



Application of high expansion degradable cotton in nasal bleeding model of dog

Bing Zhong¹ · Feng Liu¹ · Feng-Juan Yang¹ · Chun-Shu Wu¹ · Jin-Tao Du¹ · Shi-Xi Liu¹

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Abstract

Background The discomfort and complications have always been problems for nasal packing materials. This study provided a new nasal packing material called high expansion degradable cotton (HEDC).

Methods Nasal endoscopic surgery was used to establish a dog model of nasal bleeding, and wound surfaces were filled with Merocel, Nasopore and HEDC, respectively. Intraoperative and postoperative bleeding of 24 h was calculated. We evaluate the absorbability score, adhesion score, infection sore and nasal mucosal epithelium in postoperative 3, 7, 14 and 28 days. HE staining and electron microscopy were used to evaluate the recovery of nasal mucosa.

Results There was no significant difference in nasal bleeding between HEDC, Merocel and Nasopore. Nasal endoscopic examination revealed HEDC absorbability of score, adhesion score, infection score were significantly lower than Merocel and Nasopore. The epithelialization time of HEDC was significantly shorter than that of Merocel and Nasopore. HE staining showed that HEDC and Nasopore could significantly reduce scar hyperplasia on the wound surface. The results of electron microscopy suggested that HEDC could protect the edge cilia of the wound.

Conclusion HEDC could be used as new choice for hemostasis after nasal endoscopic surgery, which could reduce nasal epithelialization time, and protect wound edge cilia.

Keywords Nasal endoscopic surgery · High expansion degradable cotton · Merocel · Nasopore · Epithelization

Introduction

Endoscopic surgery is currently the most commonly used surgical method for sinusitis, nasal tumors and other nasal diseases [1, 2]. The abundant blood supply of nasal cavity leads to the inevitable massive bleeding in surgical resection, and the resection of lesions will also lead to the loss of nasal mucosa. Therefore, the control of postoperative nasal bleeding and mucosal epithelialization are important factors to promote the recovery of patients after endoscopic surgery [3]. Nasal packing is considered to be the best way to control postoperative nasal bleeding, but the difference of filling material can cause different hemostatic effect and patient experience [4]. Proper compression of the wound surface by material packing is the key to hemostasis. However, when

facial pain and nasal ventilation are taken into account, the softness and absorbability of the hemostatic material become particularly important.

In recent years, with the improvement of medical treatment, the choice of nasal packing materials has become more diversified. Fingerstall packs have been used for many years as effective padding for endoscopic nasal surgery, and in addition to effective hemostasis, the time usually taken out 2 days after surgery also reduced nasal discomfort [5, 6]. Merocel and Nasopore are the two other most commonly used nasal packing materials [7]. The strong hemostasis effect and convenient operation of the former have been clinically confirmed. The characteristics of the Merocel, which does not require endoscopic assistance, determine that it can be applied to sudden nosebleed with unknown reasons. Considering that strong expansion and supporting effect of Merocel may bring more obvious short-term hemostatic effect to nasal bleeding, we included it in this study as one of the control groups to measure hemostatic effect. However, the nondegradability and postoperative discomforts include nasal pain and obstruction of nasal ventilation

✉ Feng Liu
lfdoctorent@outlook.com

¹ Department of Otolaryngology Head and Neck Surgery, West China Hospital of Sichuan University, 37Guoxue Lane, Chengdu 610041, Sichuan Province, China

gradually reduced the clinical application of merocel, which is not very compatible with this study. The degradability and good adhesion of Nasopore make it have hemostatic effect and little postoperative discomfort. However, the hemostasis effect of Nasopore is limited for the operation with a large amount of bleeding. In addition, considering the degradation time, deciduous and price of Nasopore, there are still many restrictions on the scope of its application. HEDC is a new type of degradable nasal hemostasis material. The purpose of this study was to explore the effect of HEDC, Merocel and Nasopore on hemostasis and epithelialization of nasal mucosa in dogs with nasal bleeding models.

Materials and methods

Animals

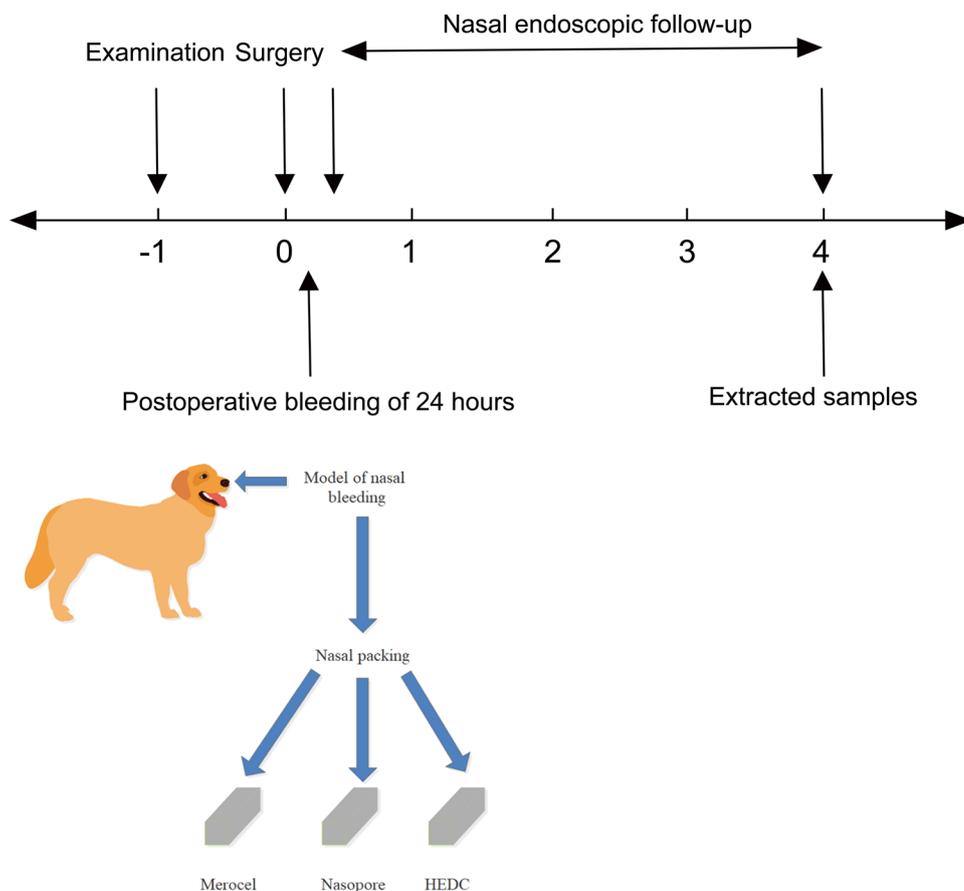
Twelve-month-old female beagles were obtained from Dashuo Laboratory Animal Co., Ltd (Chengdu, Sichuan, China). All procedures were performed according to the guide for the care and use of laboratory animals and approved by the Laboratory Animal Ethics Committee of Sichuan University (2018101A). We divided the nasal cavity

(24 sides) of all 12 dogs into Merocel group, Nasopore group and HEDC group, with eight sides of nasal cavity in each group (Fig. 1). All dogs were preoperatively examined with nasal CT and endoscopy to rule out nasal disease. The number of white blood cells, neutrophils, and platelets was measured using a blood test.

Preparation of hemostatic materials

The HEDC was obtained from Yantai Zhenghai Biologic Technology Ltd Co (Yantai, China), size was 2.5 cm × 10 cm × 0.3 cm. HEDC is a hemostatic sponge synthesized from carboxymethylcellulose and bacterial cellulose. It does not contain chemical crosslinking agent and can be degraded in the body in a short time. Appropriate pore size (20–100 μm) can regulate cell growth. Soft texture facilitates cutting and ensures adhesion to the tissue; when exposed to water, it can maintain a complete shape and quickly absorb water and expand, especially suitable for hemostasis after nasal surgery. We cropped the HEDC, Merocel (polyvinyl acetate sponge, Medtronic Xomed, Jacksonville, FL, USA) and Nasopore (lactidecaprolactone co-polyesters; Polyganics, Rozenburglaan, Groningen, The

Fig. 1 Experimental protocol



Netherlands) to the same size of 2.5 cm × 3.5 cm and ensured full coverage of the surgical wound.

Surgical steps

The operation was performed by a surgeon alone. After shrinking the nasal mucosa with cotton cotton (Sanyou medical equipment factory, Hebei, China) soaked with epinephrine (Grand Pharmaceutical Co., Ltd, Hubei, China) and lidocaine (Shanghai Zhaohui Pharmaceutical Co., Ltd, Shanghai, China) with concentration of 1:100,000 for about 1 min, 300 µl epinephrine diluted with saline (1:200,000) was injected into the internal turbinate II mucosa to contractile the blood vessels to reduce surgical bleeding (Fig. 2A, B b). The anterior part of the inner turbinate II is surgically cut to the posterior end, and then the caudal attachment is excised to remove the inner turbinate II (Fig. 2B b, c). After the aspirator clears the nasal bleeding, the wound is filled with hemostatic material (Fig. 2B d).

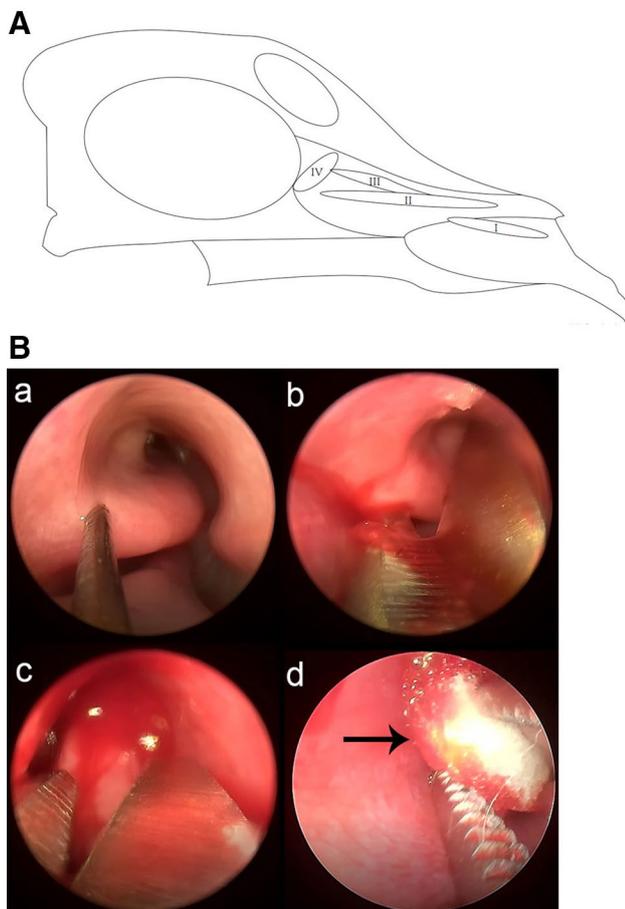


Fig. 2 A Schematic diagram of sagittal position of beagle's head. B Surgical excision of internal turbinate II and packing of hemostatic materials

Effect of hemostatic materials on epithelialization of nasal mucosa

Follow-up was conducted 1–7 days after surgery and 7–28 days after surgery by two other participants who were different from the surgeon. Nasal endoscopy was performed on the nasal passages of all dogs at 3, 7, 14 and 28 days after surgery to observe the recovery of specific value wounds and the degree of hemostatic material absorption. It is worth mentioning that MeroCel was removed 7 days after surgery due to its inabsorbability. We used the absorbability score, adhesion score, and infection score to evaluation the nasal mucosal epithelisation (Table 1). We also calculated the intraoperative hemostasis volume to exclude the errors of hemostasis effect evaluation that may be caused by intraoperative bleeding differences, and calculated the hemostasis volume of the three groups 24 h after surgery to evaluate the hemostasis effect of the corresponding hemostatic materials. Endoscopic examination was performed to compare the epithelialization time of nasal mucosa in each group. In addition, hematoxylin–eosin staining (HE) staining and electron microscopy were used to compare the effects of three hemostatic materials on regenerated tissues.

Evaluation of side effects of hemostatic materials

To rule out the possibility of nasal disease in all beagles before surgery and evaluate the effect of postoperative hemostasis materials on nasal cavity and sinus, each beagle was given nasal CT before and 28 days after surgery. Blood tests were performed at preoperatively, 3, 7, 14, and 28 days postoperatively on each beagle dog to measure leukocyte count, neutrophil count, and platelet count to assess the occurrence of inflammatory responses.

Statistical methods

SPSS 22.0 statistical software was used to analyze the data and experimental results. All data are expressed as the mean ± standard deviation (SD). The data of normal distribution were analyzed by Student's *t* test, and the signed-rank test was used to analyze the non-normal distribution of data. $P < 0.05$ indicates statistical significance.

Results

The effect of HEDC to nasal mucosa

As shown in Fig. 2A, the nasal cavity of group MeroCel was still in the state of packing on the third day after surgery, while part of Nasopore had been absorbed, and there were still obvious residues. Most of the stuffing in

Table 1 Scales used to evaluate objective findings about absorbability, adhesion, and infection

Criteria	Score
Absorbability	
Complete absorption	0
Residual material < 1/2	1
Residual material > 1/2	2
Completely residual	3
Adhesion	
No adhesion	0
Visible adhesion, no interference with nasal ventilation (the wound adheres to the same side wall)	1
Visible adhesion, interference with nasal ventilation (the wound adheres to the same side wall)	2
Adhesion of wound surface to contralateral wall (surgical release is required)	3
Infection	
No evidence of infection	0
A small amount of purulent discharge and mild edema	1
Large purulent secretions and severe edema	2
Large purulent secretions and polyposis	3

group HEDC was absorbed and decomposed, only a small amount of residual stuffing could be observed. On the 7th day after surgery, the nasal cavity of the dogs in group Merocel was removed with tamponade, which showed swelling of nasal mucosa and a small amount of bleeding. The stuffing in group Nasopore was basically absorbed, but the mucosa was still edema with a small amount of secretions. In group of HEDC, there was no residual hemostatic material in the nasal cavity, and the nasal mucosa was basically epithelialized. The epithelialization time of HEDC was significantly shorter than that of Merocel and Nasopore. It is worth mentioning that there was no significant difference in intraoperative and postoperative bleeding of 24 h in the three groups (Fig. 2B).

According to the postoperative nasal endoscopic observation, we found that the Absorbability score of HEDC was significantly lower than the Merocel and Nasopore in the postoperative 3 days, 7 and 14 days (Fig. 3C a); the adhesion score of Nasopore was higher than that of HEDC in the postoperative 3 days, while the score of Merocel was higher than that of Nasopore and HEDC (Fig. 3C b). The Infection score of HEDC was also significantly lower than that of Merocel and Nasopore on postoperative 14 days (Fig. 3C c).

HE staining showed that all three groups of dogs had different degrees of fiber and scar tissue when compared with preoperative, but Nasopore and HEDC had significantly less fiber tissue than Merocel (Fig. 4A). The results of electron microscopy showed that all the wounds in the three groups had significant scarring compared with those before surgery, but there were still nasal mucosal cilia at the edge of the wound in the HEDC group, indicating the protective effect of HEDC on the cilia at the interface of the wound (Fig. 4B).

None of the three hemostatic materials had obvious side effects

As shown in Fig. 5A, CT examination of the nose in the dogs indicated that none of the three hemostatic materials caused significant inflammation when compared with preoperative. The leukocyte count (normal range, 6.0–17.0, $10^9/L$), neutrophil count (normal range, 0.8–5.1, $10^9/L$) and platelet count (normal range, 117–460, $10^9/L$) were kept within the normal range during the test, except the neutrophil count of Nasopore was slightly higher than normal on the third and seventh day after surgery (Fig. 5B).

Discussion

Nasal endoscopic surgery is often accompanied by bleeding from the wound, and even shock in severe cases [8, 9]. In addition, chronic postoperative bleeding may prolong postoperative recovery time and increase the financial burden on patients. Nasal packing used in postoperative nasal cavity filling for a long time to reduce to inhibit wound bleeding, but the effect of clinical application of all kinds of hemostatic materials is not satisfactory. Improper packing materials may bring a strong sense of discomfort to the patient, and excessive pressure will lead to the necrosis of the nasal mucosa.

As one of the major component of HEDC, carboxymethylcellulose has been used for long term in many diseases. Januário et al. reported that carboxymethylcellulose (20%), as a treatment method for refractory chronic venous ulcer, could significantly reduce the area of the lesion and promote healing [10]. In addition, Rodrigues et al. found that

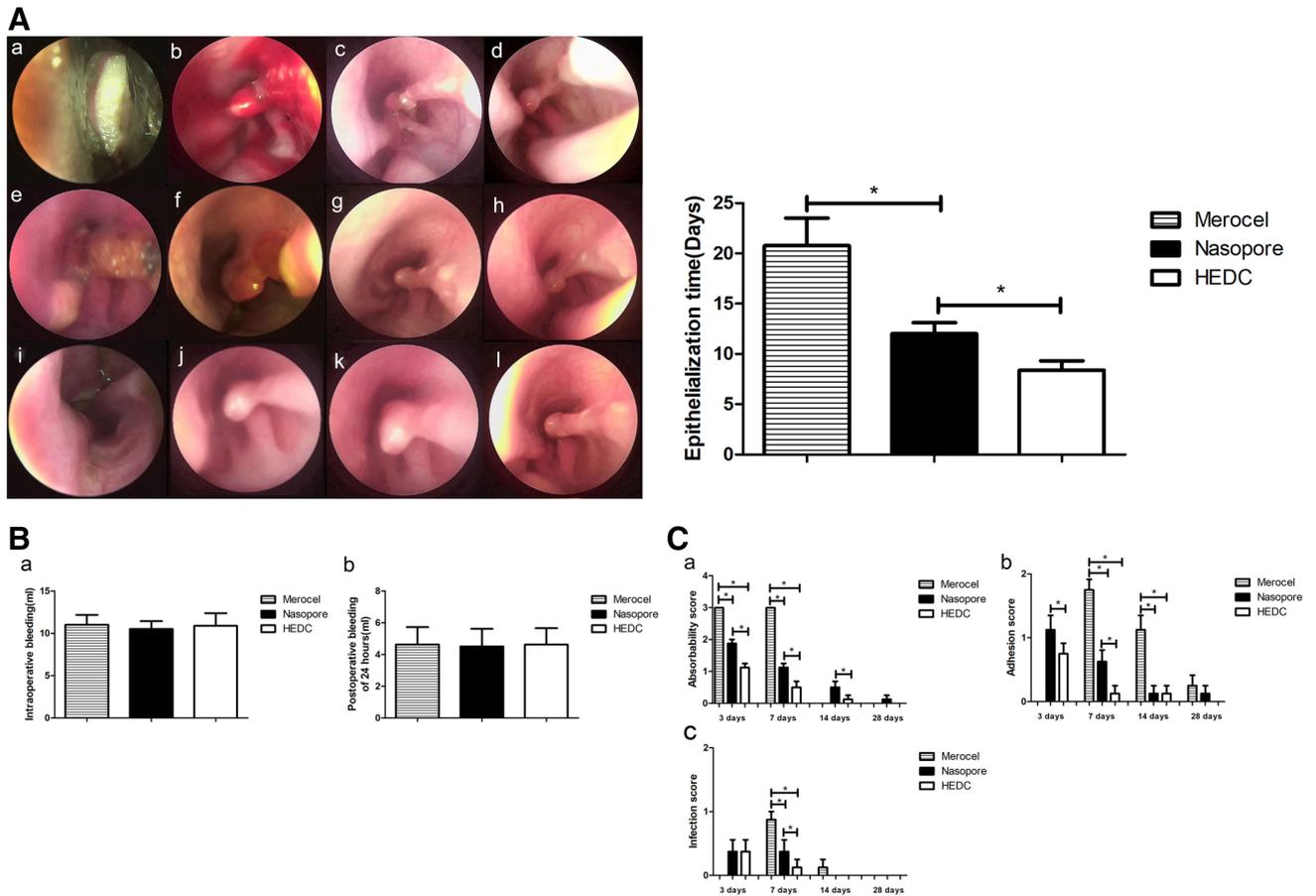


Fig. 3 A a–d Merocel group. e–h Nasopore group. i–l HEDC group. a, e and i Postoperative 3 days. b, f and j Postoperative 7 days. c, g and k Postoperative 14 days. d, h and l Postoperative 28 days. → Hemostatic materials. B intraoperative bleeding (a) and postopera-

tive bleeding of 24 h (b) in three groups. C Absorbability score (a), adhesion score (b), and infection score (c) in three groups. Merocel was removed 7 days after surgery. * $P < 0.05$

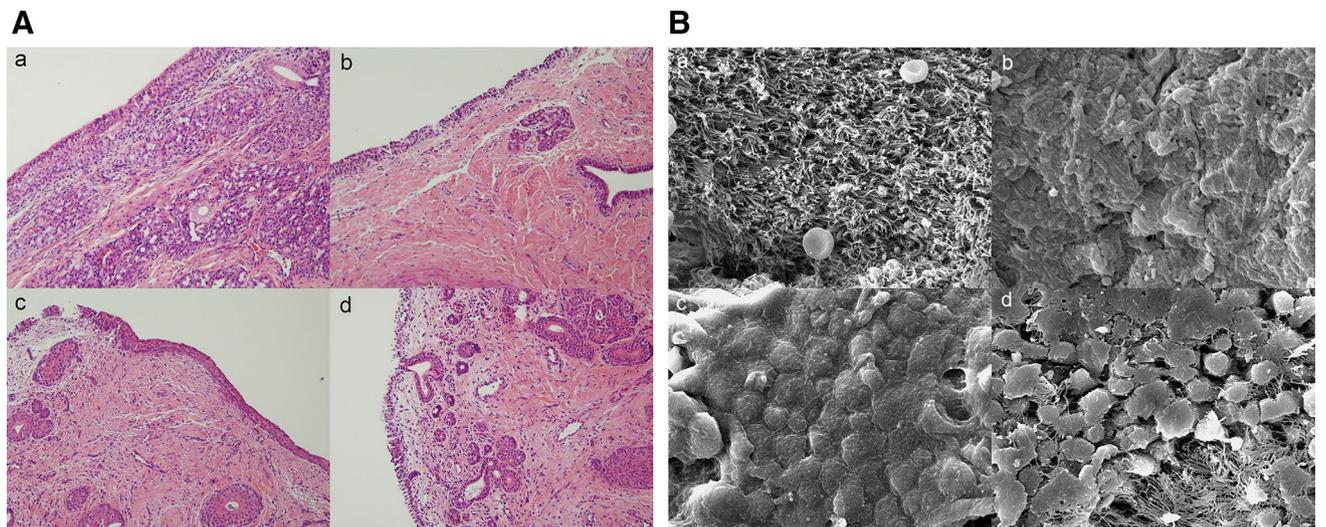
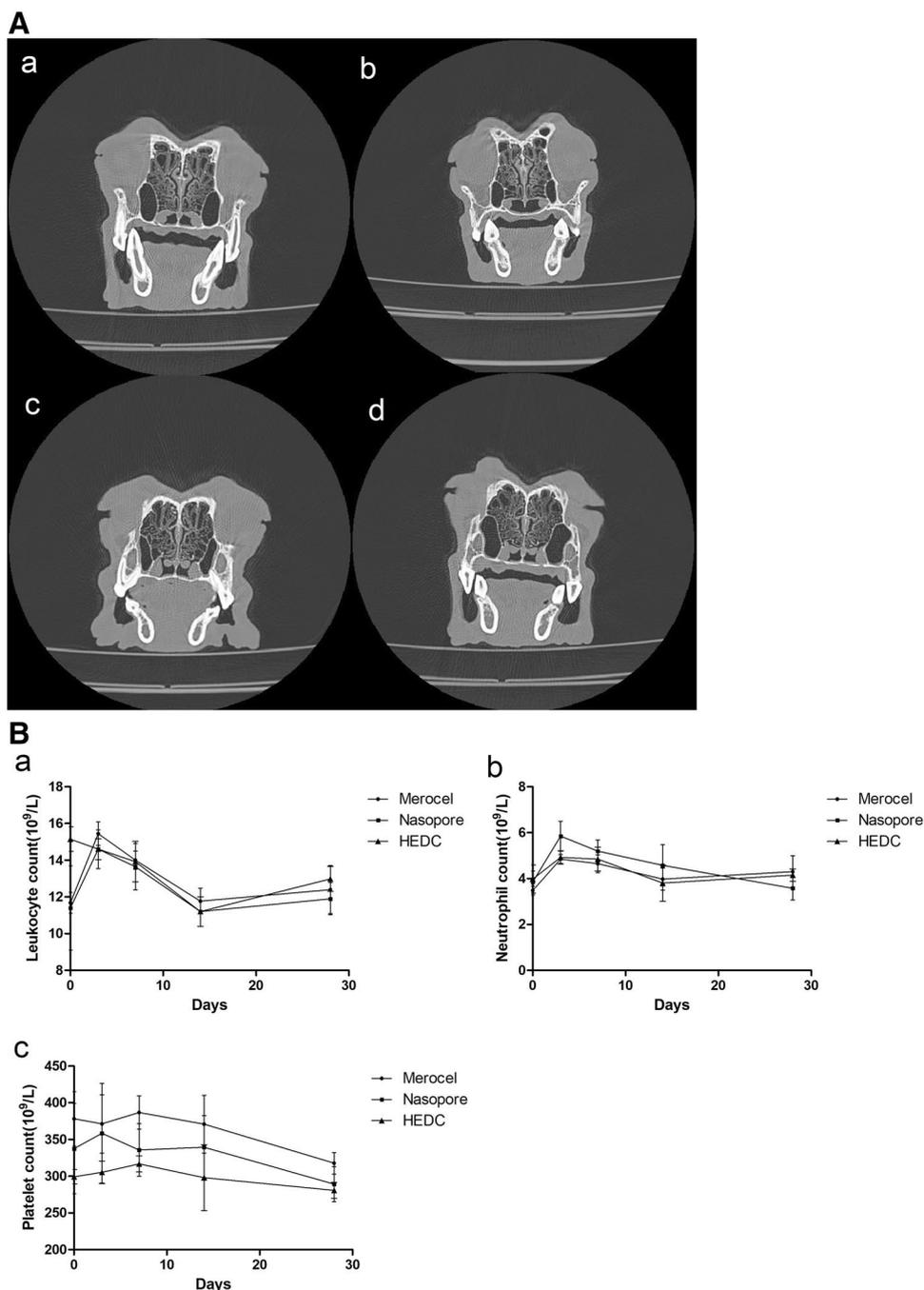


Fig. 4 A HE staining of nasal mucosa preoperatively (a) and 28 days after surgery on regenerated tissues of Merocel group (b), Nasopore group (c) and HEDC group (d). B Electron microscopy of nasal

mucosa preoperatively (a) and 28 days after surgery on regenerated tissues of Merocel group (b), Nasopore group (c) and HEDC group (d)

Fig. 5 **A** CT examination of the nose preoperatively (a) and 28 days after surgery in Merocele group (b), Nasopore group (c) and HEDC group (d). **B** The leukocyte count (a), neutrophil count (b) and platelet count (c) at preoperatively, 3, 7, 14, and 28 days postoperatively.



carboxymethylcellulose significantly promoted the proliferation of stem cells during the treatment of injury in mice [11]. Bacterial cellulose is also widely used in clinic due to its good biocompatibility, gas permeability and anti-infection. Aydogdu et al. found that nano-fiber excipients containing bacterial cellulose had favourable histocompatibility and could promote wound healing [12]. Bacterial cellulose could also significantly promote periosteum repair and improve postoperative hearing in patients with perforated tympanum [13]. This study explored the influence of Merocele, Nasopore

and HEDC on the model of nasal bleeding in dogs, HEDC could shorten the time it took for the nasal mucosa to recover to full epithelialization when compared with the other two materials. At 3 days after surgery, less than half of HEDC remained on the wound surface, showing a stronger absorbability compared with Nasopore. By the time the Merocele was extracted a week after the operation, there was significant bleeding of the wound and severe pain, although the dog had been anesthetized. In addition, the epithelialization time of HEDC was significantly shorter than that of Nasopore,

which may be related to low absorbability score, immune score, and infection score. Merocel, however, takes longer to epithelialize when compared to Nasopore.

Although compared with traditional hemostatic materials, Merocel could significantly reduce complications such as nasal septum perforation and nasal mucosal injury, its non-absorbability determines that it will cause intense pain and discomfort when removed [4, 14]. By contrast, Nasopore's absorbable nature avoids the bleeding and pain that could result from extracting a hemostatic material [15]. Sun et al. reported that Nasopore could significantly reduce postoperative nasal bleeding and postoperative discomfort of patients after dacryocystorhinostomy [16]. In our study, there was no significant difference in the amount of bleeding between the three groups during the operation, which also avoided the error in the evaluation of hemostasis effect caused by different amount of wound bleeding. Our evaluation of the amount of bleeding 24 h after surgery found that the hemostatic effects of the three materials were similar. According to the score of scale, we can find that the absorbability of HEDC is better than that of Nasopore no matter at 3 days, 7 days, 14 days or 28 days after surgery. In addition, HEDC can reduce the adhesion of wound surface of nasal surgery. It should be noted that after the removal of Merocel, the score of this group was higher than that of the other two groups. HEDC could also reduce the infection score in the nasal cavity, especially at seven days after surgery when compared to Nasopore and Merocel.

The results of HE staining suggested that HEDC and Nasopore could significantly reduce the hyperplasia of scar fibrous tissue compared with Merocel. In addition, electron microscopy showed that HEDC could well protect the nasal cilia at the edge of the wound. The mechanism of the above phenomena may be related to adequate mechanical and specific properties of carboxymethylcellulose in HEDC [17]. While a barrier containing carboxymethylcellulose has been also reported may against tissue damage by increasing the levels of free radicals, reducing superoxide dismutase (sod), glutathione S transferase enzyme activity [18].

Evaluation of the adverse effects of hemostatic materials, including local and systemic inflammation, is crucial for the selection of tamponade. The nasal CT showed no obvious signs of inflammation in the three materials. The leukocyte count and neutrophil count also fluctuated in the normal range between 0 and 28 days. Normal platelet counts exclude errors in evaluating hemostasis that may be caused by coagulation differences. Our study shows that HEDC has similar histocompatibility to the other two hemostatic materials that are already in clinical use.

It is worth mentioning that previous studies have found that Merocel may lead to more complications, such as rebleeding, nasal mucosa damage, which may bring a lot of discomfort to the patients. In our study, although Merocel

was selected as the control group due to its effective hemostatic effect in a short time, its excessive complications and removal 7 days after surgery made it not very suitable for comparing absorbable materials of the other two groups.

The study had some limitations. Firstly, a smaller sample size may limit the reliability of the results, and larger experiments are needed to further confirm our conclusions. Secondly, this is a study based on animal experiments, and given the differences between the nasal structure of dogs and the human body, further experiments are needed on whether HEDC can be used in clinical practice. In addition, this study only investigated the effect of HEDC on canine bleeding model, but whether it is suitable for hemostasis after surgery for sinusitis, nasal polyps and nasal tumors requires further studies. The nonabsorbability of Merocel is easily distinguishable from absorbable materials, especially on the 3–7 days after surgery; so subjective bias cannot be completely avoided. In addition, Merocel may cause complications that make it less suitable for the control group, which may lead to inaccurate results.

Our study showed that HEDC had similar hemostatic effect and histocompatibility compared with Nasopore and Merocel in dogs. In addition, the absorbability of HEDC is better than that of Nasopore. It is worth mentioning that HEDC could reduce nasal epithelialization time, reduce the proliferation of fibrous tissue, and protect the wound edge cilia. As a simple and convenient absorbable hemostatic material, HEDC has a very significant application value in postoperative hemostasis of nasal cavity.

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Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

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