Short Outcomes of Intraoperative Application of Berberine Hydrochloride with or without Adding Hyaluronic Acid in Endoscopic Sinus Surgery

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ABSTRACT

Background: Hyaluronic acid (HA) and berberine hydrochloride are thought to be effective postoperative factors after chronic rhinosinusitis (CRS) nasal surgery. **Objective:** This study aimed to assess the effects of berberine hydrochloride with or without adding hyaluronic acid in adult patients of chronic rhinosinusitis, with or without polyps, who were scheduled for bilateral endoscopic sinus surgery. **Patients and methods:** The patients were randomly assigned into two groups based on the way of postoperative intervention used. Thus, gel foam with berberine was used for the first group (B group), and berberine with hyaluronic acid was used for the second group (HB group). In every case, this aforementioned procedure was done in one nasal cavity of the nose with a focus on the middle meatus, but saline only was used with gel foam in the other cavity, after surgery, respectively. During the postoperative visits on 5, 10, 30, and 90,180 days, the patients were asked to complete a questionnaire. Using the VAS scale for nasal blockage, score the severity of complaints on each side independently. At each visit, evaluation of the healing process by rigid endoscopy and then by numerical scale. **Results:** On the 10th day lateralization was less in the HB group than in the B group (P value 0.033) and on the 30th day, crust formation was less in the HB group than in the B group (P value 0.031). There was a significant difference regarding synechiae on the 30th day that was less in HB group than B group (0.012). On the 30th day, the VAS scale for nasal obstruction was less in the HB group than in the B group (P value 0.022). **Conclusions:** In sino-nasal surgery, the use of absorbable nasal packing with hyaluronic acid and berberine hydrochloride improves patient comfort as well as the healing process. Nonetheless, more research is required to optimize it.

Keywords: Dressing, Berberine, Sinusitis, Surgery, Rhinology.

INTRODUCTION

Since the early days of endoscopic sinus surgery, the most important critical determinant of the procedure's outcome is the healing process. As long as options for a programmed healing process are not available, the doctor's tries are focused on avoiding healing complications like postoperative bleeding, infection, inflammation, meatus obstruction, and development of synechia [(1–9)]. The use of packing intranasally, which was at first not absorbable but is now bioresorbable, appears to reduce the incidence of complications yet does not completely eradicate them [(1, 3, 8)]. Consequently, there is a constant introduction of new pharmaceutical and non-pharmacological therapies. Steroids, antibiotics, antihistamines, and anti-inflammatories are examples of rudimentary groups of substances [(10-13)]. Treatment with humanized monoclonal antibodies is currently available, however, it is mostly utilized for individuals who also have nasal polypi and asthma [(14)].

Systemic and topical drug administration methods are possible, but considering the potential side effects, local drug application is favored. However, the application of nasal sprays or drops topically is associated with adequate penetration of these drugs into tissues following endoscopic sinus surgery (ESS) surgery [(15–20)]. The nasal dressing can be used as a carrier for topically administered medications to treat this problem [(11)].

Hyaluronic acid (HA) is a biological substance, which exists in the extracellular matrix. HA is widely used in ENT, gynecological, orthopedic, general, and cosmetic surgery because of its special hygroscopic, viscoelastic, and mucoadhesive properties as well as its high immunological and toxicological safety [(4)]. Clinical trials demonstrating the modifying effects of HA on wound healing and mucosal regeneration have been reported along with the safety, efficacy, and tolerability of HA [(10)]. Berberine (BBR) is an alkaloid of isoquinoline that exists in many plants, such as Aspapapveraceae, berberidaceae, ranunculacese, rutaceae, menispermaceous, and Rhamnaceous. Berberine is a part of Chinese traditional medicine that has different pharmaceutical outcomes [(18, 19)]. It had been initially used for the treatment of gastrointestinal inflammation due to its strong anti-inflammatory and anti-microbial properties [(20, 21)]. BBR has been demonstrated to possess anti-viral, anti-bacterial, antiproliferative, anti-fibrosis, anti-tumor, and anti-adhesion qualities besides being anti-inflammatory, BBR has been applied to clinical studies treating uveitis, cardiovascular disease, and diabetes, ocular trachoma, and cancer [(19, 20)]. This study aimed to assess the post-operative side effects and risks associated with using gel foam in conjunction with berberine hydrochloride or berberine hydrochloride with hyaluronic acid on the healing process and quality of life in adult patients who were scheduled for bilateral endoscopic sinus surgery.

PATIENTS AND METHODS

A prospective, double-blind, randomized controlled study was conducted on 60 patients with CRSw/woNP who underwent bilateral FESS at Zagazig University Hospitals. Randomly selected adult patients with chronic rhinosinusitis (with or without nasal polypi) who were refractory to maximal medical

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treatment and eligible for bilateral FESS were included in the study.

Detailed history and clinical examination including nasal endoscopy and sinonasal CT scan were performed for all included patients.

Exclusion criteria: Patients exhibiting symptoms of acute infection and patients with purulent nasal discharge.

There was no regular collection of swabs. Lund-Mackayand Lund-Kennedy scales were used to assess all patients. After randomization by a computer-based program, All 60 patients were divided into two groups (n=30 in each): **1st group**, berberine hydrochloride (B) (Krka Poland). Saline was used in one side nostril (control) and in the other side berberine hydrochloride (B) was used and named as drug side. **2nd group**, hyaluronic and berberine (HB). Saline was used in one side nostril (control) and the other side hyaluronic and berberine (HB) were used (drug side). The degree of the surgery was comparable for each patient.

As a result, antrostomy, ethmoidectomy for anterior and posterior groups, sphenoidotomy, and frontal recess type Draf 2a or 2b surgery was done.

Following the ESS procedure, gel foam packing soaked in the selected drug was put in one of the two nasal cavities, while the opposite one was managed by saline-soaked gel foam, as the control side. Each group's sides were chosen at random, with the medication being administered at a steady dose of berberine powder amount which can be detected by small sized nasal dissector to be dissolved in 5 ml saline in 1st group while in the 2nd group the same amount of berberine powder with adding 2 ml of hyaluronic acid. The operating room nurse, who had received prior training, prepared the dressings. Until the end of the study, neither the surgeon nor the individuals conducting the follow-up visits were aware of the medications used or their distribution.

All patients received the same recommendations postoperatively, which included using nasal steroids for three weeks and cleaning the nose once a day with saline solution for two weeks. Postoperative healing was assessed on the 5th, 10th, 30th, and 90th days following the surgery. Subjective complaints (headache, nasal pain, pressure, nose obstruction, itching, bleeding, and smell) were rated separately to each side using the VAS (Visual Analogue Scale) 10° with 0 representing no complaints at all, and 10 representing the greatest and most severe symptoms a patient may have.

Scent markers were used to assess the patient's sense of smell, while the Lund-Kennedy and numerical scales were used to assess the process of healing (mucosal edema, bleeding, suction of debris or secretions, formation of synechia, crustation and granulation, or lateralization).

Ethical approval: Approval was obtained from The Institutional Review Board Committee, Zagazig University (ZU-IRB #10327). Consents were taken from all patients. Every phase of the study was adhered to The Helsinki Declaration.

Statistical analysis

The acquired data was coded, processed, and analysed using SPSS version 22.0 for Windows. Using the Shapiro Walk test, data were examined for normal distribution. Relative percentages and frequencies were used to display the qualitative data. Utilizing the Chi-square test (χ^2), one may determine the disparity between two or more sets of qualitative variables. The quantitative data was presented as mean ± SD. The test power for 0.80 and statistical significance at the level of $P \leq 0.05$ were established. The Mann-Whitney test (P <.05m) was used for paired analysis and the Kruskall-Wallis test ($P \leq 0.05$m). Significant results were obtained when the p-value was equal to or less than 0.05.

RESULTS

Sixty patients (37 men and 23 women) were included in our study with a mean age of 34.57. All patients had completed visits for follow-up. Patient's demographics and baseline data were summarized in table (1).

Table (1): The patients' demographics

	Group(B) (n=30)	**Group (HB) (n=30)**	**Total**
Age (year)	42.95 ± 14.422	47.73 ± 12.447	44.68 ± 14.724
Male: Female	22:18	25:15	71:49
LundMackay CT score	17.08 ± 5.876	14.95 ± 5.198	15.59 ± 5.487
LundKennedy endoscopic score	7.85 ± 2.713	6.85 ± 2.424	7.05 ± 2.771
Operation time (min)	69.50 ± 19.865	74.75 ± 22.129	72.13 ± 20.901

Endoscopic findings analysis:

Endoscopic values of both groups were compared in table (2). No significant differences were found in the groups' records of packing resorption, granulation, secretion, bleeding intensity, or need for debris suction. These measurements, (lateralization, synechia formation and crusts, and VAS scoring for nasal obstruction) were found to be significantly different between the two groups as demonstrated in table (3). Lateralization was less in the HB group than in the B group (P value 0.033). On the 30th day, crust formation was less in the HB group than in the B group (P value 0.031). There was a significant difference regarding synechiae on the 90th day that was less in HB group than in the B group (0.012). On the 30th day, the VAS scale for nasal obstruction was less in the HB group than in the B group (P value 0.022), and 30th day for the HB group than in the B group as demonstrated in table (3). After 3 months of surgery, pain, crusting, pus, nasal discharge, and obstruction were statistically not significant between both groups (Tables 2 & 4).

Table (2): The endoscopic findings analysis (mucosal edema, secretion, crusts, and Lund-Kennedy scale points) in the days following surgery.

			Postoperative day			
Finding	**Group**	**Side**	**10**	**30**	**90**	**180**
Mucosae edema (03)	B (n=30)	Drug	0.41 ± 0.498	0.33 ± 0.577	0.46 ± 0.730	0.49 ± 0.981
		Control	0.46 ± 0.505	0.35 ± 0.486	0.46 ± 0.767	0.60 ± 1.035
		P value	0.527	0.683	1.000	0.102
	HB (n=30)	Drug	0.25 ± .439	0.46 ± 0.682	0.37 ± 0.633	0.32 ± 0.727
		Control	0.40 ± 0.496	0.67 ± 0.737	0.68 ± 0.775	0.44 ± 0.894
		P value	0.002	0.016	0.011	0.083
Secretion (03)	B (n=30)	Drug	0.41 ± 0.549	0.33 ± 0.478	0.14 ± 0.347	0.17 ± 0.382
		Control	0.72 ± 0.686	0.59 ± 0.594	0.22 ± 0.417	0.14 ± 0.355
		P value	0.003	0.016	0.257	0.317
	HB (n=30)	Drug	0.55 ± 0.552	0.62 ± 0.782	0.21 ± 0.413	0.26 ± 0.511
		Control	0.65 ± 0.622	0.54 ± .643	0.32 ± .525	0.24 ± 0.496
		P value	0.285	0.724	0.046	0.655
Crusts (01)	B (n=30)	Drug	0.82 ± 0.389	0.18 ± 0.389	0	0
		Control	0.85 ± 0.366	0.21 ± 0.410	0	0
		P value	0.317	1.000	1.000	1.000
	HB (n=30)	Drug	0.73 ± 0.452	0.26 ± 0.446	0.03 ± 0.164	0
		Control	0.83 ± 0.385	0.24 ± 0.431	0	0
		P value	0.157	1.000	0.317	1.000
LundKennedy (06)	B (n=30)	Drug	0.67 ± 0.772	0.64 ± 0.811	0.57 ± 0.867	0.54 ± 1.039
		Control	1.05 ± 0.826	0.85 ± 0.812	0.62 ± 0.953	0.60 ± 1.117
		P value	0.009	0.009	0.527	0.157
	HB (n=30)	Drug	0.68 ± 0.797	1.00 ± 1.076	0.58 ± 0.889	0.56 ± 1.021
		Control	0.95 ± 0.986	1.28 ± 1.169	0.97 ± 1.219	0.76 ± 1.458
		P value	0.087	0.096	0.008	0.084

Table (3) showed statistically significant differences between two groups at different days, in crust formation (30th day), lateralization (10th day), synechiae (30th day) and VAS scale for nasal obstruction.

Table (3): Parameters: crust formation (30th day), lateralization (10th day), synechiae (30th day), VAS scale for nasal obstruction

	HB Group (n=30)	**B Group (n=30)**	**P value**
Lateralization on the 10th day	0.23 ± .241	0.04 ± .232	0.033
Syanechia on the 30th day	0.05 ± .128	0 .13 ± .441	0.031
Crust formation on the 30th day	0.03 ± .282	0.24 ± .503	0.012
VAS scale for nasal obstruction	0.04± .383	0.24 ± .602	0.022

Patients' complaints: Patients' complaints were analyzed for each group and revealed many important differences as illustrated in table (4). In the findings of the study, there were variations in two parameters: nose blockage, and facial pressure on the 10th and 30th day for the HB group than for the B group (p value 0.041). There were no differences in the parameters of bleeding, itching, headache, or nose pain.

Table (4): Patient complaints analysis

			Patient complaints analysis.				
			Postoperative day				
Complaint	**Group**	**Side**	**2**	**10**	**30**	**90**	**180**
Facial pressure (010)	B (n=30)	Drug side	1.65 ± 2.020	0.51 ± 1.189	0.38 ± 0.963	0.24 ± 0.760	0.54 ± 1.597
		Control side	1.88 ± 2.300	0.90 ± 1.569	0.90 ± 1.774	0.57 ± 1.042	0.57 ± 1.632
		P value	0.05	0.011	0.066	0.048	0.317
	HB (n=30)	Drug side	2.18 ± 2.385	1.35 ± 1.929	1.05 ± 2.079	0.38 ± 1.479	0.29 ± 0.906
		Control side	2.88 ± 3.031	1.90 ± 2.205	1.61 ± 2.212	0.73 ± 1.677	0.35 ± 1.070
		P value	0.015	0.057	0.024	0.039	0.317
Nasal blockage (010)	A(n=30)	Drug side	3.45 ± 2.012	1.67 ± 1.722	0.95 ± 1.905	0.32 ± 0.784	0.54 ± 1.400
		Control side	3.88 ± 2.311	1.92 ± 1.723	1.46 ± 1.862	1.00 ± 1.269	0.83 ± 1.807
		P value	0.200	0.356	0.032	0.000	0.041
	HB(n=30)	Drug	2.73 ± 2.386	2.25 ± 1.932	1.39 ± 2.112	0.54 ± 1.043	0.38 ± 1.074
		Control	4.23 ± 2.796	3.43 ± 2.049	2.34 ± 2.281	1.00 ± 1.333	0.38 ± .954
		P value	0.000	0.005	0.022	0.051	1.000
Smell (010)	A(n=30)	Drug	2.60 ± 3.103	5.28 ± 3.077	7.00 ± 3.656	8.08 ± 3.303	8.34 ± 3.378
		Control	2.18 ± 3.104	4.92 ± 3.157	6.69 ± 3.599	7.95 ± 3.333	8.31 ± 3.411
		P value	0.007	0.008	0.039	0.102	0.317
	HB(n=30)	Drug	3.75 ± 3.861	6.33 ± 3.437	7.58 ± 3.210	8.97 ± 2.192	9.47 ± 1.461
		Control	3.28 ± 3.755	5.58 ± 3.713	7.03 ± 3.284	8.89 ± 2.233	9.44 ± 7.460
		P value	0.011	0.002	0.007	0.276	0.317

DISCUSSION

The type of postoperative care given after endoscopic sinus surgery is crucial in managing patients with chronic rhinosinusitis. It is important to prevent healing complications such as postoperative bleeding, infection, inflammation, meatal obstruction, and synechiae. There is ongoing debate concerning the benefits and drawbacks of biodegradable nasal packing [18]. In a double-blind, prospective, randomised experiment, **Kastl *et al.*** [7] compared the non-packing method with NasoPore and found no differences in the frequency of postoperative bleeding. However, there was a considerable decrease in the sensation of pressure in the second and third postoperative days. In a prospective, double-blind, randomised trial conducted by **Shoman *et al.*** [21]**,** there was no difference in the complaints of patients regarding pain, pressure, obstruction, swelling and bleeding, or discomfort upon removal between NasoPore and non-absorbable Merocel foam. There was no noticeable variation in the rate of bleeding. The only difference that was observed was in the mucosal healing, which improved on the Merogel side after four weeks and disappeared in the twelfth week [21]. From here idea of using Gelfoam to be the carrier for our drugs in our study. Although nasal packing alone may not completely resolve the issues, further interventions are often required. The usage of pharmaceuticals in the packaging is one of them. It is a given that HA aids in the healing process following surgery, as evidenced by several earlier studies [5, 19, 23, 24, 25]. **Amato *et al.*** [26] showed that the use of hyaluronic acid in conjunction with poly-L-lysine, and berberine hydrochloride, and a better wound healing process was demonstrated by the closure of the fibroblast gap. These results imply that hyaluronic acid and berberine hydrochloride together may be helpful for ESS. Nevertheless, only a small number of research have evaluated the effectiveness of combining hyaluronic acid with berberine hydrochloride on clinical outcomes in ESS to date.

Endoscopic sinus surgery using a biodegradable gel comprising berberine hydrochloride and hyaluronic acid was the subject of an investigation, the results showed that the biodegradable material was superior to merogel alone in terms of duration of hospital stay, post-operative symptoms, and sinus cavity status in the early stages following ESS [25].

In our study we found that, these measurements, lateralization, crusts, and VAS scale for nasal obstruction) were found to be significantly different on the 10th day. Lateralization was less in the HB group than in the B group (P value 0.033). On the 30th day, crust formation was less in the HB group than in the B group (P value 0.031). There was a significant difference regarding synechiae on the 30th day that was less in HB group than in B group (0.012).

On the 30th day, the VAS scale for nasal obstruction was less in the HB group than in the B group (P value 0.022). After 3 months of surgery, pain, crusting, pus, nasal discharge, and obstruction were statistically not significant between both groups. Our results agree with the clinical trial of **Erdoğan *et al.*** [26] who investigated the impact on edema, discharge, crusting, and mucociliary clearance of nasal irrigation solutions containing saline, xylitol, and hyaluronic acid. Researchers found that crusting was less common in the xylitol group after one week compared to the saline group (p=0.025). But otherwise, there was no difference in crusting across the three groups in the first month. In comparison with the first week, there was less crusting in the saline, hyaluronic acid, and xylitol groups in the first month (p=0.006, p=0.008, and p=0.014 respectively [27].

The advantages of our study over the previous study were in adding berberine to hyaluronic acid and using gel foam as carrier, not as irrigation, which relies on the patient not on the surgeon. Another advantage of this study is that it proved the synergistic effect of both substances together. A controlled trial was performed to examine the effects of placing HA in one side of the nasal cavity and NAP on the other side; our study compares with their findings. Three sides (8%) of patients with HA and three sides (8%) of patients with NAP had synechia at the last follow-up, accounting for 14% of the total. At least one synechia occurred in thirteen patients (35%), with ten associated with HA (27%) and nine with NAP (24%). Five sides (14%) used HA, three patients (8%) used NAP, and seven patients (19%) needed synechia lysis [27].

Our findings are not consistent with a controlled study performed by **Wormald *et al.*** [28] who studied the efficacy of merogel on one side and no packing on the other side where synechia, edema, and infection were measured at two weeks, the side packed with merogel had 35% of synechiae, 83% of edema, and 30% of mucopurulent discharge. The control side had comparable numbers, with 22.5% of synechiae, 83% of edema, and 28% of mucopurulent discharge.

Woodworth *et al.* [29] conducted a controlled, single-blinded research, an HA/CMC packing was assigned randomly to one side with the opposite unpacked side serving as a control. At 8-week follow-up, there was no difference in synechiae on the HA/CMC side compared to the control (p = 0.09). However, our results demonstrated fewer synechiae percentages in the first 4 weeks postoperatively in comparison with the control side (p = 0.031).

Our study is the first one to compare between benefits of a combination of berberine and HA versus the use of HA alone on mucosal healing improvement. The group that received both berberine and HA showed the greatest improvements in face pressure, nasal obstruction, and smell, as well as decreased mucosal edema and secretion and a lower Lund-Kennedy score, demonstrating the synergistic effects of both substances when combined.

No notable bleeding or granulation tissue was recorded, which confirmed the safety of the

combination. To obtain the best clinical outcomes and prevent any difficulties or side effects at the same time, the ideal drug concentration still needs to be determined.

CONCLUSION

The use of an absorbable nasal dressing impregnated with a combination of hyaluronic acid and berberine hydrochloride during endoscopic sinus surgery significantly improved postoperative healing and patient satisfaction. According to the study's findings, it would be imperative to conduct more research to determine the most satisfactory requirements for the dressings used and the exact amount of the drug used.

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