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The Mechanism of Action of Nanomaterials Loaded with Clarithromycin after Sinusitis Surgery under the Guidance of Dynamic Enhanced Scanning

Zihan Ren, Ruiyang Ma, Wei Li, Ning Zhao, Xiaotian Li, Aihui Yan*

Department of Otolaryngology, The First Hospital of China Medical University, Shenyang 110001, China

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ABSTRACT

This study was to explore the mechanism of action of nanomaterial-loaded clarithromycin (CLA) after sinusitis surgery. Under the guidance of dynamic enhanced scanning (DES). 120 patients with sinusitis admitted to the First Affiliated Hospital of China Medical University from July 2019 to March 2020 were selected and divided into a control group and an observation group according to the random number table method, with 60 cases in each group. Then, the CLA-containing nano-polylactic acid material was prepared, observed with the scanning electron microscope (SEM), and its drug release ability was tested. All patients underwent endoscopic sinus surgery under general anesthesia. After the surgery was completed, patients in the control group were given only CLA capsules, and patients in the observation group were given freshly prepared nanomaterial-loaded CLA, and both groups of patients were continuously observed for two weeks. After that, the patients were examined using the dynamic enhancement computed tomography (CT). The clinical efficacy, serum interleukin-4 (IL-4), interleukin-8 (IL-8), and tumor necrosis factor α (TNF-α) levels of the two groups of patients were observed. The secretions of the patients' sinuses were performed with microbial bacterial culture, and the results were observed and recorded. Results showed that the characterization and analysis of the nano drug-carrying preparation suggested that the polylactic acid nanomembrane showed linear fiber morphology, relatively dense distribution, not greatly different fiber diameter, and small porosity. Characterization under a field of view (FOV) of 500 um showed that the fiber surface was smooth and rich in content. The release of CLA showed a gradual and steady upward trend. On the 25th day, nearly 50% of the dose had been released, and it had reached more than 90% of the total release on the 55th day. According to the statistics on the clinical efficacy of patients, it was found that the number of cured and effective patients in the observation group was higher than that of the control group, while the number of ineffective cases was much lower than that of the control group. The dynamic enhanced CT examination results of the patients in the control group after treatment showed that the soft tissue mass on the posterior right side of the nasopharynx was reduced, but the pharyngeal suture still existed; while those in the observation group showed that the plain scan density was uniform, and the mastoid air cells were clear on both sides. The number of cases with *Staphylococcus aureus (S. aureus)*, *Staphylococcus saprophyticus* (*S. saprophyticus*), and *Pasteurella multocida infections* in the observation group were observably lower than those of the control group ($P< 0.05$), and it was the same case for the levels of serum IL-4, IL-8, and TNF-α. Conclusion: after dynamic enhanced CT scanning, it can be found that the nanomaterial-loaded CLA increased the utilization rate of the drug, showing good clinical efficacy, and effectively improved the clinical symptoms of patients, achieving the therapeutic effect.

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Introduction

Sinusitis is caused by an upper respiratory tract infection. Bacterial and viral infections can be concurrent inflammatory diseases, often involving maxillary sinus, ethmoid sinus, frontal sinus, and sphenoid sinus. It has a high prevalence in China and seriously affects the patient's quality of life (1). At the time of the onset, the patient may have local adverse reactions such as nasal obstruction, purulent discharge, and pain. The whole body may have clinical manifestations such as chills and fever, general discomfort, lack of energy, and loss of appetite. When the patient has a high fever, convulsions, and vomiting, it may cause systemic symptoms such as diarrhea (2). Among clinical treatments, endoscopic sinus surgery is often an extremely important treatment. The surgeon can completely remove all sinus lesions under nasal endoscopy, fully open the sinus openings, improve sinus drainage, and preserve normal tissues as much as possible. It is a minimally invasive surgery that preserves functions as much as possible. However,

*Corresponding author. E-mail: kuipu295320392100@163.com

there may be symptoms of an infection inside the nasal cavity and sinuses after surgery, so there is controversy about the clinical application of efficacy (3-5). In the development of sinusitis, it is accompanied by the expression and release of a large number of inflammatory factors, such as interleukins (IL-4 and IL-8), tumor necrosis factor - α (TNF-α), and fibrosis-related factors (6). In addition, oral drugs and artificial material implantation will be given in the clinic to prevent patients from developing complications such as infections and adhesions after surgical treatment. Although the purpose of treatment can be achieved to a certain extent, there are still certain disadvantages (7). In postoperative anti-infection treatment, macrolide antibacterial drugs are the most common auxiliary drugs, which can not only inhibit the expression of bacteria but also play an anti-inflammatory and immunomodulatory role (8). One of its representative drugs, clarithromycin (CLA), is the most widely used oral preparation, and it has a good therapeutic effect in practical clinical applications; however, its adverse reactions are many, for example, the preparation is expensive and the compliance is poor, which brings great pain to patients (9).

With the continuous development of nanotechnology, its application in the medical field has also received more attention (10). The polylactic acid fiber membrane in the nano electrospun fiber material is a biodegradable material, which can be completely decomposed into CO_2 and H_2O in nature after being discarded (11). Through photosynthesis, the two can become the raw material of lactic acid-starch. Based on this advantage, it is used as a drug carrier in medical research to carry sustained-release drugs for local treatment, which relieves the local irritation of drugs from contact with the lesion to a certain extent (12). In this study, the CLA-loaded polylactic acid was applied in the postoperative treatment of sinusitis patients to explore its anti-infection and anti-inflammatory effects and mechanisms. In addition, a dynamic enhanced CT scan was adopted in this study to observe the therapeutic effect, which can find the changes in the sinuses from the morphology. The results of this study were now reported as follows.

Materials and methods

General data

A total of 120 sinusitis patients admitted to the First Affiliated Hospital of China Medical University from July 2019 to March 2020 were selected and divided into a control group and an observation group according to the random number table method, with 60 cases in each group. Among them, there were 36 males and 24 females in the control group, aged 19 - 51 years old (with an average of 38.39 ± 3.26 years old); and the course of the disease was 2 - 11 years (with an average of 5.3 ± 1.22 years) and there were 9 cases of nasal polyps. In the observation group, there were 35 males and 25 females, aged 20 - 50 years old (with an average of 37.27 ± 3.44 years old); and the course of the disease was 2 - 10 years (with an average of 5.62 ± 1.19 years) and there were 8 cases of nasal polyps. There was no statistically great difference in gender, age, complications, and other general data between the two groups of patients (P> 0.05), and the patients in the two groups were comparable. The medical ethics committee of our hospital reviewed and approved this study. The diagnostic criteria could refer to the relevant diagnostic criteria of sinusitis in Diagnosis of Nose and Sinusitis. The inclusion criteria were defined as follows: those who met the above diagnostic criteria; patients whose duration of symptoms was more than 2 years; patients whose nasal mucosal edema can be seen on nasal endoscopy; and patients whose and their families were aware of and had signed the informed consents. The exclusion criteria were defined as follows: patients with the previous ear, nose, and throat surgery; patients with severe hematological diseases; patients with impaired consciousness; patients who were unable to communicate normally; patients who can't cooperate with the examination; patients with incomplete clinical data; patients who were allergic to the relevant treatment materials used in this study; and patients who had poor compliance with this study.

Methods

Preparation of CLA-loaded nano-polylactic acid material

1 g of polylactic acid, 5 g of dichloromethane, 3 g of N-dimethylformamide, and 10% of CLA were mixed thoroughly. After being stirred for 1 hour, the

polylactic acid material was stood for until they were completely dissolved, and then they were placed in the water bath for spinning. After ultrasonic treatment for 10 minutes, the bubbles were completely eliminated. Then, a 10 mL syringe was adopted to aspirate the solution. The diameter of the syringe needle was 0.8 mm, the voltage was set to 15 kV, and the distance between the needle and the collector was set to 15 cm. The solution was electrospinning at a feed rate of 0.3 mL/min, and finally, CLA-loaded nano-polylactic acid material can be obtained. The drug release ability was tested by observation under a scanning electron microscope (SEM).

Treatment methods

All patients were treated with endoscopic sinus surgery under general anesthesia, and the messerklinger was selected. Firstly, the diseased sinuses were opened to relieve the obstruction of the nasal cavity. During the surgery, attention should be paid to the preservation of the normal sinus mucosa. After the surgery was completed, the control group was given only CLA capsules (manufacturer: Shanghai Abbott Pharmaceutical Co., Ltd., Chinese medicine standard: H20033044, specification: 0.25 g) oral treatment, with 0.25 g/time and 2 - 3 times/d after a meal. It had to minimize the intake of spicy food and drink plenty of warm water during the medication. Patients in the observation group were given freshly prepared nanomaterial-loaded CLA. Both groups of patients were observed for two consecutive weeks.

Dynamically enhanced CT scanning

Before the examination, the patient had to follow the doctor's advice and choose a suitable position. The patient was scanned with a multi-slice spiral CT scanner (manufacturer: Beijing Bruker Technology Co., Ltd.; model: Optima CT660). An axial CT scan of the nasopharynx was performed from the level of the hard palate upward and routinely scanned to the level of the cavernous sinus. The tube current was set to 150 mAs, the tube voltage was set to 100 kV, the layer thickness was set to 5.0 mm, the layer spacing was 2.5 - 5.0 mm, the thread pitch was 1 mm, and the matrix was 512 × 512. After the scan was completed, the original data obtained were transferred to the workstation for post-processing, so that the image can be reconstructed.

Efficacy evaluation and observation indicators

Both groups of patients were continuously observed and followed up for 3 months for efficiency evaluation. If the following conditions were met, it could be determined that the patient was cured: the patient's clinical symptoms disappeared completely, the sinus opening was well opened through endoscopy and CT examination, the mucosal edema in the sinus cavity disappeared completely, no viscous or mucopurulent secretions were found, and the nasal mucosa recovered well. If the following conditions can be met, the patient treatment was effective: after treatment, the patient's clinical symptoms had been greatly improved, and the sinus mucosa recovered, but some edema was still visible. The treatment was ineffective if the following conditions were met: the patient's clinical symptoms had not improved at all, and the patient's clinical symptoms had even worsened.

Before and after the surgery, microbial and bacterial culture was performed on the secretions in the patients' sinuses, and the results were observed and recorded. Before and after treatment, 5 mL of fasting venous blood was drawn from the patients, and centrifuged at 3 000 r/min for 10 minutes to separate the serum. The serum levels of IL-4, IL-8, and TNF-α were determined by microparticle enzyme immunoassay.

Statistical analysis

Each research object was measured by the Qlab6.0 software 2D Adv spot tracking program, the data was sorted using Excel 2003, and the average value was calculated. The measurement data are expressed by the mean ± standard deviation ($\bar{x} \pm s$), and all variables conformed to the normal distribution after the normality test. Statistical analysis was performed using SPSS 23.0 statistical software. The independent-sample t-test was adopted for comparison between groups. The count data was expressed as a percentage (%), and the χ^2 test was used. $P< 0.05$ was considered as the difference was statistically significant.

Results and discussion

Characterization of nanomaterial loaded CLA under SEM

As shown in Figure 1, the polylactic acid nanomembrane showed linear fiber morphology,

relatively dense distribution, not greatly different fiber diameter, and small porosity. Characterization under a field of view (FOV) of 500 um showed that the fiber surface was smooth and rich in content (Figure 2).

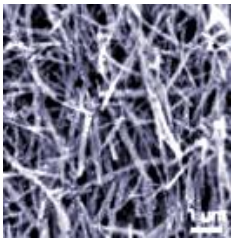

Figure 1. Characterization of nanomaterial loaded CLA (1:1 um).

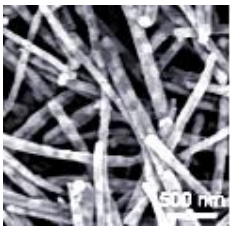

Figure 2. Characterization of nanomaterial loaded CLA (1:500 um).

Testing results of drug release ability

Figure 3 below illustrated that the release of CLA showed a gradual and steady upward trend. On the 25th day, nearly 50% of the dose had been released, and it had reached more than 90% of the total release on the 55th day.

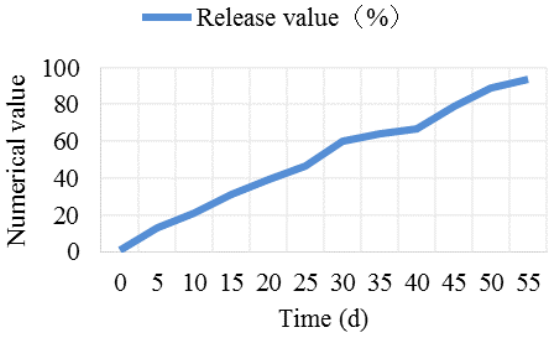

Figure 3. Testing results of drug release ability.

Clinical efficacy

As given in Figure 4, the numbers of cured and effective patients in the observation group were dramatically higher than those in the control group, while the number of ineffective cases was much lower in contrast to the control group. As illustrated in Figure 5, the total clinical effective rate of the observation group was greatly higher than that of the control group, and the difference was statistically significant ($P< 0.05$).

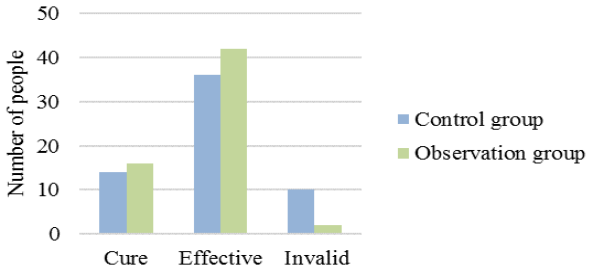

Figure 4. Clinical efficacies on patients in two groups.

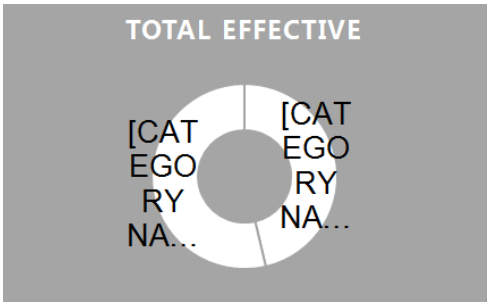

Figure 5. The total clinical effective rate.

Dynamically enhanced CT scan results

Figure 6 showed the results of dynamic enhanced CT scans in patients with sinusitis. In Figure 6A, the left pharyngeal recess of the patient became shallower, and the air column in the pharyngeal recess disappeared. Figure 6B showed the result of CT examination of the control group after treatment, which disclosed that the soft tissue mass on the right side of the nasopharynx was shrinking, but pharyngeal sutures still existed. Figure 6C showed the examination results of patients in the observation group after treatment, which suggested that the plain scan density was uniform and the bilateral mastoid air cells were clear.

Figure 6. Dynamically enhanced CT scan results. (1:500um). Note: Figure 6A showed the image of chronic sinusitis; and Figure 6B and Figure 6C showed the results after treatment of the patient in the observation group and control group, respectively.

Bacterial culture results

Figure 7 illustrated the numbers of patients with *Staphylococcus aureus (S. aureus)*, *Staphylococcus saprophyticus (S. saprophyticus)*, and *Pasteurella multocida infections* in the observation group were lower compared with those in the control group, and the difference was statistically significant (P< 0.05).

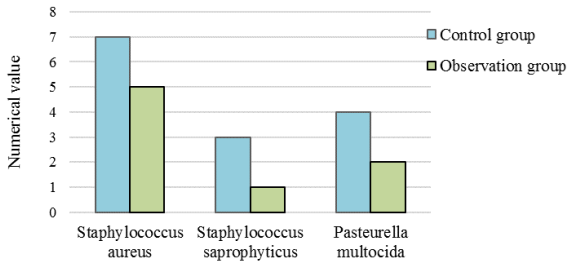

Figure 7. Bacterial culture results.

Level of IL-4, IL-8, and TNF-α

Compared with the levels before treatment, the levels of IL-4, IL-8, and TNF-α in serum of the two groups of patients decreased after treatment, and those in the observation group were lower in contrast to the levels in the control group, showing statistically obvious differences (*P*< 0.05) (Table 1).

Table 1. Comparison of levels of IL-4, IL-8, and TNF-α in serum of the two groups of patients ($\bar{x} \pm s$) (pg/mL)

Group	Cases	IL-4		IL-8		TNF-α	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	60	16.16± 1.18	9.32± 1.97*	491.32± 50.50	307.55± 31.86*	1.42± 0.72	0.56± 0.05*
Control group	60	16.12± 1.22	13.25± 1.36*	493.28± 51.52	381.05± 31.07*	1.45± 0.66	1.09± 0.16*
t-value		0.183	12.717	0.210	12.793	0.238	24.491
P-value		> 0.05	< 0.05	> 0.05	< 0.05	> 0.05	< 0.05

Note: * suggested that the difference was statistically observable in contrast to the value before treatment (*P*< 0.05).

Sinusitis is a chronic inflammatory disease of the nasal cavity and sinuses, and the course of the disease can exceed 3 months in general (13). The pathogenesis of the disease is mostly due to the excessive secretion of mucus and mucus inflammation mediated by inflammatory mediators. Among them, IL and TNF play important roles in the pathophysiological process of sinusitis (14). It can activate the host's innate immunity and adaptive immunity, and then make immune cells secreted and expressed in large quantities, all of which are flooded in the local tissues of the mucosa. In addition, it also stimulates mucin and increases the excessive secretion of mucin, which in turn increases the viscosity of mucus and makes it more difficult to be discharged. Fiber-related factors such as transforming growth factor signaling pathway can regulate cell growth, proliferation, differentiation, migration, and apoptosis, and further promote the differentiation and proliferation of fibroblasts, leading to fibrous proliferation and scar formation, which exert a crucial role in the process of tissue adhesion (15-17). The repeated effects of these inflammatory mediators in the local area make the inflammation prolonged and unhealed, and the combined effects of mucosal swelling, mucociliary clearance, and nasal polyps caused by mucosal inflammation have led to the deterioration of the disease (18).

CLA is a representative drug of the macrolide class and has been included in the guidelines for the diagnosis and treatment of sinusitis. It has a broad antibacterial spectrum, and can effectively resist hemolytic streptococcus, coryneform bacteria, chlamydia, etc. (19). According to research, when the concentration is high, CLA can play a bactericidal effect, accumulate the white blood cells in the body, and then be transported to the infection site. When the concentration is low, it can exhibit an antibacterial effect and effectively prevent the biosynthesis of bacterial protein (20). In addition, it also has a certain anti-inflammatory effect, which can regulate the expression and synthesis of cytokines and transcription factors (21). However, the long-term use of CLA for postoperative patients has disadvantages such as high cost, poor compliance, inconvenience, and toxic side effects. Nanomaterials can be applied as effective carriers to various medical sections (22-24). Therefore; it was optimized using the nanocarriers in this study. Nano-biomaterials loaded with drugs and placed in the surgical cavity can play a role in slow-release drugs, promote drainage and physical isolation, and inhibit adhesions. Compared with traditional materials, nano-materials avoid the shortcomings such as implant blockage, foreign body reaction, and pain and bleeding during the removal process. Polylactic acid is a kind of biodegradable electrospun nanomaterials. As an emerging drug carrier, it has the functions of degradable and slow-release drugs (25). On the basis of drug loading, it also exerts a drug-stent synergistic effect, which can

inhibit the formation of blood vessels and play the anti-adhesion effect. The nanomaterial-loaded CLA prepared in this study can well control the release of the drug, avoid the irritation caused by the drug directly acting on the human body, and significantly reduce the side effects. The results of this study showed that the release of CLA showed a gradual and steady upward trend. Nearly 50% of the dose had been released on the 25th day, and it had reached more than 90% of the total release on the 55th day. The numbers of cured and effective patients in the observation group were visibly higher than the numbers in the control group, while the number of ineffective cases was remarkably lower in contrast to that in the control group; and the total clinical effective rate in the observation group was higher greater than that of the control group. Such results suggested that nanomaterial-loaded CLA can achieve long-term treatment results by slowly releasing the drug, which not only reduced the dosage of the drug but also effectively reduced the multiple effects of repeated drug use in patients (26-28).

In order to observe the therapeutic effect of patients more intuitively, a dynamic enhanced CT scan was adopted in this study, which showed a high qualitative ability for lesions, a high detection rate for small lesions, and a very clear display of the vascular structure. The dynamic enhanced CT examination results of the patients in the control group after treatment showed that the soft tissue mass on the posterior right side of the nasopharynx was reduced, but the pharyngeal suture still existed; while those in the observation group showed that the plain scan density was uniform, and the mastoid air cells were clear on both sides.

Conclusions

In summary, 120 patients with sinusitis were selected in this study to explore the role of nanomaterial-loaded CLA after sinusitis surgery, and the patients were checked and compared through the application of a dynamic enhanced CT scan. It was found that the total clinical effective rate of the observation group was significantly higher than that of the control group. The left pharyngeal recess of the patient became shallower, and the air column in the pharyngeal recess disappeared. The result of CT examination of the control group after treatment disclosed that the soft tissue mass on the right side of the nasopharynx was shrinking, but pharyngeal sutures still existed. The examination results of patients in the observation group after treatment suggested that the plain scan density was uniform and the bilateral mastoid air cells were clear. In addition, numbers of patients with S. aureus, *S. saprophyticus*, and *Pasteurella multocida* infections in the observation group were lower compared with those in the control group; and the levels of IL-4, IL-8, and TNF-α in serum of the two groups of patients decreased after treatment compared with the levels before treatment. Therefore, the therapeutic effect was good, and such a treatment method was worthy of clinical promotion and application. With the popularization and use of nanotechnology, researchers apply it to the field of biomedicine. The characterization and analysis of the nano drug-carrying preparation suggested that the polylactic acid nanomembrane showed linear fiber morphology, relatively dense distribution, not greatly different fiber diameter, and small porosity. Characterization under a FOV of 500 um showed that the fiber surface was smooth and rich in content. The release of CLA showed a gradual and steady upward trend. The release of CLA showed a gradual and steady upward trend. On the 25^{th} day, nearly 50% of the dose had been released, and it had reached more than 90% of the total release on the 55^{th} day. Therefore, the nanomaterial-loaded CLA increased the utilization rate of the drug, showing good clinical efficacy, and it was worthy of further clinical promotion and use. The shortcoming of this study was that the sample size of the study was small, which led to some deviations in the results. Therefore, it was necessary to expand the sample size and carry out further research to obtain more scientific and objective research data and provide more reliable reference value for clinical application.

Acknowledgments

Not applicable.

Conflict interest

The authors declare that they have no conflict of interest.

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