Hyaluronic acid for post sinus surgery care: systematic review and meta-analysis

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Hyaluronic acid for post sinus surgery care: systematic review and meta-analysis

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Outlines:

- Introduction
- Hyaluronic acid
- Methods and materials
- Inclusion criteria
- Exclusion criteria
- Study population
- Result
- Desiccation
- Limitations
- Conclusion
Introduction

- CRS affects 10–15% of the Western population and has adverse effects on health-related QOL. Endoscopic sinonasal surgery is indicated for the treatment of CRS refractory to medical treatment.

- Nasal adhesions or synechiae are a common cause of ESS failure, resulting in poorer outcomes and a higher likelihood of revision surgery, with adverse effects on patients’ health-related quality of life scores.

- Poor wound healing can result in an increased amount of tissue remodelling and subsequent scarring, leading to impaired mucociliary clearance due to loss of functioning respiratory epithelium.
Hyaluronic acid

- Hyaluronic acid is a physiological macromolecule from the family of the glycosaminoglycan.

- Synthesised by the **cellular plasma membrane** and highly concentrated in the **extracellular matrix**.
  - Skin, lung, and intestine contain more than 50% of the HA in the body.
  - Synovial fluid, skin, umbilical cord, and vitreous body of the eye are rich in HA content.

- Its has particular binding mechanisms and architectural configuration within the connective tissue have effects on **stability, lubrication, water homeostasis, molecule filtering and cell behaviour modification** (such as anti-inflammatory modulation).
Used for

- Use in **cosmetic surgery, ophthalmology, orthopaedics, general surgery and gynaecology**

- Application of hyaluronic acid aids in the **healing of acute and chronic wounds and burns**.

- Augments mucociliary clearance and has been shown to reduce the frequency of acute exacerbations of **chronic bronchitis**.

- In ORL, hyaluronic acid has been found to promote wound healing and preserve ostial patency following endonasal endoscopic dacryocystorhinostomy in primary chronic dacryocystitis.
Materials and methods

searched for randomised controlled trials (RCTs) of hyaluronic acid versus a control for post-endoscopic sinus surgery care in the following electronic databases:

- **Cochrane** Central Register of Controlled Trials (‘CENTRAL’),
- **Medline** (1966 to May 2015),
- **Embase** (1988 to May 2015),
- **Cumulative Index to Nursing and Allied Health Literature** (‘CINAHL’) (1984 to May 2015).
Inclusion criteria

- RCTs that evaluated hyaluronic acid preparations in patients following sinus surgery compared to standard treatments (including control saline preparations), for subsequent meta-analysis.
Exclusion criteria

- Studies not relating directly to the comparison of hyaluronic acid with a control.
- Patient follow up of less than four weeks
Study population

- **Adults** with a diagnosis of unilateral or bilateral chronic rhinosinusitis with or without nasal polyposis, as per the ‘EPOS’ 2012 guidelines on primary endoscopic sinus surgery.

- Studies on children and cystic fibrosis patients were excluded, as the mucosal immunity and physiology in these patients may be different to that of normal adults with rhinosinusitis.

- All cases of hyaluronic acid preparations for post-endoscopic sinus surgery care were **compared** to controls, including placebo (standard treatments included saline or nasal packs) and no active treatments (standard treatment with no intervention).

- All types of hyaluronic acid preparations were reviewed.
Primary outcome measures

- To meet the minimum criterion for the systematic review, studies were required to report the rate of synechiae formation as an outcome according to endoscopic appearance.

- The endpoint of outcome follow up was at least four weeks post-operatively, which represents a routine follow-up timeframe.

Secondary outcome measures

- The qualitative synthesis included studies that reported on: safety, other endoscopic measures such as discharge, crusting or oedema, and patient-reported symptom scores.
Results

FIG. 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses (‘PRISMA’) flow diagram. CRS = chronic rhinosinusitis
The studies grouped into three types of hyaluronic acid preparations

- **Absorbable dressing packs of hyaluronic acid (8 studies):**
  - 4 studies against a standard non-absorbable pack,
  - 3 studies were controlled with an unpacked side
  - 1 study compared hyaluronic acid against an absorbable gelatine stent.

- **Non-absorbable dressing packs impregnated with hyaluronic acid (1 study)**
  - against an absorbable gelatine stent.

- **And topical preparations such as nebulized ampules, sprays and creams. (3 studies)**
Outcomes include:

- Endoscopic evaluation,
- Subjective scores,
- Safety,
- And secondary objective parameters such as rhinomanometry findings.

The quality of studies was generally poor, with only one study achieving a quality score of 5 out of 5 using the Joanna Briggs Institute tool.

- Only three studies addressed incompleteness of data. (*franklin & wright et al.*, *shi et al.*, *wormald et al.*).

- Four studies failed to disclose how the products used were obtained (*Kimmelman et al.*, *catalano & roffman*, *cantone et al.*, *macchi et al.*).
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Study type</th>
<th>Participants (n)</th>
<th>Mean age ± SD (range); years</th>
<th>Follow-up duration (weeks)</th>
<th>Financial disclosures</th>
<th>JBI quality score (/5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gouteva et al. (2014)</td>
<td>Observational, open-label</td>
<td>49</td>
<td>33.12 ± 11.04 (15–58)</td>
<td>8</td>
<td>Spray provided by Ursapharm Arzneimittel (Saarbrücken, Germany)</td>
<td>1</td>
</tr>
<tr>
<td>Cantone et al. (2014)</td>
<td>Single-centre, double-blinded RCT</td>
<td>124</td>
<td>41.4 ± 2.4 &amp; 42.4 ± 1.4</td>
<td>5</td>
<td>NR</td>
<td>3</td>
</tr>
<tr>
<td>Shi et al. (2013)</td>
<td>Prospective, single-blinded RCT</td>
<td>54</td>
<td>NR</td>
<td>12</td>
<td>Funding provided by BioRegen Biomedical (Changzhou, China)</td>
<td>3</td>
</tr>
<tr>
<td>Gelardi et al. (2013)</td>
<td>Single-centre, single-blinded RCT</td>
<td>36</td>
<td>47 ± 14</td>
<td>5</td>
<td>Sponsored by Yabro, IBSA (Lugano, Switzerland)</td>
<td>3</td>
</tr>
<tr>
<td>Macchi et al. (2013)</td>
<td>Single-centre, randomised, double-blinded, placebo-controlled</td>
<td>46</td>
<td>37 ± 14 &amp; 40 ± 15</td>
<td>12</td>
<td>NR</td>
<td>4</td>
</tr>
<tr>
<td>Woodworth et al. (2010)</td>
<td>Multicentre, prospective, single-blinded RCT</td>
<td>53</td>
<td>49 (21–81)</td>
<td>8</td>
<td>Funding provided by Gyrus ENT (Bartlett, TN, USA)</td>
<td>2</td>
</tr>
<tr>
<td>Berlucchi et al. (2009)</td>
<td>Multicentre, prospective, double-blinded RCT</td>
<td>66</td>
<td>NR</td>
<td>12</td>
<td>Sponsored by Fidia Advanced Biopolymers (Abano Terme, Italy)</td>
<td>4</td>
</tr>
<tr>
<td>Franklin &amp; Wright (2007)</td>
<td>Single-centre, prospective, double-blinded RCT</td>
<td>70</td>
<td>NR</td>
<td>26</td>
<td>Study supported by Medtronic Canada (Mississauga, ON, Canada)</td>
<td>5</td>
</tr>
<tr>
<td>Kim et al. (2007)</td>
<td>Single-centre, randomised, double-blinded RCT</td>
<td>26</td>
<td>40 (18–61)</td>
<td>4</td>
<td>Product provided by Biorane (Seoul, South Korea)</td>
<td>3</td>
</tr>
<tr>
<td>Wormald et al. (2006)</td>
<td>Multicentre, prospective, single-blinded RCT</td>
<td>42</td>
<td>41.5 ± 16.6</td>
<td>8</td>
<td>Funding provided by Medtronic Xomed (Jacksonville, FL, USA)</td>
<td>4</td>
</tr>
<tr>
<td>Miller et al. (2003)</td>
<td>Multicentre, single-blinded RCT</td>
<td>37</td>
<td>39.1 ± 11.0 (20–64)</td>
<td>8</td>
<td>Funding provided by Medtronic Xomed (Jacksonville, FL, USA)</td>
<td>3</td>
</tr>
<tr>
<td>Catalano &amp; Roffman (2003)</td>
<td>Prospective, observational, non-randomised</td>
<td>115</td>
<td>47.3 ± 15.8</td>
<td>10</td>
<td>NR</td>
<td>1</td>
</tr>
<tr>
<td>Kimmelman et al. (2001)</td>
<td>Randomised, prospective, observational</td>
<td>10</td>
<td>NR</td>
<td>5</td>
<td>NR</td>
<td>2</td>
</tr>
</tbody>
</table>

SD = standard deviation; JBI = Joanna Briggs Institute; RCT = randomised controlled trial; NR = not reported.
<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Intervention</th>
<th>Control or comparator</th>
<th>Endoscopic outcomes</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shi et al. (2013)</td>
<td>Hyaluronic acid absorbable gel dressing injected post-op &amp; on post-op day 2, with standard sinus packing</td>
<td>Standard sinus packing applied directly post-op then no treatment on post-op day 2</td>
<td>Endoscopic assessment of re-epithelialisation, frequency of obstructing synechiae, crusting &amp; mucosal oedema</td>
<td>No statistical difference of re-epithelialisation &amp; crusting at post-op week 12. Less oedema &amp; synechia at 12 weeks</td>
</tr>
<tr>
<td>Woodworth et al. (2010)</td>
<td>Hyaluronic acid/carboxymethylcellulose absorbable dressing applied directly post-op</td>
<td>Unpacked contralateral side</td>
<td>Endoscopic evaluation of adhesion formation</td>
<td>No difference in synechiae incidence rate at week 8. Subjective difference on visual analogue scores</td>
</tr>
<tr>
<td>Berlucchi et al. (2009)</td>
<td>Hyaluronan resorbable nasal pack applied directly post-op</td>
<td>Standard non-resorbable nasal dressing</td>
<td>Endoscopic image for synechiae (% of cavities with adhesions), re-epithelialisation, crusts, secretions, mucosa &amp; granulation tissue</td>
<td>Significantly lower synechiae formation in MeroGel group at 4 &amp; 12 weeks</td>
</tr>
<tr>
<td>Franklin &amp; Wright (2007)</td>
<td>Hyaluronic absorbable dressing applied directly post-op</td>
<td>Contralateral side had non-absorbable sinus packing</td>
<td>Endoscopic severity score</td>
<td>Non-significant trend towards reduced endoscopic severity score in hyaluronic acid absorbable dressing group at 26 weeks</td>
</tr>
<tr>
<td>Kim et al. (2007)</td>
<td>Hyaluronic acid (0.25% w/v) &amp; carboxymethylcellulose (0.49% w/v) inflated into a non-absorbable pack, &amp; applied directly post-op &amp; on post-op day 3–4</td>
<td>Normal saline inflated into non-absorbable pack</td>
<td>Post-op adhesion incidence rate, severity of synechiae, Lund–Mackay score</td>
<td>Adhesion rate significantly lower in hyaluronic acid/carboxymethylcellulose group compared to controls, with lower adhesions according to Lund–Mackay scoring at 2 &amp; 4 weeks</td>
</tr>
<tr>
<td>Wormald et al. (2006)</td>
<td>Absorbable hyaluronic acid pack into middle meatus applied directly post-op</td>
<td>No packing on side contralateral to hyaluronic acid pack</td>
<td>Endoscopic scoring assessment of synechiae, infection &amp; oedema</td>
<td>In context of adhesions, oedema or infection, hyaluronic acid packing demonstrated no significant benefit, but no detrimental effects, at 6–8 weeks</td>
</tr>
<tr>
<td>Miller et al. (2003)</td>
<td>Hyaluronan absorbable dressing applied directly post-op</td>
<td>Non-absorbable dressing on contralateral side</td>
<td>Photo-endoscopy for synechiae formation, oedema &amp; infection</td>
<td>No difference between hyaluronic acid &amp; non-absorbable packs at 8 weeks</td>
</tr>
<tr>
<td>Catalano &amp; Roffman (2003)</td>
<td>Absorbable hyaluronic acid stent applied directly post-op</td>
<td>Contralateral Gelfilm stent</td>
<td>Endoscopic synechiae evaluation, granulation tissue, stent retention</td>
<td>Hyaluronic acid based absorbable stent resulted in significantly less adhesion formation, with no appreciable difference in granulation, congestion or infection at week 12</td>
</tr>
<tr>
<td>Kimmelman et al. (2001)</td>
<td>Hyaluronan gel with absorbable dressing applied directly post-op</td>
<td>No controlled treatment</td>
<td>Synechiae, mucosal regeneration &amp; mucosal status</td>
<td>Significant difference in synechiae formation at week 5, with no statistical difference in other outcomes at week 5</td>
</tr>
</tbody>
</table>

Post-op = post-operative(ly); w/v = weight/volume
### TABLE III
**STUDIES USING HYALURONIC ACID AS A NEBULISED PREPARATION**

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Intervention</th>
<th>Control or comparator</th>
<th>Endoscopic outcomes</th>
<th>Other outcomes</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gouteva <em>et al.</em> (2014)⁴³</td>
<td>0.25 mg/ml hyaluronic acid &amp; 2% dexamethasone spray, 1–2 puffs 3 times daily</td>
<td>Standard cleaning therapy with saline irrigation</td>
<td>NR</td>
<td>Rhinomanometry, rhinoscopy, subjective nasal obstruction scoring</td>
<td>No statistical difference between hyaluronic acid plus dexamethasone &amp; standard saline control</td>
</tr>
<tr>
<td>Cantone <em>et al.</em> (2014)³⁹</td>
<td>9 mg hyaluronic acid &amp; saline solution nasal douche twice daily</td>
<td>Saline solution nasal douche</td>
<td>Endoscopic score</td>
<td>Visual analogue scale, SNOT-22, SF-36</td>
<td>Improvement of all outcome parameters</td>
</tr>
<tr>
<td>Gelardi <em>et al.</em> (2013)⁴²</td>
<td>Intranasal sodium hyaluronate 9 mg nebulised twice daily</td>
<td>Saline irrigation</td>
<td>Nasendoscopic mucosal examination</td>
<td>Mucociliary clearance measured by ciliary mucous transport time via charcoal powder &amp; saccharin during rhinoscopy. Symptoms &amp; tolerability</td>
<td>Intranasal hyaluronic acid post-FESS for polyposis improves mucociliary clearance physiology</td>
</tr>
<tr>
<td>Macchi <em>et al.</em> (2013)⁴⁰</td>
<td>9 mg nebulised sodium hyaluronic acid plus saline wash twice daily</td>
<td>5 ml saline wash control</td>
<td>Endoscopy on dichotomous scale for nasal dyspnœa, secretions, patency of paranasal sinuses, synechiae</td>
<td>Biofilm on cytology</td>
<td>Hyaluronic acid plus saline wash significantly different in terms of nasal dyspnœa, nasal mucosa physiology &amp; ciliary motility cytologically</td>
</tr>
</tbody>
</table>

NR = not reported; SNOT-22 = 22-item Sino-Nasal Outcome Test; SF-36 = 36-Item Short Form Survey; FESS = functional endoscopic sinus surgery
Meta-analysis of adhesion rates

- **7 studies** (involving 324 patients and 565 sinus cavities) that met the criteria for analysis in the quantitative part of the study.

- The most common reported parameter was **adhesion formation**, with lower adhesion rates in the hyaluronic acid group compared to the control group at 4–12 weeks post-operatively (odds ratio = 0.42, 95% CI = 0.27–0.64).

- **The meta-analysis excluded the studies by Catalano and Roffman and Kimmelman et al. because they had no randomisation and no control respectively**.

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**FIG. 2**

Meta-analysis of adhesion formation frequency on endoscopy for hyaluronic acid versus control groups. M-H = Mantel–Haenszel; CI = confidence interval; df = degrees of freedom
Discussion

The meta-analysis found that adhesion formation occurred in **42 out of 283 cases (15 %)**, with a risk ratio of 0.52 (95 % CI = 0.37–0.72; I² = 36 %), compared to **81 out of 282 cases (29 %)** in the control arm of the meta-analysis.
Subjective outcomes

- **Cantone et al.** (122 participants) investigated the effect of nebulised hyaluronic acid on quality of life, and reported improvements in subjective parameters at day 30 post-operatively, including:
  - visual analogue scale (mean of 3.8 vs 5.6 points, p < 0.05),
  - sinus nasal obstruction test (22-item Sino- Nasal Outcome Test) (sum score mean of 47.8 ± 25.4 vs 59.33 ± 23.2, p < 0.05)
  - medical short form-36 (mean of 83.7 per cent vs 73 per cent, p < 0.05).

- **Macchi et al.** supported symptomatic relief with nebulised hyaluronic acid, demonstrating slightly improved satisfaction with regard to reported nasal dyspnoea in the interventional group compared to the control group (odds ratio = 21.36; 95% CI = 1.07–426.56).
Other outcomes

- **Macchi et al.**
  - **Ciliary motility**, was favoured in the treated group; improvement in terms of ciliary function scores was reported in 87% of participants in the treated group compared to 11% of those in the control group (p < 0.001).
  - **Numbers of fungi**, treated group had lower with a frequency of 0, versus 1 in controls (p = 0.044).
  - **Biofilm presence**, was higher in hyaluronic acid participants (47.8 per cent, compared to 17.4 per cent in controls), but this difference was **not statistically** significant (p = 0.057).
Cont. Other outcomes

- **Gelardi et al.**
  - **Mucociliary clearance,** reported that at one month post-operatively, as measured by the saccharin and charcoal test, was faster in the hyaluronic acid group compared to the saline control group (14.3±2.5 vs 23.6±3.3 minutes respectively; p= 0.000).

- **Nasal obstruction,** Participants in the hyaluronic acid group reported less compared to controls (2 vs 3 participants respectively, p = 0.023)

- And less **rhinorrhoea** (4 vs 10 participants respectively, p = 0.039).
Cont. Other outcomes

- **Gouteva et al.**
  - Involved the use of a spray containing hyaluronic acid.
  - Mucosal regeneration was measured by rhinoscopy sum score, representative of the efficacy of a spray preparation of 0.25 mg/ml hyaluronic acid with 2% dexpanthenol, which was applied 3 times a day following nasal cavity surgery and compared to a saline spray.
  - Rhinoscopy scoring was **not significantly** different between the hyaluronic acid with dexpanthenol spray group and the saline spray group at week 6 post-operatively.
Study limitations

- Surgical technique may be a confounding factor where institutions perform endoscopic sinus surgery differently to one another, and the post-operative complication rates may be different, resulting in variable findings.

- The studies comprised primary endoscopic sinus surgery cases, and therefore the effect of hyaluronic acid on the revision sinus surgery population is unknown.

- Unpacked sinus cavities may be more useful in future research to determine the effect of topical post-operative preparations, which may reduce confounding.

- There is poor and conflicting evidence on how absorbable versus non-absorbable packs differ in the post-operative setting, although the trend appears to favor absorbable preparations.
Conclusion

The meta-analysis included 7 studies that showed a significant improvement in adhesion formation at least four weeks post-operatively.

Several different hyaluronic acid preparations have been studied, demonstrating beneficial endoscopic outcomes of lower adhesion rates in primary chronic rhinosinusitis post-surgical patients.

Further research is required to establish the most effective preparation for clinical practice.
Thank you ..