Effectiveness of Hyaluronic Acid Nasal Drops in Post Functional Endoscopic Sinus Surgery

Efektivitas Tetes Hidung dengan Asam Hialuronat pada Pasien Pasca Bedah Sinus Endoskopik Fungsional

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ABSTRACT

Functional Endoscopic Sinus Surgery (FESS) is commonly performed on patients with chronic rhinosinusitis (CRS) that has not improved through medical treatment. Hyaluronic acid (HA) has a vital role in wound healing and mucosa repair. This study aimed to determine the effectiveness of nasal drops using HA on clinical symptom scores, quality of life, and endoscopic features in post-FESS patients. This study was conducted with a pre- and post-test randomized control group design in 50 CRS patients undergoing FESS (25 males, 25 females, aged 18 to 55 years) at Dr. Kariadi General Hospital Medical Center Semarang from May to November 2019. The treatment group received additional HA therapy, while the control group only received standard therapy. Subjects were assessed with clinical symptom scores, quality of life, and endoscopic features before and after treatment. The statistical analysis was performed between the control and treatment groups using the Mann-Whitney test. There were significant differences between the control and treatment groups on clinical symptom scores (nasal congestion p = 0.001, runny nose p = 0.027) and endoscopic features (edema p = 0.001, secret p = 0.001, crusts p = 0.001). The therapy in post-FESS patients was using nasal drops, the treatment group was given HA, and the control group was given a placebo. Nasal drops using HA in the treatment group show improvement in clinical symptom scores of nasal congestion and runny nose, as well as the endoscopic appearance of edema, secret, and crusts.

Keywords: Endoscopic features, functional endoscopic sinus surgery, clinical symptom, hyaluronic acid

ABSTRAK

Tindakan Bedah Sinus Endoskopik Fungsional (BSEF), dilakukan pada pasien dengan Rinosinusitis kronis (RSK) yang tidak membaik dengan pengobatan medis. Asam hialuronat (AH) berperan penting dalam proses penyembuhan luka dan perbaikan mukosa. Penelitian ini bertujuan mengetahui efektivitas tetes hidung menggunakan AH pada skor gejala klinis, kualitas hidup dan gambaran endoskopik pada pasien pasca BSEF. Penelitian dilakukan dengan desain pre dan post-test randomized control group design pada 50 pasien RSK yang dilakukan BSEF (25 laki-laki, 25 perempuan; usia 18 hingga 55 tahun) di Rumah Sakit Umum Pusat dr. Kariadi Semarang bulan Mei hingga November 2019. Kelompok perlakuan mendapat tambahan terapi AH, sedangkan kelompok kontrol hanya mendapat terapi standar. Subjek dinilai skor gejala klinis, kualitas hidup dan gambaran endoskopik sebelum dan setelah terapi, dan dilakukan analisis statistik antara kelompok kontrol dan perlakuan menggunakan uji Mann Whitney. Terdapat perbedaan yang signifikan antara kelompok kontrol dan perlakuan pada skor gejala klinis (hidung buntu p = 0.001, hidung beringus p = 0.027) dan gambaran endoskopik (edema p = 0.001, sekret p = 0.001, krusta p = 0.001). Terapi pada pasien pasca BSEF menggunakan tetes hidung, pada kelompok perlakuan mendapatkan AH dan kelompok kontrol mendapatkan placebo. Tetes hidung dengan AH pada kelompok perlakuan memperlihatkan perbaikan skor gejala klinik hidung buntu dan hidung beringus, serta gambaran endoskopik edema, sekret dan krusta.

Kata Kunci: Asam hialuronat, bedah sinus endoskopik fungsional, gambaran endoskopik, gejala klinik
INTRODUCTION

Chronic rhinosinusitis (CRS) is inflammation of the nasal mucosa and paranasal sinuses that lasts more than 12 weeks and is accompanied by several clinical symptoms (1). The prevalence increased with age, with a mean of 2.7% and 6.6% in the age groups of 20-29 and 50-59 years, respectively. According to the European Position Paper on Rhinosinusitis and Nasal Polyps 2012 (EPOS 2012), the clinical symptoms of CRS consist of two or more, such as nasal congestion, runny nose/postnasal drip, facial pain, and loss of smell (2). The degree of rhinosinusitis can be assessed subjectively using the visual analogue scale (VAS), while the quality of life can be assessed using the Sino-Nasal Outcome Test 20 (SNOT 20). The assessment of rhinosinusitis can be assessed objectively using endoscopy and computed tomography (CT scan). The most commonly used endoscopy assessment is the Lund-Kennedy endoscopic scoring system, which assesses scars, crusts, edema, polyps, and secretion (3).

Patients with CRS can be treated with antibiotics, corticosteroids, nasal irrigation, and some additional therapies referring to patient complaints, such as decongestants, mucolytics, analgesics (4). Functional Endoscopic Sinus Surgery (FESS) is indicated for CRS patients who have been given maximal medical therapy but have not improved (5). FESS is a minimally invasive surgery on the nose and paranasal sinuses using an endoscopic device. The principle of FESS in CRS is to remove the tissue that causes the closing of the sinus ostium and facilitate drainage while maintaining normal sinus function (1,2,6).

Hyaluronic acid (HA) is the main component of the extracellular matrix found in airway epithelial cells, serous glands of the nasal mucosa and tracheobronchial mucosa, which biologically functions as interstitial and connective tissue components (7). HA has a vital role in the wound healing process and mucosal surface repair, so with HA administration, wound healing process would be faster, which biologically functions as interstitial and connective tissue found in airway epithelial cells, serous glands of the nasal mucosa and tracheobronchial mucosa, extracellular matrix found in airway epithelial cells, serous glands of the nasal mucosa and tracheobronchial mucosa.

METHOD

The study was conducted with a pre- and post-test randomized control group design at the ENT clinic of Dr. Kariadi General Hospital Medical Center Semarang from May to November 2019. The study protocol was approved by the Health Research Ethics Committee of Dr. Kariadi General Hospital Medical Center Semarang through the ethical clearance letter No.210/EC/KEPK-RSDK/2019. Sampling in this study is using unpaired numerical comparative method with single count, and 50 subjects were included. The research subjects were 50 people who met the inclusion criteria, namely CRS patients with diagnostic criteria based on EPOS, undergoing FESS, aged 18-55 years, had complete medical record data, and agreed to participate in the study. Patients with sinonasal malignancies were excluded.

Standard therapy was given after FESS in both groups, namely antibiotics, tranexamic acid, paracetamol, methylprednisolone, and nasal irrigation. The treatment group received additional therapy of 0.1% HA nasal drops, while the control group was given a placebo containing 0.9% NaCl. Double randomization was performed on the 0.1% HA and placebo bottles, which had the same shape, size, and color and were numbered according to the randomization table. The patient will be assessed clinical symptoms measured using VAS for the symptoms of nasal congestion, runny nose, facial pain, and anosmia/hyposmia, the quality of life using SNOT 20, and endoscopic features based on Lund-Kennedy criteria before surgery, one week after surgery, two weeks after surgery and four weeks after surgery.

Variables assessed were the clinical symptoms measured using VAS for the symptoms of nasal congestion, runny nose, facial pain, and anosmia/hyposmia, the quality of life using SNOT 20, and endoscopic features based on Lund-Kennedy criteria. The VAS uses a 10 cm horizontal line with verbal descriptions to express the condition of clinical symptoms, a value of 0 if the subject has no complaints and a value of 10 if the symptoms are very disturbing. SNOT 20 consists of 20 questions, each question has a range of 0-5 where 0 = no complaints, 1 = mild complaints, 2 = mild to moderate complaints, 3 = severe complaints, and 5 = very severe complaints. Lund Kennedy's endoscopic criteria have a range from 0 to 20, by assessing polyps (score 0 = no polyps, 1 = polyps in the middle meatus), 2 = polyps arise and out from the middle meatus; edema (score 0 = no edema, 1 = mild to moderate edema, 2 = severe edema), discharge (score 0 = none, 1 = clear with light discharge, 2 = mucopurulent discharge), scar tissue (score 0 = no scar tissue, 1 = little scar tissue, 2 = many scar tissue); and crusting (value 0 = no crusting, 1 = slight crusting, 2 = many visible crusting) (9). Other variables assessed were polyps, allergic rhinitis, diabetes mellitus, and smoking. Statistical analysis was performed using the Mann-Whitney and Chi-square test, The Mann-Whitney test was used because this study is an unpaired numerical comparative study, two groups with single measurement and abnormal data distribution. The Chi-square test is used in table 1 because the data are nominal, unpaired and single measured. Statistical analysis was performed using with SPSS 15 software.

RESULTS

A total of 50 study subjects consists of 25 males and 25 females with an average age of 35.96 ± 13.39 years. Table 1 shows no differences in the confounding factors, such as polyps, diabetes mellitus (DM), smoking, and allergic rhinitis, between the control and treatment groups. The side effect of the dry nose was more common in the treatment group.

Clinical symptom scores show significant differences in nasal congestion and runny nose between the treatment and control groups p <0.05 (Table 2).

Table 1. Characteristics of research subjects

| Variable          | Control n=25 | Treatment n=25 | p      |
|-------------------|--------------|----------------|--------|
| Age (average age range) | 35.96 ± 13.39 | 33.84 ± 12.17 | 0.5534 |
| Sex               |              |                |        |
| Male              | 14 (56%)     | 11 (44%)       | 0.3968 |
| Female            | 11 (44%)     | 14 (56%)       |        |

**Table 1.** Characteristics of research subjects
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| Variable          | Control | Treatment | p   |
|-------------------|---------|-----------|-----|
|                  | Group   | n=25      | n=25 |
| Polyp             |         |           |     |
| No                | 19 (76%)| 20 (80%)  | 0.733‡ |
| Yes               | 6 (24%) | 5 (20%)   |     |
| DM                |         |           |     |
| No                | 25 (100%)| 25 (100%) | –   |
| Yes               | 0 (0)   | 0 (0)     |     |
| Smoking           |         |           |     |
| No                | 23 (92%)| 24 (96%)  | 1.000¥ |
| Yes               | 2 (8%)  | 1 (4%)    |     |
| Allergic Rhinitis |         |           |     |
| No                | 15 (60%)| 14 (56%)  | 0.774¥ |
| Yes               | 10 (40%)| 11 (44%)  |     |
| Side Effect       |         |           |     |
| None              | 24 (96%)| 23 (92%)  | 1.000¥ |
| Dry nose          | 1 (4%)  | 2 (8%)    |     |

Note: * Significant (p < 0.05); ¥ Chi square

Table 2. Differences in clinical symptom scores between the treatment and control groups

| Clinical symptom score | Time of Examination | Group          | Mean±SD | p     |
|------------------------|---------------------|----------------|---------|-------|
|                        |                     | Treatment      | Control |       |
|                        |                     | Mean±SD        | Mean±SD |       |
| Nasal Congestion       | Before Operation    | 5.52 ± 2.71    | 5.32 ± 2.56 | 0.921† |
|                        | 1st Week            | 2.72 ± 2.13    | 3.44 ± 2.00 | 0.188‡ |
|                        | 2nd Week            | 0.68 ± 1.35    | 2.08 ± 1.71 | 0.001* |
|                        | 4th Week            | 0.44 ± 0.92    | 0.96 ± 1.24 | 0.074‡ |
| Runny Nose             | Before Operation    | 4.52 ± 2.87    | 3.80 ± 2.12 | 0.294‡ |
|                        | 1st Week            | 2.16 ± 2.01    | 2.56 ± 1.71 | 0.357‡ |
|                        | 2nd Week            | 1.12 ± 1.69    | 1.76 ± 1.48 | 0.078‡ |
|                        | 4th Week            | 0.52 ± 1.01    | 1.12 ± 1.20 | 0.027* |
| Facial Pain            | Before Operation    | 3.64 ± 3.55    | 2.08 ± 2.60 | 0.117† |
|                        | 1st Week            | 1.28 ± 1.75    | 1.00 ± 2.08 | 0.275‡ |
|                        | 2nd Week            | 0.40 ± 0.96    | 0.68 ± 1.68 | 0.855‡ |
|                        | 4th Week            | 0.24 ± 0.66    | 0.12 ± 0.60 | 0.332‡ |
| Loss of Smell          | Before Operation    | 2.80 ± 3.88    | 1.80 ± 2.78 | 0.653‡ |
|                        | 1st Week            | 2.32 ± 3.66    | 1.68 ± 2.72 | 0.769‡ |
|                        | 2nd Week            | 1.32 ± 2.50    | 1.00 ± 1.87 | 0.825‡ |
|                        | 4th Week            | 0.84 ± 1.93    | 0.76 ± 1.23 | 0.480‡ |

Note: * Significant (p < 0.05); ‡ Mann whitney

The difference in the quality of life scores between the treatment and control groups (Table 3) shows no significant differences between the two groups p >0.05.

The endoscopic features based on the Lund-Kennedy score (Table 4) show significant differences in the endoscopic features of edema, secret, and crusts between the treatment (Figure 1) and control groups (Figure 2).

DISCUSSION

Chronic rhinosinusitis (CRS) incidence is commonly found...
in adulthood. The lowest age of the subjects of this study was 18 years old, while the highest was 55 years old, with an average age of 35 years in the control group and 33 years in the treatment group. Similar results were obtained in Denpasar (2016) reported that the highest CRS onset is at the age range of 31-45 years (40,16%) (10). This is influenced by the formation of sinususes, where the sinuses are fully developed at the age of 20. The anatomy and physiology of the sinuses change with age, such as decreased ciliary beat frequency, decreased nasal vasculature, and decreased nasal mucous secretion (11).

Risk factors for CRS can be intrinsic and extrinsic that can affect the prognosis and postoperative wound healing. Of all subjects in this study, 42% were found allergic rhinitis, 6% were smoking, and 22% were polyps. Patients with a history of allergic rhinitis can experience failure in postoperative wound healing due to persistent mucociliary dysfunction (12). Smoking can slow down wound healing because nicotine interferes with the oxygen supply to the tissues (13). Polyps cause high recurrence, so that it can affect the outcome of surgery (14,15). This affects the wound healing process after FESS.

The side effect of topical medication that patients complained about in this study was the dry nose, while HA side effects, such as nosebleeds or drug allergies, were not found. Dry nose sensation can be the side effect of nasal irrigation (16), and is not the side effect of HA. Currently, there is no information regarding the side effects of topical hyaluronic acid administration.

Clinically, significant differences were found in the symptoms of nasal congestion between the treatment and control groups. It happens because HA can repair damaged nasal mucosa and modulate cellular function, either related to nasal pathology or FESS procedures. HA can protect sinonasal epithelium caused by the postoperative inflammatory process (17), and reduce the occurrence of crusts and edema so that nasal congestion is reduced (18). The score of runny nose symptoms was significantly different between the treatment and control groups. HA can reduce the production of glandular secretions in the nose and inhibit the inflammatory process so that the production of secretions is reduced (18). This is in accordance with Cantone’s study, which found a significant difference in the group given hyaluronic acid, especially in clinical symptoms (7).

Clinical symptoms score of facial pain and loss of smell did not show significant differences in the control and treatment groups. Pain and nasal congestion in CRS are caused by contact points or pressure on sinus inflammation that presses the trigeminal nerve in the sinonasal mucosa (19). FESS, besides opening the ostiomeatal complex, also removes pathological tissue so that it returns the remodeling process (20).

FESS is a procedure of cleaning the pathological tissue caused by an inflammatory process, aiming to reduce the inflammatory process and create a conducive environment for normal mucosal regeneration (21-23). After FESS, the quality of life of research subjects in both groups will improve, so the quality of life scores between the treatment and control groups show no significant difference.

There were no significant differences in the endoscopic appearance of polyps and scar tissue in the control and treatment groups. FESS removes the pathological mucosal tissue, removes the pathological bone while maintaining normal mucosa as optimal as possible, and widens the ostium to improve mucociliary transport. A good mucociliary transport of the nose will promote the migration of healthy cells and the replacement of damaged cells. FESS will decrease the number of polyps, edema, or erythema (21,24), so that post-FESS CRS patients will experience the same improvement between treatment and control.

The endoscopic features of edema, secret, and crusts show significant differences between the control and treatment groups. It can occur because HA plays a role in the binding mechanism and architectural configuration in connective tissue that has an effect on stability, lubrication, water homeostasis, molecular filtration, and inhibit the inflammatory process. HA also plays a role in the recovery of nasal mucosal wounds, increases nasal mucociliary transport, accelerates reapithelialization to reduce the production of crusts, secret, and edema. These results are in accordance with Cassano’s study (22).

This study assesses clinical improvement, quality of life, and endoscopic features until the 4th-week post-operation, and it became the limitation of this study because this study has not been able to assess the overall wound healing process that the wound healing process ends in the 6th month postoperative.

This study shows that nasal drops using HA in patients post-FESS showed improvement in clinical symptoms (nasal congestion and runny nose) and endoscopic features (edema, secret, and crusts) compared to those without HA.
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