Abstracts

Objective: We employed a steroid-eluting, sinus-bioabsorbable device for local treatment after surgery for eosinophilic chronic rhinosinusitis (ECRS). One year later, we investigated its efficacy in suppressing recurrence and reducing the use of oral steroids.

Methods: At one year after ECRS surgery, both 18 cases treated with a postoperative steroid-eluting, sinus–bioabsorbable device (Post-ST group) and 25 cases receiving conventional postoperative therapy (Post-Con group) showed significant improvement in the nasal symptoms (nasal obstruction, nasal discharge and olfactory dysfunction CT score and threshold test (discrimination test).

Results: The olfactory dysfunction, CT score and threshold test were significantly improved in the Post-ST group compared with the Post-Con group, but the polyp score was not. The mean total number of oral steroid tablets ingested during one year after surgery was 24.3±2.8 tablets in the Post-ST group, which was significant lower than the 36.3±3.7 tablets used in the Post-Con group.

Conclusion: The above results indicate that insertion of a steroid-eluting, sinus–bioabsorbable device after ECRS surgery can reduce the oral steroid intake while maintaining long–term suppression of disease recurrence.

1．Introduction

Endoscopic sinus surgery (ESS) is often selected as treatment of severe eosinophilic rhinosinusitis (ECRS). However, it was reported that, postoperatively, polyps recur in ≥30% of cases after one year and in 40% of cases after 1.5 years [1,2]. At the same time, the postoperative sense of smell improves [3]. The quality of the change in the olfactory dysfunction is considered a good indicator of the fluctuation in the inflammatory state in ECRS [3,4]. One of the many clinical features of ECRS is the efficacy of oral steroid. Oral steroid is very effective even for decreased olfactory function at the time of postoperative recurrence. Patients become dependent on oral steroid, while discontinuation of oral steroid increases the likelihood of relapse [5]. However, as in the case of severe asthma, long-term use of oral steroid always leads to adverse reactions. These characteristics diminish the meaning of performing ESS. It is expected that topical steroids, which exert a lesser systemic burden, will be effective for controlling ECRS. However, it was reported that topical steroids have little efficacy in treating postoperative relapse of ECRS [6].

A method for effective use of a topical steroid to treat the nasal mucosa was reported in which a steroid-eluting, bioabsorbable device was inserted directly into the ethmoid sinus after it had been surgically opened, resulting in prevention of mucosal edema and adhesion [7–12]. As a bioabsorbable device, Gelfoam impregnated with triamcinolone acetonide® was inserted into the olfactory cleft [7], while a Propel™ spacer impregnated with mometasouroate was used to control recurrent sinusitis [8–11] and a triamcinolone acetonide®–impregnated Nasopore™ dressing was inserted into the ethmoid sinus to reduce postoperative use of oral steroid. Also, a Sinu-Foam spacer was used as packing to stop postoperative bleeding [13]. However, in each report, a steroid-impregnated bioabsorbable device was inserted once into the opened ethmoid sinus during the surgery, and clinical efficacy was shown in the evaluation performed within 6 months. Also, there was no evaluation of recurrence of the ECRS in the ≥1 year after the surgery, which is the time period when recurrence is most likely. On the other hand, in Japan, the health insurance system does not cover any of the above–mentioned

bioabsorbable devices other than Gelfoam®.

In our earlier study [14], we used Surgicel® (©Ethicon, Inc., USA) as the bioabsorbable device which was disappeared within about 2 weeks. Surgicel® was inserted into the opened ethmoid sinus and the olfactory cleft at the time of recurrence after surgery for ECRS. When the device was impregnated with triamcinolone acetonide®, evaluation performed after 1 month showed reduced mucosal edema in the ethmoid sinus and improvement of the olfactory dysfunction [14].

At present, an important task after ECRS surgery is long-term prevention of recurrence while avoiding manifestation of adverse reactions. In this study, our protocol for post–ESS therapy incorporated local steroid treatment using Surgicel® and triamcinolone acetonide®, and we investigated whether the rate of recurrence for 1 year after the surgery and the amount of oral steroid used postoperatively could be reduced.

2. Materials and methods

The subjects were 43 ECRS patients whose pre-operative CT showed pan-nasal inflammation, and all the patients underwent first-time ESS that was performed by the same surgeon. As described in the JSREC study [14], ECRS was diagnosed on the basis of a score of ≥11 points and a tissue eosinophil count of 70 cells/HPR.

2.1. Patients were allocated into the following two postoperative treatment groups (Table 1).

Post–Con group: Twenty-five patients underwent ESS in 2015–2016. They consisted of 18 cases of ECRS with asthma and 7 cases of ECRS with AIA. To promote epithelialization of the wound site after surgery, the patients were administered a macrolide antibiotic at 1 tablet/day for 2 weeks, followed by 1 tablet/day for about 1

month (macrolide therapy) [15]. At the same time, 1 celestamine combination tablet®, which contains betamethasone (0.25 mg) and D-chlorpheniramine maleate (2 mg) (Merck & Co., Inc., Tokyo, Japan), was ingested daily for one month. The celestamine combination tablet® was then discontinued. A topical steroid and a leukotriene receptor antagonist (LTRA) were used once per day and nasal irrigation was performed with saline solution, and the course was observed (Figure 1).

Post–ST group: Eighteen patients underwent ESS in 2016–2017. They consisted of 10 cases of ECRS with asthma and 8 cases of ECRS with AIA. Macrolide therapy [15] was administered in the same manner as in the Post–Con group, and 1 celestamine combination tablet® was ingested daily for 1 month. Then local steroid treatment was started with Surgicel® and triamcinolone acetonide®. The treatment was performed once or twice for one month. No topical steroid or LTRA was used in this group, but the patients were instructed to perform nasal irrigation(Figure 1).

The local steroid treatment using Surgicel® and triamcinolone acetonide® was performed as follows. First, several cotton swabs impregnated with 4% xylocaine and 5,000–fold diluted adrenaline® were inserted into the surgically opened ethmoid sinus and the olfactory cleft region in order to shrink the nasal mucosa. Then one sheet of Surgicel® was divided into 4 equal parts and inserted into both the ethmoid area and the olfactory cleft (Figure 2). Next, triamcinolone acetonide® was dripped onto the Surgicel®. Half a vial (20 mg) was used for each side.

For each treatment group, if the once-improved olfactory disorder recurred due to a cold, etc., an antibiotic was prescribed for a maximum of one week and an oral steroid

(1 celestamine combination tablet®/day) for a maximum of 2 weeks. The patients were given permission to make a judgment to discontinue the medicines if the olfactory dysfunction improved. At the next outpatient visit, each patient was asked the number of celestamine tablets he/she had ingested.

2.2. The clinical efficacy in the two groups was compared at one year after surgery by evaluating the following 6 items.

1) Nasal symptoms: Evaluation of nasal obstruction, nasal discharge and olfactory disorder using a VAS (visual analog scale) (Figure 3).

   We used a VAS, a self-administered test consisting of a linear scale, to evaluate the severity of the patients' subjective symptoms from 1 (none) on the far left to 7 (severe) on the far right.

2) Endoscopic nasal findings: The intranasal polyp score was evaluated using the following scale: 0 (no polyps), 1 (small polyps localized in the middle nasal meatus), 2 (polyps extending from the middle nasal meatus to the nasal cavity, or olfactory cleft polyps), and 4 (polyps filling the nasal cavity) (Figure 4).

3) CT score: The image of each sinus, i.e., the anterior and posterior ethmoid sinus, frontal sinus, sphenoid sinus and maxillary sinus, was assigned a score of 0–2 (Lund & Mackay) [17] (Table 2).

4) Evaluation of olfaction (T&T olfactometer recognition threshold test）: The

   T&T test consists of five odorants: (A) b-phenyl ethyl alcohol, which smells like a rose; (B) methyl cyclopentenolone, which smells like burning; (C) iso-valeric acid, which smells like sweat; (D) g-undecalactone, which smells like fruit; and (E) skatole, which smells like garbage (Takasago Industry, Tokyo, Japan). Examinations were performed by a single clinical laboratory technician to limit examiner bias. Both detection (○) and recognition (X) thresholds for each odorant were obtained and averaged. Olfactory severity was categorized into

five classes according to the mean T&T recognition threshold. Patients were diagnosed as having normal olfactory acuity (normosmia), mild, moderate and severe disorder (hyposmia), and olfactory anesthesia (anosmia), when the mean T&T recognition threshold was 1.0 or less (<1.0), between 1.1 and 2.5, between 2.6 and 4.0, between 4.1 and 5.5, and 5.6 or greater (5.6<), respectively.

The postoperative olfactory change was evaluated (ΔT&T= preoperative T&T recognition threshold–postoperative T&T recognition test). The patients were classified into four levels of improvement: “cure” when the mean postoperative T&T recognition threshold was 2.0 or less (＜＝2.0), “remission” when ΔT&T was 1.0 or more, but not as good as cure, “exacerbation” when ΔT&T was -1.0 or less, and “no change” when the finding was other than those described above [17].

5) Number of steroid tablets ingested during 1 year after surgery: However, the number of celestamine combination tablets® ingested immediately after the surgery was not counted .

6) Measurement of ACTH and cortisol levels in blood at one year after the surgery.

3. Statistical analysis

Data are presented as the mean±standard error of mean. Statistical significance was assessed by nonparametric T tests using Prism (ver 5.0; GraphPad Software, Inc., San Diego, CA, USA). A p-value of <0.05 was considered significant.

4. Results

In the Post–ST group, the total number of times that Surgicel® was inserted into both ethmoid sinuses per patient during 1 year was 30–40 times (mean: 36.3 times). None of the patients developed an infection due to the Surgicel® itself, and observation of the

nasal cavity at the next outpatient visit found that the Surgicel® had disappeared in all patients. Damage to the nasal mucosa because of frequent insertion of Surgicel® led to partial adhesion in 22.2% of the cases in the Post–ST group (in the middle nasal meatus in 10/36 sides; in the olfactory cleft in 6/36 sides). However, there were no cases of severe adhesion that prevented continuation of the Surgicel® and triamcinolone acetonide® treatment.

The subjective symptoms (nasal obstruction, nasal discharge and olfactory dysfunction) were found to be significantly improved in both treatment groups at 1 year post-ESS compared with before the surgery (Figure 5). The improvement in olfactory dysfunction was significantly greater in the Post–ST group than in the Post–Con group.

The mean polyp score in the Post–Con group was 6.39 before the ESS and 1.73 after the surgery, while the values in the Post–ST group were 6.06 and 1.39. The improvement was significant in both treatment groups (Figure 6).

The mean CT score total number in the Post–Con group improved from 15.52±0.68 before the ESS to 5.64±0.48 after the surgery, while the change in the Post–ST group was 14.22±0.84 from 4.17±0.31. The improvement was significant in both treatment groups. At 1 year post-ESS, there was a significant difference in the CT scores between the two groups (Figure 7).

The degree of improvement in the sense of smell was compared between the Post–Con group (n=16; 10 cases of ECRS with asthma, and 6 cases of ECRS with AIA） and the Post–ST group (n=18) for the cases for which the T&T olfactometer recognition threshold test was able to be performed before and after the ESS. In the Post–Con group, the mean T&T olfactometer recognition threshold after ESS was 3.97±0.15, and the ΔT&T was 0.55±0.19. On the other hand, in the Post-ST group, the post–ESS value was 3.62±0.14, with ΔT&T of 1.14±0.17. Both the Post–Con group and Post–ST group showed significant improvement from before to after the ESS. Post-ESS, there was no significant correlation between the Post–Con group and the Post–ST group, but ΔT&T

was significantly improved in the Post–ST group compared with the Post–Con group. The rate of improvement, i.e., cure and remission combined, was 37.5% (6/16) in the Post–Con group and 61.1% (11/18) in the Post–ST group (Figure 8).

In both treatment groups, the number of steroid tablets ingested showed a tendency to increase as the time passed after surgery approached 1 year. The number of steroid tablets ingested were 0 in the Post-ST group and 2.44±0.84 tablets in the Post-Con group during 0-3 months, 0.47±0.47 tablets and 4.32±0.79 tablets during 3-6 months, 5.13±2.10 tablets and 8.48±1.25 tablets during 6-9 months, 11.47±2.15 tablets and 19.04±2.52 tablets during 9-12 months. There were significantly difference of the number of steroid tablets ingested in both groups during 0-3 months, 3-6 months, 9-12 months. The total number of steroid tablets ingested at 1 year after the surgery was significantly smaller in the Post–ST group (24.3±2.8 tablets) than in the Post–Con group (36.3±3.7 tablets (Figure 9).

At 1 year after the surgery, the blood level of ACTH (normal range: 7.0–56.0 pg/ml) for the cases for which measurement was possible was within the normal range in both treatment groups: 13.2-39.8 (mean: 28.5) in the Post–Con group (n=16; 10 cases of ECRS with asthma, and 6 cases of ECRS with AIA） and 11.4–52.1 (mean: 30.3) in the Post–ST group (n=18). The blood level of cortisol (normal range: 4.0–23.9 pg/ml) was also within the normal range in both groups: 5.1–19.9 (mean: 13.1) in Post–Con group and 6.9–22.1 (mean: 15.8) in the Post–ST group.

5. Discussion

After ESS surgery for ECRS, it is common to use LTRA and topical steroids after nasal irrigation with saline solution at home [18]. However, those treatments cannot be expected to afford sufficient suppression of relapse of the once–improved olfactory function. For that reason, frequent use of oral steroids is necessitated, and dependence on steroid drugs tends to develop [5].

The significance of ESS for ECRS is to fully open each paranasal sinus and thoroughly perform postoperative local treatment [19]. In Europe and the United States, various bioabsorbable devices have been inserted into the surgically opened ethmoid sinus, and

together with use of steroids it was possible to directly control sinus inflammation [8–12]. After ESS, Gelfoam® was inserted into the olfactory cleft and triamcinolone acetonide® was administered, and evaluation of the olfactory function after 8 weeks found that the olfactory dysfunction was significantly improved [7]. In addition, Nasopore™, a bioabsorbable device, and triamcinolone acetonide® were employed, and evaluation after 6 months showed efficacy in promoting postoperative epithelialization [12]. Also, Nasopore™ was inserted postoperatively, and a group administered oral prednisone 30 mg and a group not administered that drug were compared [20]. The two groups showed no difference in the improvement in the subjective symptoms and the local findings at 2 months following the surgery [20]. That same study concluded that good results could be obtained when only a local steroid was used, without using any oral steroid [20]. However, the results in the above reports were based on evaluation of the relatively short-term efficacy of treatment administered immediately after surgery, whereas ECRS shows a high likelihood of recurrence at around 1 year after the surgery [1,2]. Moreover, in Japan, many bioabsorbable devices have not been commercialized .

In this study, we used Surgicel®, a bioabsorbable device that is frequently used in the field of otolaryngology. The reason is that Surgicel® has hemostatic action as its main action, but it also has bacteriostatic action, with no infections being observed, and it is absorbed within about 2 weeks. Since it can be divided into small pieces that can be easily inserted through the narrow middle meatus and olfactory cleft after surgery, it is a considered to be suitable as an absorbable device that can be used in the nasal sinuses. We inserted Surgicel® into the postsurgical ethmoid sinuses and olfactory cleft and dripped triamcinolone acetonide® onto it to administer local steroid treatment as part of our post–ESS treatment protocol. We then clinically evaluated the cases at 1 year after the surgery.

During the one-year period of local treatment using Surgicel® and triamcinolone acetonide®, Surgicel® was frequently inserted into the ethmoid sinuses of each patient, for a mean of about 36 times per year. There is a possibility that such frequent, long-term use might cause damage to the nasal mucosa of the middle nasal meatus and olfactory

cleft. In fact, even in our present study, approximately 22% of cases showed partial adhesion of the middle nasal meatus and olfactory cleft, suggesting that care must be taken in regard to excessive nasal mucosal damage.

One year post–ESS, the subjective symptoms, polyp score and CT score were each significantly improved in both the Post-Con group and the Post-ST group. In particular, the Post-ST group showed significant improvement in the olfactory dysfunction, CT score, and the ΔT&T of the T&T olfactometer recognition threshold test. From the above, it can be concluded that local treatment using the combination of Surgicel® and triamcinolone acetonide® is a therapeutic method worthy of inclusion in the protocol for post–ESS treatment.

Furthermore, as shown in Figure 9, the number of oral steroid tablets used post–ESS was significantly less in the Post-ST group, and it can be thought that reduction of steroid use was achieved. With the topical steroid therapy used in the Post-ST group, the steroid is absorbed into the blood via the local mucosa. Moreover, there is a risk that use of a corticosteroid drug may cause adrenal suppression. However, in this study, neither the blood ACTH nor cortisol level showed any abnormality after 1 year of treatment, and the possibility of adrenal suppression was thought to be minimal.

6. Conclusion

Based on the above results, long-term local treatment using a steroid–impregnated, bioabsorbable device, Surgicel®, can be expected to have a relapse–suppressing effect after ESS for ECRS, while reducing the total dose of oral corticosteroid. However, since Surgicel® is absorbed within two weeks and frequent postoperative treatment is needed, development of a device that can be retained in the paranasal sinuses on a long-term basis without causing infections is to be desired.

Ethics committee

This study was performed as a retrospective, case-control study after being

approved by the Institutional Ethics Committee of Dokkyo Medical Hospital (No. 27028).

Disclosure Statement

There were no conflicts of interest in this study.

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Legends

Table 1. Post–Con group and Post–ST group patient backgrounds.

Table 2. Lund & Mackay CT score.

Figure 1. Postoperative treatment protocols of Post–Con group and Post–ST group.

Post–Con group: Patients underwent post–ESS therapy consisting of ingestion of macrolide tablets and celestamine combination tablets® for 1 month. After that, the celestamine combination tablets ® were discontinued, a leukotriene receptor antagonist (LTRA) and a topical steroid were used, and nasal irrigation was performed with saline solution .

Post–ST group: Patients underwent post–ESS therapy consisting of ingestion of macrolide tablets and celestamine combination tablets® for 1 month. After that, local steroid treatment was started with Surgicel® and triamcinolone acetonide®.

For each treatment group, if the once-improved olfactory disorder recurred due to a cold, etc., an antibiotic was prescribed for a maximum of one week and an oral steroid (1 celestamine combination tablet®/day) for a maximum of 2 weeks.

Figure 2. Local steroid treatment using Surgicel® and triamcinolone acetonide® (left nasal cavity).

Figure 3. Vas score of nasal symptoms.

Figure 4. Endonasal endoscopic polyp score.

Figure 5. Comparison of nasal symptoms between the Post–Con group and the Post–ST group.

The subjective symptoms (nasal obstruction, nasal discharge and olfactory dysfunction) were found to be significantly improved in both treatment groups at 1 year post-ESS compared with before the surgery. The improvement in olfactory dysfunction was significantly greater in the Post–ST group than in the Post–Con group.

Figure 6. Comparison of polyp scores between the Post–Con group and the Post–ST group.

The mean polyp score was significantly improved in both the Post–Con group and the Post–ST group at 1 year post–ESS compared with prior to the surgery. There was no significant difference between the groups.

Figure 7. Comparison of CT scores between the Post–Con group and the Post–ST group.

At 1 year post-ESS, significant improvement was seen in both the Post–Con group and the Post–ST group. There was a significant difference in the CT scores between the two groups.

Figure 8. Comparison of improvement in olfactory disorder between the Post–Con group and the Post–ST group.

Both the Post–Con group and the Post–ST group showed significant improvement from before to after the ESS. Post-ESS, there was no significant correlation between the Post–Con group and the Post–ST group, but ΔT&T was significantly improved in the Post–ST group compared with the Post–Con group. The rate of improvement, i.e., cure and remission combined, was 37.5% (6/16) in the Post–Con group and 61.1% (11/18) in the Post–ST group.

Figure 9. Comparison of total numbers of postoperative oral steroid tablet intake between the Post–Con group and the Post–ST group.

In both treatment groups, the number of steroid tablets ingested showed a tendency to increase as the time passed since surgery approached 1 year. There were significantly difference of the number of steroid tablets ingested in both groups during 0-3 months, 3-6 months, 9-12 months. The total number of steroid tablets ingested at 1 year after the surgery was significantly smaller in the Post–ST group than in the Post–Con group.