inflammatory and immunosuppressive effects, are considered a well-accepted treatment for this impairment.[6] Nonetheless, while systemic steroids have been proven to improve olfactory function, topical steroids have not shown the same efficacy as the systemic therapy. A possible explanation is delivery problems of the topical agent to the narrow, highly located olfactory cleft.[7] Long-term systemic steroid therapy might cause serious side effects.

Balloon catheter dilatation is an established, minimally invasive procedure for treatment of rhinosinusitis.[8] The technique is based on the Seldinger technique, in which a guidewire is placed in the narrow chamber it is intended to expand, and then a balloon dilatation catheter is advanced over the guidewire into the targeted ostium. The balloon is gradually inflated to 8–12 atmospheres of pressure to dilate the thin space by compressing the mucosa and by creating micro-fractures in the bone surrounding the narrow space.[9]

A recent study showed the feasibility of dilatation of the olfactory cleft.[8] That study was conducted on three subjects with constitutional stenosis of the olfactory cleft and hyposmia. No complications were described during or after the procedure, and the patients' olfaction performance improved following it.

The current exploratory study aimed to examine how balloon dilatation of the olfactory cleft may affect drug penetrance into this anatomical area. Improved delivery of topical steroids to the olfactory cleft may have clinical applicability in patients suffering with olfaction impairment.

Materials and methods

Ethical considerations

This study was approved by the Central University Research Ethics Committee of the University of Liverpool (reference number: 4473). Twelve thawed, fresh-frozen adult

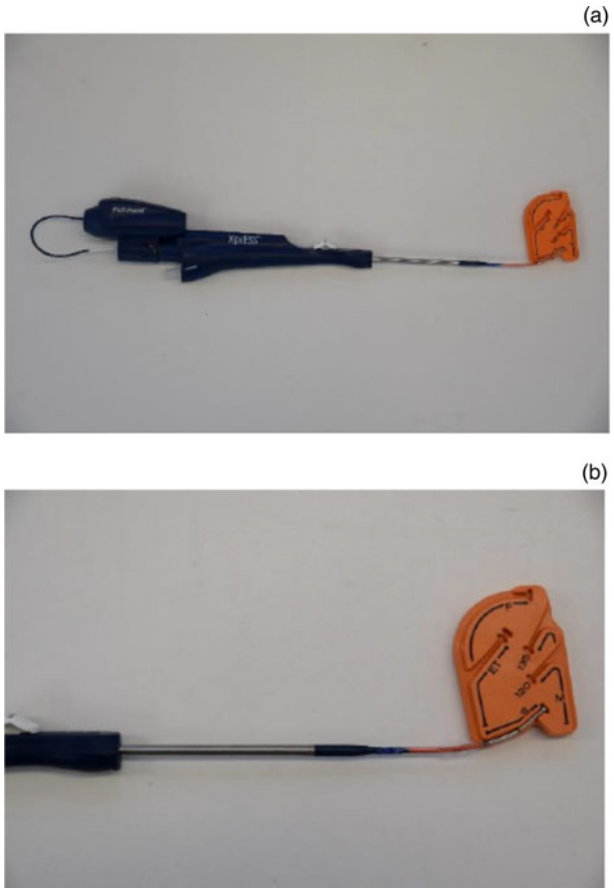

Fig. 1. (a) A 6 mm diameter balloon of the XprESS LoProfile ENT dilatation system (Stryker Entellus Medical). (b) The malleable tip of the device was configured for the sphenoid sinus using the supplied bending tool.

cadaver heads – 24 nasal cavities in total – were available for this study. The specimens were defrosted 8–10 days before the procedure and no signs of post-mortem oedema were observed.

Balloon dilatation of olfactory cleft

A fellowship-trained rhinologist undertook all endoscopic endonasal balloon dilatation. The procedure followed the previously described technique.[10] Balloon dilatations were performed with a 0-degree rigid endoscope connected to a monitor and camera system (Karl Storz, Tuttlingen, Germany). The 6 mm diameter balloon of the XprESS LoProfile ENT dilatation system (Stryker Entellus Medical, Plymouth, Minnesota, USA) was utilised in this study (Figure 1a). The malleable tip of the device was configured for the sphenoid sinus using the supplied bending tool (Figure 1b).

The anatomical insertion of the middle turbinate to the skull base was then identified. An imaginary horizontal line was drawn across the leading edge of the turbinate, bisecting the half of the vertical height between the skull base and the inferior free edge of the middle turbinate. The tip of the dilatation device was advanced under direct endoscopic vision into the area between the nasal septum and the middle turbinate to the line bisecting the half-height of the middle turbinate (Figure 2a). With the balloon device held stable, the light-emitting diode light fibre was advanced to facilitate endoscopic confirmation of the tip with the skull base. The balloon was then inflated for 20 seconds using the supplied inflation syringe (Figure 2b).

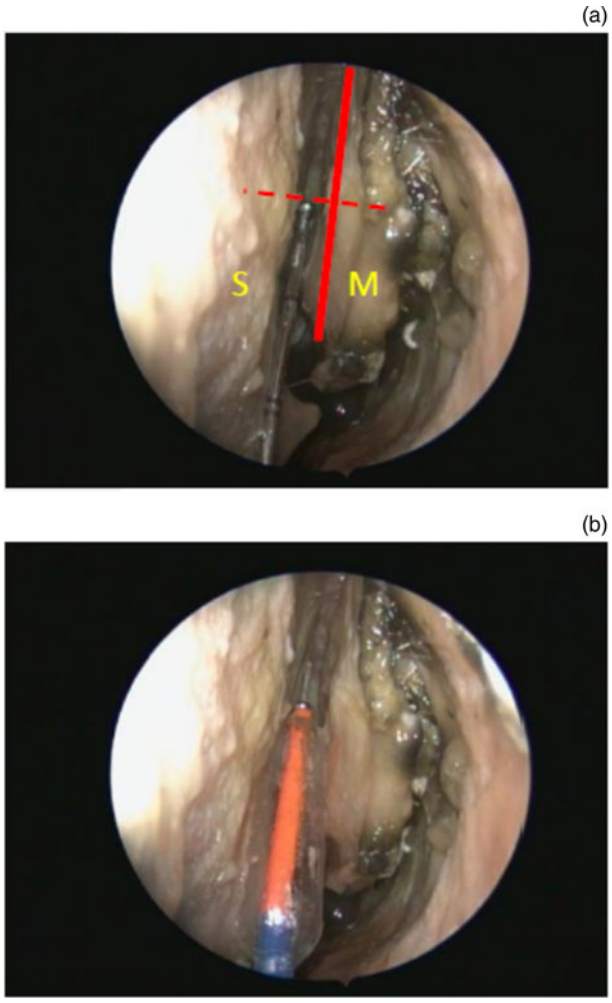

Fig. 2. (a) An imaginary horizontal line was drawn across the leading edge of the turbinate (dotted line) bisecting the half of the vertical height between the septum ('S') and inferior edge of the middle turbinate ('M'). (b) The tip of the dilatation device was advanced into the area between the nasal septum and middle turbinate. The light-emitting diode light fibre was advanced to facilitate endoscopic confirmation of the tip with the skull base. The balloon was then inflated, bisecting the half-height of the middle turbinate.

Fig. 3. Mygind head position.

Drug delivery and endoscopic assessment

At the beginning of the study, each nasal cavity was irrigated with copious water before endoscopic inspection was performed and debris suctioned. For consistency, two designated members of the team undertook positioning of the specimens, and another completed the endoscopic examinations. Diluted blue-

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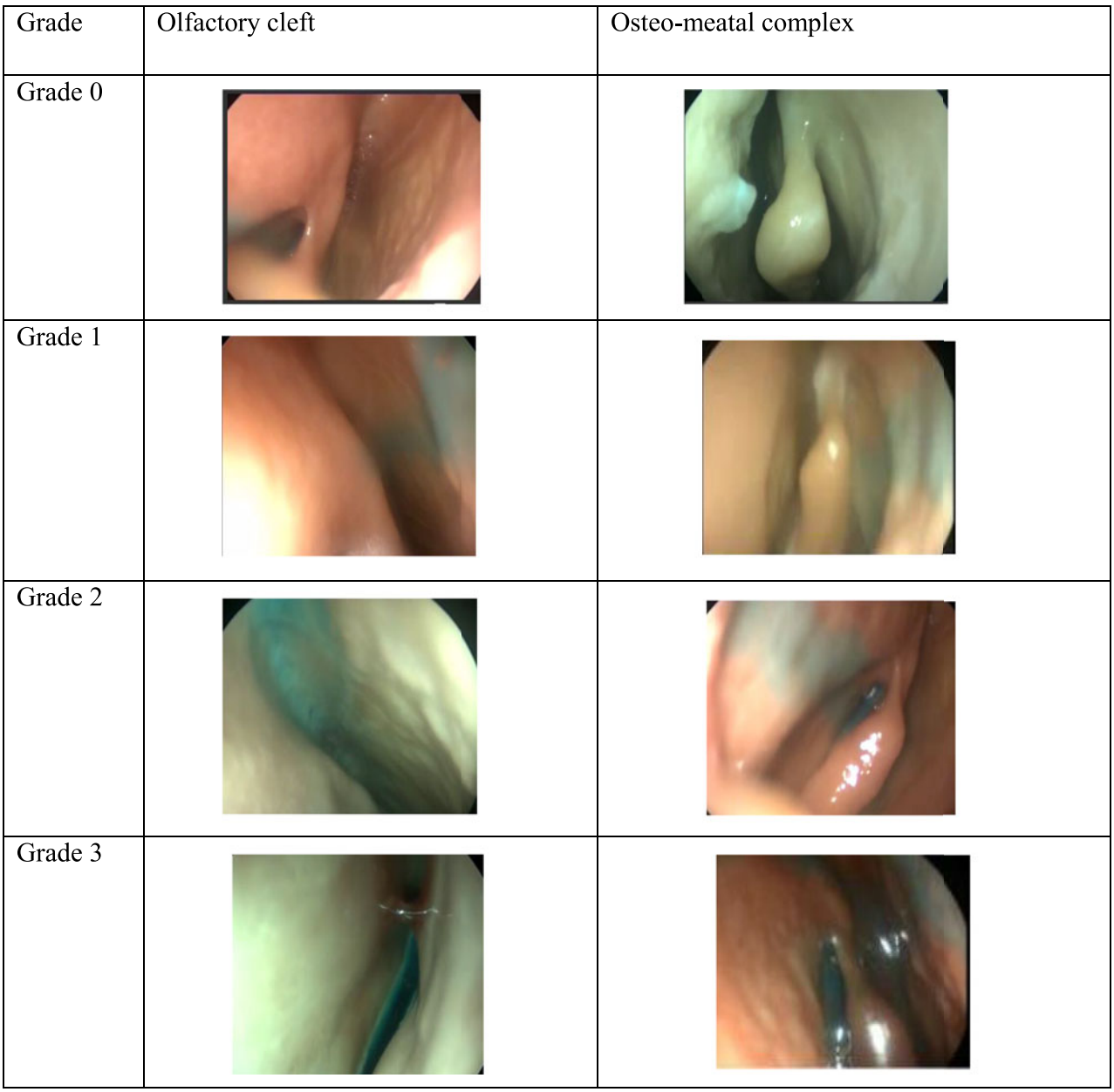

Fig. 4. Scale to assess extent of staining: 0 = absent (no dye visualised); 1 = minimal (only trace dye visualised on parts of mucosa); 2 = moderate (dye clearly visible on most or all parts of mucosa); and 3 = heavy (dye heavily stained on mucosa or pooling of dye within site).

colour food dye was instilled into both nasal cavities with a pipette. The specimens were held in the Mygind position (supine and head extended; Figure 3) for a minimum of 30 seconds prior to endoscopic examination, with a 0-degree rigid endoscope connected to a monitor and camera system (Karl Storz). Endoscopic assessment and video recording of the olfactory cleft and osteo-meatal complex were undertaken. The nasal cavities were then irrigated with copious water before suction. Endoscopic examination was repeated to ensure that the diluted dye was completely flushed out. This process was replicated for all specimens, and after completion of the balloon dilatation procedure, the protocol was repeated once again.

Nasal drop penetrance assessment

Two independent and blinded observers watched the anonymised endoscopic videos and evaluated the extent of blue dye staining in the olfactory cleft and osteo-meatal complex in each nasal cavity. The extent of staining followed a similar scale (Figure 4), based on a study reported by Kidwai *et al.*[11] A four-point Likert scale was used: 0 = absent (no dye visualised); 1 = minimal (only trace dye visualised on parts of mucosa); 2 = moderate (dye clearly visible on most or all parts of mucosa); and 3 = heavy (dye heavily stained on mucosa or pooling of dye within site).

Statistical analysis

Statistical analysis was performed using the SigmaPlot software package, version 12 (Systat Software, San Jose, California, USA). Analysis of variance testing was performed. In order to determine inter-rater reliability, the Cronbach's alpha statistic was calculated. A p-value of less than 0.05 was considered statistically significant.

Results

Five nasal cavities were excluded: three because of nasal septal deviation, which obstructed the endoscopic view of the olfactory cleft, and another two because of poor recorded video

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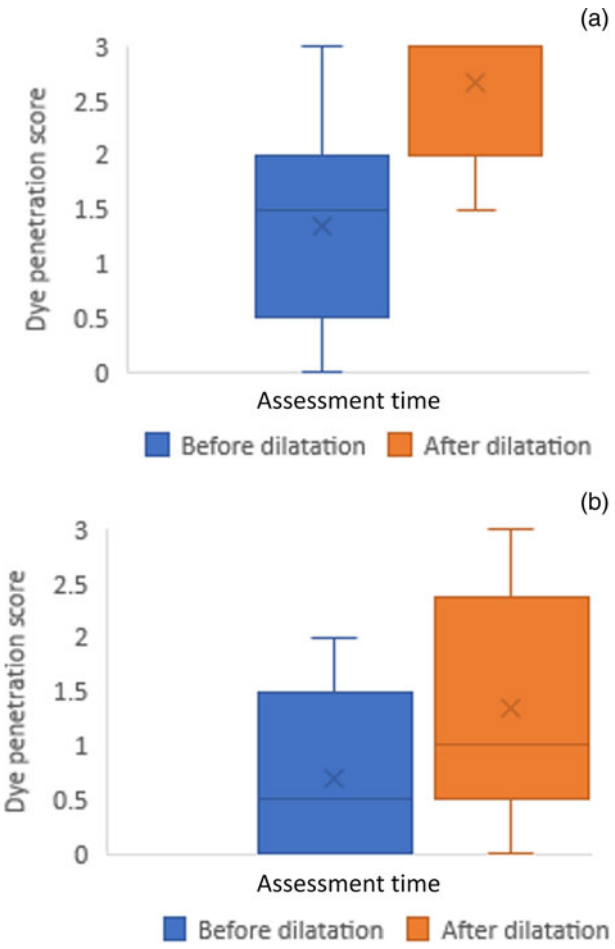

Fig. 5. (a) The dye penetration score for the olfactory cleft before and after balloon dilatation. The score significantly improved from 1.34 before the procedure to 2.66 after the procedure ($p < 0.05$). (b) The dye penetration score for the osteo-meatal complex before and after balloon dilatation. The score improved from 0.74 before the procedure to 1.34 after the procedure, but the change was not statistically significant. X = mean score.

quality, which precluded assessment of dye staining. The study protocol was completed in 19 nasal cavities, totalling 38 recorded videos for assessment. The Cronbach score for inter-observer reliability was 0.98.

Prior to balloon dilatation, the mean score for olfactory cleft dye staining was 1.34 (standard deviation (SD) = 0.93), and for the osteo-meatal complex it was 0.74 (SD = 0.79). Following balloon dilatation, the mean olfactory cleft score statistically significantly improved, to 2.66 (SD = 0.55, $p < 0.05$) (Figure 5a). Although the osteo-meatal complex score also increased, to 1.34 (SD = 1.13), this change was not statistically significant ($p = 0.06$) (Figure 5b).

Discussion

Synopsis of key or new findings

Our exploratory study demonstrated improvement in topical drug delivery to the olfactory cleft following balloon dilatation of the cleft. The results suggest potential clinical applicability whereby optimising drug delivery to the olfactory cleft may improve olfactory function. We recognise that a possible complication of this procedure may result in obstruction of the osteo-meatal complex because of lateralisation of the middle turbinate.[12] However, our results did not demonstrate a decrease in the penetrance of the nasal drops to the osteo-meatal complex.

Study strengths

Endonasal balloon dilatation is an established technique, undertaken by many ENT surgeons each year.[13] Nonetheless, the use of this technique at the olfactory cleft is novel. We believe the procedure is simple and associated with an easy learning curve. As with other endonasal balloon procedures, it may be possible to undertake dilatation of the olfactory cleft in an office setting, but we acknowledge that further clinical studies are required to assess the efficacy of this intervention. Each use of the balloon catheter device allows widening of the olfactory corridor to a maximum diameter of 6 mm, with a constant pressure of 12 atmospheres. This avoids the use of excessive pressure or uncontrolled pressure within the olfactory cleft, which may result in complications such as cerebrospinal fluid (CSF) leak or excessive lateralisation of the middle turbinate. In our experience with the technique, the light-emitting diode light fibre at the tip of the balloon catheter instrument serves as a useful adjunct to confirm the position of the balloon in relation to the cribriform plate and skull base.

Comparisons with other studies

There is only one previous publication on dilatation of the olfactory cleft. Jankowski *et al.*[8] performed dilatation of the olfactory cleft in three patients with stenosis of the olfactory cleft; using a curved aspirator with a blunt olive-shaped tip and a thin Cottle septum elevator.

The amount of force exerted by a hand-held instrument is subjective and operator-dependent. Consequently, there is a real risk of causing CSF leak by fracturing the insertion of the middle turbinate at the skull base or perforating the cribriform plate.[14] When the device is inflated, a uniform pressure is exerted along the entire external surface of the balloon.

Recognising the possible complications of applying direct pressure on the olfactory cleft walls (the cribriform plate, the insertion points of the middle turbinate and septum), we decided to perform the procedure below an imaginary vertical line bisecting the middle turbinate into two halves, applying most of the pressure of the balloon dilatation device on the lower part of the middle turbinate and the middle part of the septum. This technique permitted widening and enlargement of the olfactory funnel, allowing nasal drops to enter the olfactory funnel easily with minimal risk of CSF leak.

A preliminary study conducted by our group examined the safety of our technique of balloon dilatation of the olfactory cleft in 10 cadavers. The results showed no fracture lines at the skull base or olfactory cleft following the procedure.[10]

The Mygind position is a well-known head position for delivery of nasal drops.[15] The classic Mygind position requires the head to be turned to each side and again to the original position, holding each position for 30 seconds. As our main goal was to deliver the nasal drops to the nasal roof in the olfactory cleft area, we decided to adopt the variation of the Mygind position described by Charlton *et al.*,[16] and to simply keep the head at a central location without turning the head to both sides.

Clinical applicability of study

The current coronavirus pandemic has increased the public's awareness of olfactory impairment. Growing evidence describes hyposmia and parosmia as the leading symptoms and a possible marker of the disease. Studies have found that approximately 80 per cent of the olfactory symptoms resolve

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within three weeks, but the long-term consequences of the remaining 20 per cent are unknown.[17,18] Balloon dilatation of the olfactory cleft may provide a simple, office-based procedure to improve topical drug delivery to the olfactory cleft.

- Corticosteroids are a well-known, popular treatment for olfactory impairment due to sinonasal diseases
- Systemic steroids have been proven to improve olfactory function
- Topical steroids have not shown the same efficacy, probably because of delivery problems to the narrow, highly located, olfactory cleft
- Balloon catheter dilatation is a well-known, minimally invasive, well-controlled, office-based procedure
- There was significant improvement in topical drug delivery to the olfactory cleft following balloon dilatation of the cleft
- Improvement in topical steroid delivery to the olfactory cleft could have a major impact on olfactory impairment

The clinical applicability of this study needs to be assessed by further research on the repeatability and consistency of the data observed in the present study before transitioning to a clinical setting.

Conclusion

This exploratory study revealed significant improvement in topical drug delivery to the olfactory cleft following balloon dilatation. Improvement in the delivery of topical steroids to the olfactory cleft may result in better olfactory function, but this will need to be thoroughly assessed in clinical studies.

Competing interests. None declared

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