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REVIEW ARTICLE

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

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Abstract

Background: Wound healing after endoscopic sinus surgery may result in adhesion formation. Hyaluronic acid may prevent synechiae development. A systematic review was performed to evaluate the current evidence on the clinical efficacy of hyaluronic acid applied to the nasal cavity after sinus surgery.

Methods: Studies using hyaluronic acid as an adjunct treatment following endoscopic sinus surgery for chronic rhinosinusitis were identified. The primary outcome was adhesion formation rates. A meta-analysis was performed on adhesion event frequency. Secondary outcome measures included other endoscopic findings and patient-reported outcomes.

Results: Thirteen studies (501 patients) met the selection criteria. A meta-analysis of adhesion formation frequency on endoscopy demonstrated a lower risk ratio in the hyaluronic acid intervention group (42 out of 283 cases) compared to the control group (81 out of 282) of 0.52 (95 per cent confidence interval = 0.37–0.72). Hyaluronic acid use was not associated with any significant adverse events.

Conclusion: Hyaluronic acid appears to be clinically safe and well tolerated, and may be useful in the early stages after sinus surgery to limit adhesion rate. Further research, including larger randomised controlled trials, is required to evaluate patient- and clinician-reported outcomes of hyaluronic acid post sinus surgery.

Key words: Rhinitis; Surgery; Quality Of Life; Drug Therapy; Hyaluronic Acid

Introduction

Chronic rhinosinusitis affects 10–15 per cent of the Western population and has adverse effects on health-related quality of life.[1,2] Chronic rhinosinusitis is attributed to multifactorial causes such as environmental factors and host characteristics.[3] Endoscopic sinonasal surgery is indicated for the treatment of chronic rhinosinusitis refractory to medical treatment.[4] Nasal adhesions or synechiae are a common cause of endoscopic sinus surgery failure, resulting in poorer outcomes and a higher likelihood of revision surgery,[5] with adverse effects on patients' health-related quality of life scores.[6] Adhesions are associated with middle turbinate lateralisation and may cause secondary obstruction to the osteomeatal complex, resulting in symptomatic failure and an increase in the need for revision endoscopic sinus surgery.[7]

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.[8,9] Other complications include bleeding, mucosal oedema and infection. Various surgical measures such as the use of mucosal sparing techniques, stents, absorbable and non-absorbable nasal packing, and biodegradable materials are used to minimise adhesion formation.[8,9] All of these have their benefits, and the potential risk for predisposition to granuloma formation and increased discomfort upon removal of the nasal pack.[10]

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. Its 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).[11] The unique hygroscopic, viscoelastic and mucoadhesive capability of hyaluronic acid, together with its high immunological and toxicological safety, have led to its use in cosmetic surgery, ophthalmology, orthopaedics, general surgery and

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gynaecology.[12] Furthermore, there is evidence that the application of hyaluronic acid aids in the healing of acute and chronic wounds and burns.[13–15] Hyaluronic acid also augments mucociliary clearance and has been shown to reduce the frequency of acute exacerbations of chronic bronchitis.[16]

The mucosal regenerative properties may be beneficial in the post sinus surgery environment, where the normal physiological processes are disrupted in a wound. The modulating effect of hyaluronic acid in wound healing and mucosal regeneration has been demonstrated in clinical trials following sinonasal surgery, in which safety, tolerability and efficacy of a hyaluronic acid cream were reported.[17] Recent studies have supported the role of hyaluronic acid in improving endoscopic and cytological parameters of chronic rhinosinusitis.[18] Animal studies similarly show mucosal surface restoration with the use of hyaluronic acid following sinus surgery, particularly in preventing stenosis.[19–22]

Alternative strategies include a wide range of materials such as absorbable and non-absorbable spacers, spacers impregnated with steroid, mitomycin C applied locally, and Silastic splints (used to promote ostial patency and wound regeneration in the sinus environment after surgical disruption).[23]

In otorhinolaryngology, hyaluronic acid has been found to promote wound healing and preserve ostial patency following endonasal endoscopic dacryocystorhinostomy in primary chronic dacryocystitis.[24]

The effect of hyaluronic acid following endoscopic endonasal sinus surgery for chronic rhinosinusitis is not well defined. Hence, a systematic review was conducted on the existing literature to evaluate endoscopic outcomes compared to standard regimens and controls for preventing post sinus surgery complications.[25,26]

Materials and methods

A systematic review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') statement as a framework. The review was registered with Prospero, an international prospective register of systematic reviews (CRD42014013610).

Search strategy

The following electronic databases were searched for randomised controlled trials (RCTs) of hyaluronic acid versus a control for post-endoscopic sinus surgery care: the Cochrane Central Register of Controlled Trials ('CENTRAL'), Medline (1966 to May 2015), Embase (1988 to May 2015), and the Cumulative Index to Nursing and Allied Health Literature ('CINAHL') (1984 to May 2015). A hand search of bibliographic references was undertaken in relevant articles, to ensure a comprehensive search.

Inclusion criteria

The studies included in the review were RCTs that evaluated hyaluronic acid preparations in patients following sinus surgery compared to standard treatments (including control saline preparations), for subsequent meta-analysis. Studies meeting the National Health and Medical Research Council levels II and III evidence that were not RCTs were considered in the qualitative review. Two investigators were involved with independently assessing study eligibility. In the event of discrepancies between investigators, consensus was achieved through discussion. A title and abstract screen was completed, and studies measuring the efficacy of hyaluronic acid using endoscopic outcomes were selected.

Exclusion criteria

Studies not relating directly to the comparison of hyaluronic acid with a control, or those with patient follow up of less than four weeks, were excluded. The full text was obtained for selected articles and these were critically evaluated.

Study population

Participants were adults with a diagnosis of unilateral or bilateral chronic rhinosinusitis with or without nasal polyposis, as per the 'EPOS' European Position Paper on Rhinosinusitis and Nasal Polyps 2012 guidelines on primary endoscopic sinus surgery.[4] 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.[27,28] 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.

Data extraction

An independent extraction process was undertaken by two of the investigators (EF and MG). Any disagreements were resolved through discussion (between EF and MG). Extracted data included: baseline study

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characteristics (design, study year, setting), population characteristics (disease type, disease location, operation type), operation technique, data relating to the intervention (e.g. preparation type and hyaluronic acid dosing), follow-up duration and primary outcome measures (synechiae). Strict limits were applied to studies included in the meta-analysis. These studies had to meet eligibility criteria, including hyaluronic acid nasal pack use, in order for homogeneous assessment, as well as endoscopic outcomes.

Quality appraisal

The quality of studies was assessed using the Joanna Briggs Institute appraisal assessment tool (scored out of 5).[29] The tool has a structured evaluation for specific types of studies, including qualitative, quantitative and systematic review protocols.

Statistical analysis

The statistical aspects of the meta-analysis were calculated using RevMan software version 5.2.[30] The number of events of sinonasal adhesion in the hyaluronic acid group were recorded and compared to the control group. Risk ratio and confidence intervals (CIs) for adhesion formation frequency were calculated using the Mantel–Haenszel method. The I^2 test was used to assess for heterogeneity. The results were considered significant if the 95 per cent CIs did not include '1.0' for the risk ratio.

Results

A total of 2760 studies were identified in the search, with 1554 unique records after duplicates were removed (Figure 1). Of these, 32 studies were eligible for full text review, of which 13 studies (involving 501 participants) met the selection criteria (Table I).[31–43] The analysis included five double-blinded, randomised controlled trials (RCTs) (National Health and Medical Research Council level II), five single-blinded trials and three prospective studies (National Health and Medical Research Council III). Seven RCTs met the standards for selection into the meta-analysis.

The studies could be grouped into three types of hyaluronic acid preparations, including absorbable dressing packs of hyaluronic acid, non-absorbable dressing packs impregnated with hyaluronic acid, and topical preparations such as nebulised ampules, sprays and creams (Table I). Eight studies used resorbable hyaluronic acid nasal dressings or packs, of which seven were RCTs. Of these, four studies were controlled against a standard non-absorbable pack,[31–34] three studies were controlled with an unpacked side[35–37] and one study compared hyaluronic acid against an absorbable gelatine stent.[38] One study used non-absorbable packing that was impregnated with hyaluronic acid. Three RCTs utilised 9 mg of hyaluronic acid in 3 ml of normal saline, applied for 60–90 seconds twice daily.

Outcomes in post sinus surgery care with hyaluronic acid usage included 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 (Table I). Only three studies addressed incompleteness of data.[32,34,35] Four studies failed to disclose how the products used were obtained.[36,38–40]

Nasendoscopic evaluation

There were mixed outcomes when comparing absorbable hyaluronic acid packs to placebo pack controls (Table II). Franklin and Wright found that endoscopic severity scoring at post-operative week two was significantly lower in the hyaluronic acid absorbable pack group.[32] However, there was no statistically significant difference in the primary outcome measure of adhesion formation, or secondary outcome measures of oedema or infection frequency, on endoscopic analysis at six months, although there was a trend favouring improvement.[32]

Berlucchi *et al.* found that hyaluronic acid dressings had a significant effect on adhesion rates, with less than 5 per cent of sinonasal cavities found to have adhesions compared to controls; the latter of which had 23 per cent of non-obstructing and 8 per cent of obstructing adhesions at 12 weeks on endoscopic evaluation ($p < 0.001$).[33] Similarly, Shi reported a significant difference in synechiae (both obstructing and non-obstructing), oedema crusting and mucopurulent discharge, with these being significantly lower in the treated group ($p = 0.0481$).[34] In contrast, Miller *et al.* could not find any significant difference in the rate of adhesion formation, oedema or infection at eight weeks' follow up between intervention and control.[31]

Kim *et al.* compared a standard non-absorbable pack soaked in 6 ml of hyaluronic acid with carboxymethylcellulose against a non-absorbable pack with a normal saline preparation, and reported a significantly lower adhesion frequency in the treatment group.[41] That study found that the incidence of adhesions in terms of endoscopic scoring on a four-point severity scale was significantly lower in the treated hyaluronic acid/carboxymethylcellulose group compared to the control group (3 per cent and 18 per cent respectively; $p = 0.02$).[41]

Three studies compared the use of hyaluronic acid dressing against an unpacked contralateral middle meatus (Table II). Woodworth *et al.* used hyaluronic acid/carboxymethylcellulose dressings and found no significant difference between the packed and unpacked sides with any grade of adhesions ($p = 0.09$).[37] A single-blinded study by Wormald *et al.* found no difference in primary adhesion rates ($p = 0.109$), or other secondary endoscopic parameters including infection and mucosal oedema ($p = 0.317$ and $p = 0.704$ respectively), at six to eight weeks post-operatively when compared to an unpacked side.[35]

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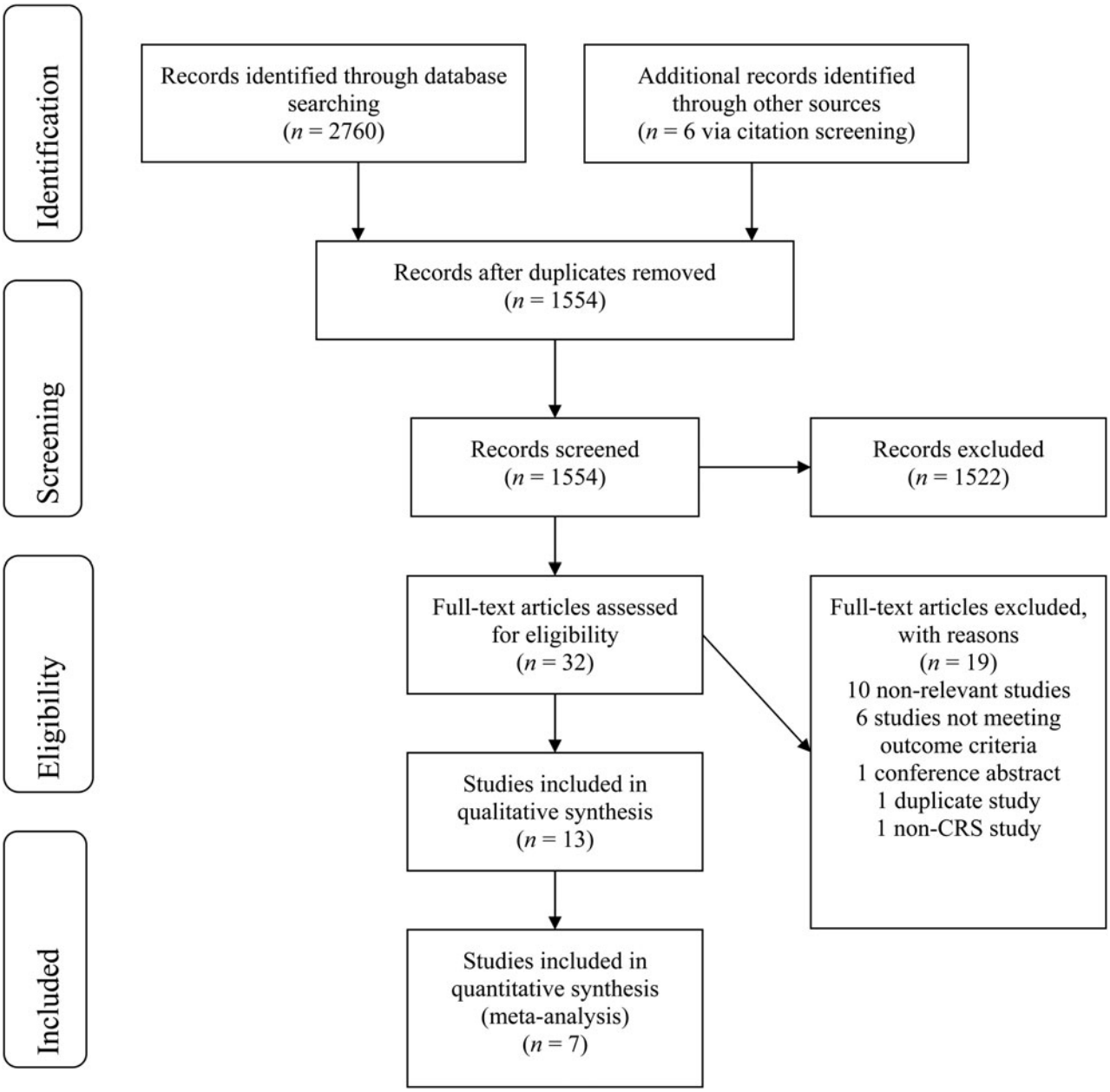

FIG. 1
Preferred Reporting Items for Systematic Reviews and Meta-Analyses ('PRISMA') flow diagram. CRS = chronic rhinosinusitis

A prospective observational study by Kimmelman suggested that adhesion formation and meatal stenosis frequency was lower in the interventional group compared to a non-active treatment group at five weeks ($p < 0.05$), but there were no other differences (including in mucosal oedema) observed at that time point.[36]

Catalano and Roffman conducted a prospective non-randomised study comparing the use of MeroGel against Gelfilm, and found that use of the hyaluronic acid dressing in association with a minimally invasive surgical technique minimised the mucosal scarring, with lower adhesion formation on endoscopic examination at 12 weeks (0 adhesions in the intervention group *vs* 4 in the control group; $p = 0.04$).[38] However, there were no differences in secondary outcome measures in terms of the frequency of granulation, oedema or infection.

Three studies utilised nebulised hyaluronic acid delivery, with endoscopic endpoints (Table III).[39,40,42] Macchi conducted a pilot study using 9 mg nebulised hyaluronic acid for 15 consecutive days per month for 3 months versus 5 ml nebulised normal saline twice daily.[40] Adhesion formation was similar between the hyaluronic acid with saline group and the saline nebuliser only group, with incidences of 34.8 per cent and 39.1 per cent (not significant) respectively. There was no difference in improvement for other secondary endoscopic parameters, including oedema and sinus patency, at the end of the three-month

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TABLE I
STUDY CHARACTERISTICS

Study (year)	Study type	Participants (*n*)	Mean age ± SD (range); years	Follow-up duration (weeks)	Financial disclosures	JBI quality score (/5)
Gouteva *et al*. (2014)[43]	Observational, open-label	49	33.12 ± 11.04 (15–58)	8	Spray provided by Ursapharm Arzneimittel (Saarbrücken, Germany)	1
Cantone *et al*. (2014)[39]	Single-centre, double-blinded RCT	124	41.4 ± 2.4 & 42.4 ± 1.4	5	NR	3
Shi *et al*. (2013)[34]	Prospective, single-blinded RCT	54	NR	12	Funding provided by BioRegen Biomedical (Changzhou, China)	3
Gelardi *et al*. (2013)[42]	Single-centre, single-blinded RCT	36	47 ± 14	5	Sponsored by Yabro, IBSA (Lugano, Switzerland)	3
Macchi *et al*. (2013)[40]	Single-centre, randomised, double-blinded, placebo-controlled	46	37 ± 14 & 40 ± 15	12	NR	4
Woodworth *et al*. (2010)[37]	Multicentre, prospective, single-blinded RCT	53	49 (21–81)	8	Funding provided by Gyrus ENT (Bartlett, TN, USA)	2
Berlucchi *et al*. (2009)[33]	Multicentre, prospective, double-blinded RCT	66	NR	12	Sponsored by Fidia Advanced Biopolymers (Abano Terme, Italy)	4
Franklin & Wright (2007)[32]	Single-centre, prospective, double-blinded RCT	70	NR	26	Study supported by Medtronic Canada (Mississauga, ON, Canada)	5
Kim *et al*. (2007)[41]	Single-centre, randomised, double-blinded	26	40 (18–61)	4	Product provided by Biorane (Seoul, South Korea)	3
Wormald *et al*. (2006)[35]	Multicentre, prospective, single-blinded RCT	42	41.5 ± 16.6	8	Funding provided by Medtronic Xomed (Jacksonville, FL, USA)	4
Miller *et al*. (2003)[31]	Multicentre, single-blinded RCT	37	39.1 ± 11.0 (20–64)	8	Funding provided by Medtronic Xomed (Jacksonville, FL, USA)	3
Catalano & Roffman (2003)[38]	Prospective, observational, non-randomised	115	47.3 ± 15.8	10	NR	1
Kimmelman *et al*. (2001)[36]	Randomised, prospective, observational	10	NR	5	NR	2

SD = standard deviation; JBI = Joanna Briggs Institute; RCT = randomised controlled trial; NR = not reported

TABLE II
SUMMARY OF STUDY FINDINGS FOR HYALURONIC ACID NASAL PACKS

Study (year)	Intervention	Control or comparator	Endoscopic outcomes	Conclusions
Shi *et al.* (2013)[34]	Hyaluronic acid absorbable gel dressing injected post-op & on post-op day 2, with standard sinus packing	Standard sinus packing applied directly post-op then no treatment on post-op day 2	Endoscopic assessment of re-epithelialisation, frequency of obstructing synechiae, crusting & mucosal oedema	No statistical difference of re-epithelialisation & crusting at post-op week 12. Less oedema & synechia at 12 weeks
Woodworth *et al.* (2010)[37]	Hyaluronic acid/carboxymethylcellulose absorbable dressing applied directly post-op	Unpacked contralateral side	Endoscopic evaluation of adhesion formation	No difference in synechiae incidence rate at week 8. Subjective difference on visual analogue scores
Berlucchi *et al.* (2009)[33]	Hyaluronan resorbable nasal pack applied directly post-op	Standard non-resorbable nasal dressing	Endoscopic image for synechiae (% of cavities with adhesions), re-epithelialisation, crusts, secretions, mucosa & granulation tissue	Significantly lower synechiae formation in MeroGel group at 4 & 12 weeks
Franklin & Wright (2007)[32]	Hyaluronan absorbable dressing applied directly post-op	Contralateral side had non-absorbable sinus packing	Endoscopic severity score	Non-significant trend towards reduced endoscopic severity score in hyaluronic acid absorbable dressing group at 26 weeks
Kim *et al.* (2007)[41]	Hyaluronic acid (0.25% w/v) & carboxymethylcellulose (0.49% w/v) inflated into a non-absorbable pack, & applied directly post-op & on post-op day 3–4	Normal saline inflated into non-absorbable pack	Post-op adhesion incidence rate, severity of synechiae, Lund–Mackay score	Adhesion rate significantly lower in hyaluronic acid/carboxymethylcellulose group compared to controls, with lower adhesions according to Lund–Mackay scoring at 2 & 4 weeks
Wormald *et al.* (2006)[35]	Absorbable hyaluronic acid pack into middle meatus applied directly post-op	No packing on side contralateral to hyaluronic acid pack	Endoscopic scoring assessment of synechiae, infection & oedema	In context of adhesions, oedema or infection, hyaluronic acid packing demonstrated no significant benefit, but no detrimental effects, at 6–8 weeks
Miller *et al.* (2003)[31]	Hyaluronan absorbable dressing applied directly post-op	Non-absorbable dressing on contralateral side	Photo-endoscopy for synechiae formation, oedema & infection	No difference between hyaluronic acid & non-absorbable packs at 8 weeks
Catalano & Roffman (2003)[38]	Absorbable hyaluronic acid stent applied directly post-op	Contralateral Gelfilm stent	Endoscopic synechiae evaluation, granulation tissue, stent retention	Hyaluronic acid based absorbable stent resulted in significantly less adhesion formation, with no appreciable difference in granulation, congestion or infection at week 12
Kimmelman *et al.* (2001)[36]	Hyaluronan gel with absorbable dressing applied directly post-op	No controlled treatment	Synechiae, mucosal regeneration & mucosal status	Significant difference in synechiae formation at week 5, with no statistical difference in other outcomes at week 5

Post-op = post-operative(ly); w/v = weight/volume

TABLE III
STUDIES USING HYALURONIC ACID AS A NEBULISED PREPARATION

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

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

study ($p > 0.05$). Nebulised hyaluronic acid was associated with a more normal appearance in mucosal integrity compared to saline (91.3 per cent *vs* 52.2 per cent respectively, $p = 0.007$). Cantone *et al.* similarly demonstrated that nebulised hyaluronic acid was associated with a better Lund–Kennedy endoscopic mean score than the control (1.43 ± 1.85 *vs* 4.16 ± 3.35, $p = 0.0001$).[39] A study by Gelardi *et al.* using nebulised hyaluronic acid showed that the median exudate score was also lower in the sodium hyaluronate group compared to the control group (0 *vs* 4 respectively, $p < 0.05$).[42]

Meta-analysis of adhesion rates

There were 7 studies (involving 324 patients and 565 sinus cavities) that met the criteria for analysis in the quantitative part of the study (Figure 2). 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 per cent CI = 0.27–0.64).

Subjective outcomes

Only one study employed patient-reported outcome tools to investigate the effect of hyaluronic acid on quality of life. A double-blinded RCT conducted by Cantone *et al.* (involving 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 the total 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, $p < 0.05$) and medical short form-36 (mean of 83.7 per cent *vs* 73 per cent, $p < 0.05$).[39]

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 per cent CI = 1.07–426.56).[40]

Safety profile

Seven of the 13 studies in this systematic review reported on safety in terms of adverse events.[32–34,36,39,41,43] Six studies found that topical hyaluronic acid preparations to the post-surgical nasal cavity were safe. Gouteva *et al.* reported one participant with an intolerance to an ingredient in the hyaluronic acid nebulised preparation, resulting in mild transient irritation.[43] Satisfaction was generally better than in the control group, and statistically better compared to the non-absorbable packing group.[43] Tolerability, as measured by general patient satisfaction scales, was reported in four studies, which demonstrated at least equal judgement by patients on tolerance for all preparations.[38–40,42]

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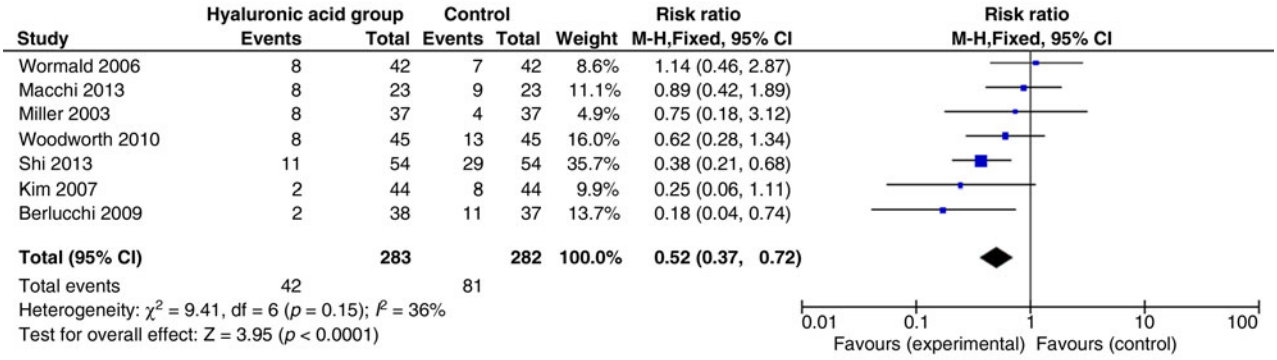

FIG. 2

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

Other outcomes

Three studies using microbiological, saccharin and charcoal, and rhinomanometric techniques provide useful information regarding recovery of the sinus mucosa following post-operative sinus care. Macchi *et al*. established that ciliary motility, as measured by phase contrast microscopy, was favoured in the treated group; improvement in terms of ciliary function scores was reported in 87 per cent of participants in the treated group compared to 11 per cent of those in the control group ($p < 0.001$).[40] The study also found that hyaluronic acid participants had lower numbers of fungi, with a frequency of 0, versus 1 in controls ($p = 0.044$). In addition, there was a trend for higher biofilm presence in the hyaluronic acid participants (47.8 per cent, compared to 17.4 per cent in controls), but this difference was not statistically significant ($p = 0.057$).[40]

A study by Gelardi *et al*. reported that at one month post-operatively, mucociliary clearance, 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; $p = 0.000$).[42] Participants in the hyaluronic acid group also reported less nasal obstruction compared to controls (2 *vs* 3 participants respectively, $p = 0.023$) and less rhinorrhoea (4 *vs* 10 participants respectively, $p = 0.039$).

One open-label study was included in the qualitative synthesis, which involved the use of a spray containing hyaluronic acid.[43] 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 per cent dexpanthenol, which was applied three 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 six post-operatively.

Discussion

This systematic review evaluates the effects of hyaluronic acid on endoscopic outcomes following endoscopic sinus surgery for patients with chronic rhinosinusitis. The endoscopic outcomes evaluated included adhesion formation. Despite the development of minimally invasive surgical techniques, complications following sinus surgery can occur, with adhesions cited as the most common issue.[2,3] In order to avoid post-operative failure, surgical techniques and devices have been used, both in the intra-operative and post-operative periods, with diverse findings.[4,5]

This systematic review evaluates and compares 13 studies involving 501 participants with chronic rhinosinusitis treated with hyaluronic acid preparations following endoscopic sinus surgery. Hyaluronic acid may be a useful adjunct to saline irrigation following endoscopic sinus surgery for chronic rhinosinusitis, as evidenced by lower endoscopic adhesion formation in the meta-analysis, significant objective features of mucosal healing including reduced saccharin clearance delay and histological improvement, and patient-reported satisfaction in terms of perceived symptoms and quality of life.

Adhesion rates

Four of the nine studies using hyaluronic acid packs demonstrated a significant reduction in the rate of adhesions on endoscopic examination. Berlucchi *et al*. showed that resorbable nasal packing was associated with lower adhesion formation than non-resorbable nasal dressings after 12 weeks.[33] Kim *et al*. found objective evidence, using the Lund–Mackay scoring system, to indicate that adhesion rates were lower at four weeks post-operatively.[41] Those patients using hyaluronic acid packs were more likely to have no adhesions, defined as grade 0, and lower numbers of grade 1 adhesions, defined as adhesions limited to the middle turbinate, as compared to the controls. Studies by Catalano and Roffman[38] and Kimmelman *et al*.[36] also supported lower adhesion rates in non-randomised controlled environments. In the post-operative stage, at up to 12 weeks, adhesion formation appears to be lower than in the controls, as demonstrated by the meta-analysis. The other five studies showed no difference in adhesion rate.

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The meta-analysis found that adhesion formation occurred in 42 out of 283 cases (15 per cent), with a risk ratio of 0.52 (95 per cent CI = 0.37–0.72; I^2 = 36 per cent), compared to 81 out of 282 cases (29 per cent) in the control arm of the meta-analysis. The 29 per cent synechiae formation rate in the control group found in the meta-analysis is comparable to the 18.9–44 per cent adhesion rate after endoscopic sinus surgery reported in non-packed controls in the literature.[6,44,45] The meta-analysis excluded the studies by Catalano and Roffman[38] and Kimmelman *et al.*[36] because they had no randomisation and no control respectively (Figure 2). Given the heterogeneity of the control preparations and the study methodologies, however, the true effect is unclear. Larger, better-conducted studies may better ascertain the actual effect of hyaluronic acid on adhesion formation.

Although Shi *et al.* reported improvement of re-epithelialisation up to 8 weeks post-operatively in their intervention group, their hyaluronic acid side was refilled on day 2 post-operatively, with the control side not having similar treatment, and this may have influenced the early outcomes.[34] At 8–12 weeks, there is weak evidence that hyaluronic acid packs have an anti-adhesion effect, with only 1 of 6 studies demonstrating long-term evidence of reduced synechiae formation.[33]

Safety and tolerability

Absorbable hyaluronic acid dressing preparation appears to be well tolerated, according to patient satisfaction scores across two of the studies when compared with non-absorbable packs.[32,33] Lower adhesion rates suggest an improvement of the mucosal surface healing process compared to the control. The nebulised preparation poses difficulties for patients because of the need for specialised devices to deliver the drug, the monthly or daily frequency, and the time required for each nebulisation (which could be overly time consuming for the patient).[18,40] Despite this, it is a well-tolerated, safe and non-aggressive drug delivery method.

It is clear that hyaluronic acid in all preparations is safe and well-tolerated by patients, as evidenced by only one adverse event not related directly to hyaluronic acid, and the overall satisfaction with its use in absorbable nasal packs.[43]

Quality assessment

The quality assessment demonstrated that bias may play a role in the strength of this review, given the low rate of blinding and poor frequency of reporting of incomplete data. None of the studies included in the systematic review stated that they had used the Consolidated Standards of Reporting Trials ('CONSORT') standard for randomised controlled trial publishing and reporting.[46]

Study limitations

There are a number of limitations to the studies included in this review. 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. In addition, the studies comprised primary endoscopic sinus surgery cases, and therefore the effect of hyaluronic acid on the revision sinus surgery population is unknown. Lastly, 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 favour absorbable preparations.[47]

Conclusion

This systematic analysis of 501 patients in 13 studies found that the use of hyaluronic acid in post-operative care following sinus surgery for chronic rhinosinusitis appears to be useful as an adjunct, in addition to routine care, for the recovery of mucosal physiology, as demonstrated by lower adhesion rates. The meta-analysis included seven 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.

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