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Efficacy of Carragelose® Nasal Spray Impregnated Versus Mupirocin Ointment Impregnated Nasal Packs on Mucosal Healing after Endoscopic Sinus Surgery: A Double-Blind, Non-Randomized, Right-Left Side Comparison

ABSTRACT

Objective: To determine the efficacy of carragelose® nasal spray versus mupirocin ointment impregnated nasal packs on postoperative mucosal healing among chronic rhinosinusitis with nasal polyposis (CRSwNP) patients after endoscopic sinus surgery (ESS).

Methods:

Design: Double-Blind, Non-Randomized, Right-Left Side Comparison

Setting: Tertiary Government Training Hospital

Participants: Fifteen (15) patients diagnosed with chronic rhinosinusitis with nasal polyposis (CRSwNP) who had ESS were included in the study. Nasal packs (Netcell®) impregnated with carragelose® nasal spray or mupirocin ointment were respectively applied in right and left nostrils. Postoperative mucosal healing was graded by a blinded consultant using the Lund-Kennedy Endoscopic Scoring System and Perioperative Sinus Endoscopy (POSE) scoring system.

Results: Six patients (12 nasal sides) completed the study. Comparing nasal packs impregnated with carragelose® nasal spray mupirocin ointment, the carragelose® group had lower Lund-Kennedy median scores than the mupirocin group on the 7th post-operative day; and this was statistically significant (p = .027). There were no significant differences in Lund-Kennedy postoperative scores on days 4 (p = .217), 14 (p = .171) and 28 (p = .151).

Conclusion: Carragelose® nasal spray impregnated nasal packs may be comparable with, and may be an alternative to mupirocin ointment impregnated nasal packs in terms of postoperative mucosal healing among ESS patients with CRSwNP.

Keywords: *carragelose; mupirocin; nasal pack, endoscopic sinus surgery, nasal polyp*

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Application of nasal packs is common practice after endoscopic sinus surgery (ESS) to control post-operative bleeding, facilitate re-mucosalization of the sinonasal cavity and convey medications to the operative site.[1-3] In our institution, mupirocin topical ointment USP, 2% has been commonly used to impregnate nasal packs with good experience and no untoward effects.[2-4] However, mupirocin is not the only available agent. Various medications can be applied to nasal packs and there appears to be no agreement on which drug is better.[5-6]

Carragelose® is a polysaccaharide carbohydrate obtained from red seaweeds, *Chondrus crispuse* species.[6] This species is common in the Atlantic Ocean and also abundant in the Philippines.[6] It is used for meat processing, personal care and pet food products and in recent years as medicine.[6] Carragelose® is claimed to have multiple properties including anticoagulant, antithrombotic, anti-tumor and immunomodulatory.[6-8] Carragelose® nasal spray (Betadine™ Marinomed Biotech AG, Mundipharma Laboratories GmbH) is used to shorten the duration of common colds primarily by trapping and clearing viruses in mucus, hindering their binding or entry into the cell.[6] To the best of our knowledge, a search of HERDIN, MEDLINE (PubMed), Cochrane and Google Scholar revealed no published study on the use of carragelose® on nasal packing after ESS.

As part of our quest for alternative medications to apply on nasal packs, this study was conducted to determine the efficacy of carragelose® nasal spray - impregnated versus mupirocin ointment - impregnated nasal packs on postoperative mucosal healing after ESS for chronic rhinosinusitis with nasal polyposis (CRSwNP).

METHODS

This prospective, double-blind, non-randomized, right-left side comparison was conducted with approval of the Bioethics Committee of the Quezon City General Hospital. Patients diagnosed with CRSwNP who underwent ESS from October 2018 to August 2019 were considered for inclusion in the study. The following were excluded: patients with past history of nasal surgery because of a tumor other than nasal polyp, recurrent nasal polyposis, presence of co-morbidities such as diabetes mellitus, uncontrolled hypertension, immunocompromised condition, those on anticoagulant therapy and with bleeding disorders.

The sample size was computed with mean difference and standard deviations based on the data presented in the study of Promentilla *et al*.[9] A significance level of 0.05 and power of 80% were used in computation. A drop-out rate of 20% was used to calculate the adjusted sample size using the following formula.

$$n \geq \frac{2\sigma^2\left(Z_{\alpha/2} + Z_{\beta}\right)^2}{d^2}$$

$$n_{adjusted} = 1.2(n)$$

Where:

n is the minimum sample size for each group to detect whether the stated difference exists between the two means

$Z_{\alpha/2}$ is the critical value of the normal distribution at α/2 (e.g. for a confidence level of 95%, α is 0.05 and the critical value is 1.96)

Z_{β} is the critical value of the normal distribution at β (e.g. for a power of 80%, β is 0.2 and the critical value is 0.84),

σ^2 is the population variance; and

d is the difference you would like to detect.

The sample size used in this study had a 95% confidence level and a power of 80%, with detectable difference of 1.0 and standard deviation of 1.0. The ideal sample size was 16 subjects with a total of 32 nasal sides.

Histories with emphasis on rhinologic problems were obtained, and otorhinolaryngoscopic examinations, nasal endoscopies and subsequent grading of nasal polyposis using the Lund-McKay classification were performed. Preoperatively, patients were prescribed cefuroxime 500mg/tab twice a day for one week and prednisone 20mg/tab every eight hours for one week. The ESS was performed on each patient by an assigned ear, nose and throat (ENT) senior surgical resident. In patients with an antrochoanal polyp, ESS with Caldwell-Luc procedure was performed on the affected side with ESS on the contralateral side for chronic rhinosinusitis.

After surgery, an ENT surgical resident who was not part of the study inserted a 4cm x 2cm nasal pack (Netcell®) impregnated with carragelose® nasal spray or mupirocin ointment in the right and left nostrils respectively, under supervision by the principal investigator. The patients (still under anesthesia) were blinded to this treatment. The identity of medications was not concealed from the surgeons because the containers were recognizable and the medications were applied differently: carragelose® was sprayed on the right nasal packs after pack insertion, while mupirocin was coated on the left nasal packs before pack insertion.

Intravenous cefuroxime 750mg every 8 hours and ketorolac 30mg as needed were given post-operatively for the first 24 hours after surgery then shifted to oral cefuroxime 500mg/tab twice daily and celecoxib 200mg/cap twice daily as needed for the next 7 days.

Nasal packs in both nostrils were removed on the 4th post-operative day then nasal saline irrigation with suctioning to clean the nasal cavity was followed by video-endoscopy using a Karl-Storz Tricam SL II and Xenon Nova 300, all performed by the assigned surgeon. Patients visited the out-patient department on the 7th, 14th and 28th post-operative days for follow-up and documentation of post-operative site healing using the same video nasal endoscopy set-up, also performed by the same surgeon.

The Lund-Kennedy Endoscopic Scoring System[10] and Perioperative Sinus Endoscopy (POSE) scoring system[11] were used to grade postoperative mucosal healing. The former scored each of 5 parameters (presence of nasal polyp, discharge severity of mucosal edema, scarring, crusting) on a scale of 0 to 2.[10] The latter additionally assessed the middle turbinate (normal, synechia, lateralized), middle meatus (normal, narrowed, complete obstruction / stenosis) maxillary sinus content (normal, edema or thin discharge, purulent or allergic mucin), maxillary and ethmoid cavity, as well as frontal and sphenoid sinuses (if operated on), also scoring each on a scale of 0 to 2.[11] A Lund-Kennedy score of 10 or POSE score of 16 were used to indicate post-operative complications which may compromise healing; with lower scores signifying better healing.

A blinded ENT consultant graded the recorded video endoscopic findings of each patient (for the 4th, 7th, 14th, and 28th day) in one sitting, using the Lund-Kennedy Endoscopic Scoring System[10] and Perioperative Sinus Evaluation Scoring System.[11]

The consultant-recorded score, and demographic and clinical characteristics of patients were collated, tabulated and recorded in Microsoft® Excel version 2016 (Microsoft Corp., Redmond WA USA). Numerical data were summarized using mean, median and standard deviation with minimum and maximum values. Categorical data were presented as frequencies and percentages. Group means of numerical variables were computed, then compared using Mann-Whitney U test and Friedman test at 5% level of significance. Additional computations were performed using PH Stat version 4.51 (Prentice-Hall, Inc., Pearson Education, London, UK).

RESULTS

Initially, there were 17 patients who satisfied inclusion and exclusion criteria, but two patients did not complete the study because one was diagnosed postoperatively with inverting papilloma and another had profuse bleeding due to hypertension. Hence, a total of 15 patients (30 nasal cavities) were initially included in this study; 8 males (53.3%) and 7 females (46.7%) with mean age of 41.8 ± 15.8 years (range 14 to 74 years old).

Twelve (12) out of 15 patients were diagnosed with chronic rhinosinusitis with bilateral nasal polyposis and underwent bilateral endoscopic sinus surgery under general anesthesia. Two (2) out of these 12 patients had deviated nasal septum and underwent septoplasty as well. Three (3) out of 15 patients were diagnosed with chronic rhinosinusitis with antrochoanal polyp and underwent bilateral endoscopic sinus surgery and a Caldwell-Luc procedure under general anesthesia. One patient was lost to follow-up on day 7 and 4 patients each were lost to follow up on days 14 and 28. Hence, only 6 patients or 12 nasal cavities completed the study.

Lund-Kennedy median scores were only significantly different on day seven for the carragelose® side (Mdn = 2.50, IQR = 2.50) compared to the mupirocin side (Mdn = 4.00, IQR = 3.75) [Mann-Whitney *u* = 50.0; p = .027]. They were not significant on day four (carragelose® Mdn = 3.00, IQR = 2.00; mupirocin Mdn = 5.00, SD = 3.75) [Mann-Whitney *u* = 82.0; p = .217]; day 14 (carragelose® Mdn = 2.00, IQR = 1.25; mupirocin Mdn = 4.00, IQR = 4.00) [Mann-Whitney *u* = 39.0; p = .171]; and day 28 (carragelose® Mdn = 2.00, IQR = 1.25; mupirocin Mdn = 2.00, IQR =2.00) [Mann-Whitney *u* = 38.5; p = .151]. *(Table 1)*

Using the Friedman test statistic to evaluate differences in medians among the Lund-Kennedy scores on the carragelose® side showed significant differences ($\chi^2(3) = 15.1$, $p = .002$); evaluation of the mupirocin side also showed significant differences in medians ($\chi^2(3) = 16.2$, $p = .001$). *(Table 1)*

Table 1. Comparison of Lund-Kennedy scores for Carragelose® and Mupirocin Sides

Days from operation	n	Carragelose® Side		Mupirocin Side		Mann-Whitney U-test	
		Median	IQR	Median	IQR	U-score	P-value
4	15	3.00	2.00	5.00	3.75	82.0	.217ns
7	14	2.50	2.50	4.00	4.25	50.0	.027sig
14	11	2.00	1.25	4.00	4.00	39.0	.171ns
28	11	2.00	1.25	2.00	2.00	38.5	.151ns
Friedman Test		n = 11		n = 11			
		df = 3		df = 3			
		Chi-square = 15.1		Chi-square=16.2			
		P-value = .002sig		P-value = .001sig			

Peri Operative Sinus Evaluation (POSE) median scores were not significant on day four (carragelose® Mdn = 5.00, IQR = 0.25; mupirocin Mdn = 5.00, IQR = 1.50) [Mann-Whitney *u* = 82.0; p = .217]; day seven (carragelose® Mdn = 4.00, IQR = 2.25; mupirocin Mdn = 5.00, IQR = 2.25) [Mann-Whitney *u* = 70.5; p = .210]; day 14 (carragelose® Mdn = 3.00, IQR = 1.50; mupirocin Mdn = 4.00, IQR = 2.00) [Mann-Whitney *u* = 40.0; p = .481]; and day 28 (carragelose® Mdn = 2.00, IQR = 1.25; mupirocin Mdn = 3.00, IQR = 3.25) [Mann-Whitney *u* = 33.0; p = .218].

Using the Friedman test statistic to evaluate differences in medians among the POSE scores on the carragelose® side showed significant differences ($\chi^2(3) = 22.3$, $p = < .001$); evaluation of the mupirocin side also showed significant differences ($\chi^2(3) = 15.1$, $p = .002$). *(Table 2)*

Table 2. Comparison of Peri Operative Sinus Evaluation (POSE) scores for Carragelose® and Mupirocin Sides

Days from operation	n	Carragelose® Side		Mupirocin Side		Mann-Whitney U-test	
		Median	IQR	Median	IQR	U-score	P-value
4	15	5.00	0.25	5.00	1.50	82.0	.217 ns
7	14	4.00	2.25	5.00	2.25	70.5	.210 ns
14	10	3.00	1.50	4.00	2.00	40.0	.481 ns
28	10	2.00	1.25	3.00	3.25	33.0	.218 ns
Friedman Test		n = 10		n = 10			
		df = 3		df = 3			
		Chi-square = 22.3		Chi-square = 15.1			
		P-value < .00 sig		P-value = .002 sig			

The overall post-operative outcomes based on Lund-Kennedy Endoscopic Scoring System median scores were significant on day seven (carragelose® Mdn = 2.50, IQR = 2.00; mupirocin Mdn = 4.00, IQR = 2.00) [Mann-Whitney $u = 50.0$; p = .027]. They were not significant on day four (carragelose® Mdn = 3.00, IQR = 2.00; mupirocin Mdn = 5.00, IQR = 1.00) [Mann-Whitney $u = 82.0$; p = .217]; day 14 (carragelose® Mdn = 2.00, IQR = 4.00; mupirocin Mdn = 4.00, IQR = 1.00) [Mann-Whitney $u = 39.0$; p = .171] and day 28 (carragelose® Mdn = 2.00, IQR = 2.00; mupirocin Mdn = 2.00, IQR = 1.00) [Mann-Whitney $u = 38.5$; p = .151]. *(Table 3)*

The overall post-operative outcomes based on POSE median scores were not significant on day four (carragelose® Mdn = 5.00, IQR = 1.00; mupirocin Mdn = 5.00, IQR = 1.00) [Mann-Whitney $u = 82.0$; p = .217]; day seven (carragelose® Mdn = 4.00, IQR = 1.00; mupirocin Mdn = 5.00, IQR = 1.00) [Mann-Whitney $u = 70.5$; p = .210]; day 14 (carragelose® Mdn = 3.00, IQR = 1.00; mupirocin Mdn = 4.00, IQR = 1.00) [Mann-Whitney $u = 40.0$; p = .418] and day 28 (carragelose® Mdn = 2.00, IQR = 3.00; mupirocin Mdn = 3.00, IQR = 1.00) [Mann-Whitney $u = 33.0$; p = .218]. *(Table 4)*

DISCUSSION

Our findings suggest that carragelose® nasal spray-impregnated nasal packs may be comparable with mupirocin ointment-impregnated nasal packs in terms of postoperative mucosal healing after ESS for chronic rhinosinusitis with nasal polyposis (CRSwNP).

A previous study by Promentilla *et al*., found that dexamethasone-impregnated absorbable nasal packs yielded better post-operative outcomes than saline-impregnated absorbable packing[9] while a study by Grzeskowiak *et al*. found that bethamethasone and ciprofloxacin-impregnated nasal packs resulted in a better post-operative healing process than saline.[12] Another study by Sabarinath *et al*. found that triamcinolone - impregnated nasal packs decreased mucosal edema and crusting in the post-operative nasal cavity.[13] The outcomes in the aforementioned studies may be attributed to the anti-inflammatory effect of steroids, but there may be concerns with their safety, adverse effects, and acceptability to prospective users.[14]

Table 3. Comparison of post-operative outcomes for Carragelose® and Mupirocin Sides based on Lund-Kennedy Endoscopic Scoring System

Lund-Kennedy	Day 4				Day 7				Day 14				Day 28			
	Carragelose®		Mupirocin		Carragelose®		Mupirocin		Carragelose®		Mupirocin		Carragelose®		Mupirocin	
	Md	IQR	Md	IQR	Md	IQR	Md	IQR	Md	IQR	Md	IQR	Md	IQR	Md	IQR
Polyp	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U-score | P-value	97.50		.539		76.5		.329		55.0		.748		60.5		1.000	
Edema	2.00	1.00	2.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.00	1.00	1.00	1.00
U-score | P-value	105.5		.775		98.0		1.00		51.5		.562		39.0		.171	
Discharge	1.00	1.00	1.00	1.00	0.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.00
U-score | P-value	109.5		.902		38.5		.050		48.0		.438		50.5		.519	
Scarring	0.00	1.00	0.00	1.00	0.00	1.00	1.00	1.00	0.00	1.00	1.00	1.00	0.00	0.00	0.00	1.00
U-score | P-value	102.5		.683		81.0		.454		49.5		.478		49.5		.478	
Crusting	0.00	2.00	1.00	2.00	1.00	1.00	1.00	0.00	0.00	1.00	1.00	1.00	0.00	0.00	0.00	0.00
U-score | P-value	81.5		.683		81.5		.454		48.5		.438		60.5		1.00	
Overall LUND	3.00	2.00	5.00	1.00	2.50	2.00	4.00	2.00	2.00	4.00	4.00	1.00	2.00	2.00	2.00	1.00
U-score | P-value	82.0		.271		50.0		.027 s		39.0		.171		38.5		.151	

s significant using Mann-Whitney U-test

Table 4. Comparison of post-operative outcomes for Carragelose® and Mupirocin Sides based on POSE

POSE	Day 4				Day 7				Day 14				Day 28			
	Carragelose®		Mupirocin		Carragelose®		Mupirocin		Carragelose®		Mupirocin		Carragelose®		Mupirocin	
	Md	IQR	Md	IQR	Md	IQR	Md	IQR	Md	IQR	Md	IQR	Md	IQR	Md	IQR
Middle Turbinate	1.00	0.00	1.00	0.00	1.00	1.00	1.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
U-score|P-value	87.0		.305		44.0		.190		50.0		1.00		50.0		1.00	
Middle Meatus: Stenosis	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00
U-score|P-value	108.5		.870		58.0		.561		45.0		.739		41.5		.529	
Middle Meatus: Maxillary Sinus Content	1.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00	0.00	0.00	1.00	0.00	0.00	0.00	1.00
U-score|P-value	112.5		1.00		57.0		.608		39.5		.436		35.0		.280	
Mucosal Edema	1.00	1.00	1.00	0.00	1.00	0.00	1.00	0.00	1.00	1.00	1.00	1.00	0.50	1.00	1.00	1.00
U-score|P-value	92.0		.412		50.5		.347		50.0		1.00		41.0		.529	
Polypoid Change	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	1.00	0.00	0.00	0.00	0.00
U-score|P-value	90.0		.367		66.0		1.00		50.0		1.00		50.0		1.00	
Polyposis	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00	0.00	1.00	0.00	1.00	0.00	0.00
U-score|P-value	105.0		.775		65.5		.976		43.5		.631		48.5		.912	
Discharge	0.00	1.00	0.00	1.00	0.00	1.00	1.00	0.00	1.00	1.00	1.00	1.00	0.00	1.00	0.50	1.00
U-score|P-value	105.0		.775		38.5		.091		50.0		1.00		41.0		.529	
Crusting	0.00	1.00	1.00	1.00	0.00	1.00	0.00	0.50	0.50	1.00	0.50	1.00	0.00	0.00	0.00	0.00
U-score|P-value	105.0		0.775		64.5		.928		50.0		1.00		50.0		1.00	
Overall POSE	5.00	1.00	5.00	1.00	4.00	1.00	5.00	1.00	3.00	1.00	4.00	1.00	2.00	3.00	3.00	1.00
U-score|P-value	82.0		.271		70.5		.210		40.0		.418		33.0		.218	

[S]significant using Mann-Whitney U-test

Carragelose® (or carrageenan) appears to be a potent inflammatory agent, demonstrated in an experiment on rodent and mice leucocytes to produce tumor necrosis factor – alpha and a potent macrophage activator.[15] Perhaps the anti-inflammatory effect is mediated by the action of macrophages on neutrophilic inflammation that occurs during wound repair.[16]

In contrast with steroids, carragelose® when used as a topical medication intranasally is relatively safe. Hebar *et al*. claim that 0.12% iota-carrageenan (active ingredient of carragelose nasal spray) applied intranasally will not penetrate nasal mucosa and does not reach the blood stream, concluding that it is clinically safe specially when applied topically on nasal mucosa.[17] Given its mechanism to promote wound healing and its other biological attributes, carragelose® may be a promising post-operative medication on patients who underwent ESS.

Because our study can only suggest that carragelose® and mupirocin may be comparable in terms of a relatively good effect on postoperative mucosal healing, a trial involving a larger sample should be initiated to validate these findings.

The Lund and Kennedy Endoscopic Scoring System[10] and Wright and Agrawal's Perioperative Sinus Endoscopy Scoring System or the POSE Scoring System[11] were used in this study. Using the 2-scoring systems may confer advantages in terms of content validity and sensitivity to change with the additional information regarding secondary sinuses and the ethmoid cavity.[16] Although reliable, using POSE was taxing on the part of the blinded consultant because of the detailed features of the parameters especially when grading in 4 separate sessions.

Limitations of this study include lack of randomization that should have been initiated at the outset to minimize differences and to ensure equal chances of distribution, in this case both nasal cavities. The small sample size of participants that completed the study is another limitation. Instead of the minimum computed sample size of 16 per group (32 sides), we ended up with only 6 participants (12 sides). Ideally, both drugs should have been concealed in similar containers although this was not feasible because of the differing consistencies

(liquid in a plastic bottle and ointment in tube form) of the commercially available stock preparations in the market. However, we believe that both patients and the consultant who evaluated the videorecorded endoscopic examinations were sufficiently blinded.

For future studies, we recommend increasing the number of participants to meet the minimum sample size, ensuring proper randomization, using similar containers, using a simple but reliable scoring system, and limiting the number of days of observation.

Despite all these limitations, the findings of our study may still suggest that carrageenan® nasal spray impregnated nasal packs are comparable with mupirocin ointment coated nasal packs and may be a viable alternative for post-operative care among patients who undergo ESS.

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