Clinical study protocol

Project name: Single-arm, single-center clinical study of endoscopy combined with intraoperative navigation-assisted treatment of giant mandibular bone cysts

Sponsor: Sun Yat-sen Memorial Hospital, Sun Yat-sen University

Version number: V5.0

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Project Leader: Wang Yan

Plan signature confirmation:

Statement of compliance

Comply with the provisions of the Good Practice for the Quality Management of Clinical Trials for Drugs and the Measures for the Management of Investigator-Initiated Clinical Studies in Healthcare Institutions (Trial) and the Declaration of Helsinki, and commit to conduct this study in accordance with this protocol, participants must be trained to conduct the study after obtaining written approval of the Ethics Committee and written informed consent of the subject, The revised plan needs to be re-approved.

I. Program summary

In this study, with the assistance of endoscopic technology and intraoperative navigation technology, the removal and curettage of large odontogenic jaw cyst occurred in the mandible were performed to reduce the rate of postoperative nerve injury. A series of complications, such as residual lesion, pathological fracture, nerve injury and so on, were caused by the enlargement of incision due to limited visual field and the doubt in determining the boundary of cyst. In this study, endoscopic technique enabled the surgeon to obtain sufficient field of view in small incision, better understand the characteristics of the lesion, protect the inferior alveolar neurovascular bundle, prevent intraoperative pathological fracture and shorten the operation time. The intraoperative navigation technology allows doctors to accurately locate the anatomical positions of each bone in the maxillofacial region, and the navigation probe can accurately judge each orientation of the sac cavity. At the same time, the adapter is used to integrate the navigation and endoscopy, so that the endoscope can not only play the role of obtaining a clear vision but also play the function of real-time positioning. In this study, we compared the efficacy of traditional extraction and curettage with endoscopic navigation assistance in the treatment of giant mandibular bone cysts. In this study, the rate of inferior alveolar nerve injury 1 month after surgery was taken as the main outcome index, and the recurrence rate 1 year after surgery was taken as the secondary outcome index, to explore whether endoscopic combined with intraoperative navigation-assisted treatment of giant mandibular bone cyst could achieve lower postoperative nerve injury rate and postoperative recurrence rate.

II. Introduction

2.1 Research theoretical basis/background

Odontogenic jaw cyst is a unique disease affecting the mouth and mandible. Its occurrence is closely related to the development and formation of dental tissue and inflammation. The four most common odontogenic jaw cysts include periapical cyst, odontogenic cyst, residual cyst, and odontogenic keratosis cyst[1]. Most cysts grow slowly and may have only mild or no symptoms. When cysts grow larger, they can damage the surrounding tissue, leading to maxillofacial swelling, infection, root resorption, nerve damage, pathological fracture, and even malocclusion[2]. Smaller odontogenic jaw cysts can be removed directly by surgery, while the treatment of larger odontogenic jaw cysts remains controversial. Some scholars believe that fenestration decompression is an effective and conservative treatment[3], but some scholars believe that although fenestration decompression is less traumatic, patients will be accompanied by discomfort during the long healing period, and direct surgery to remove the complete lesion is the best choice[4].

In a previous retrospective study of 25 patients with large mandibular cysts who underwent traditional removal and curettage surgery, 8 patients developed symptoms of nerve damage after surgery, with a postoperative nerve damage rate of up to 32%.

It can be seen that how to effectively reduce the rate of nerve damage after surgery for giant mandibular bone cysts is still a difficult problem[5]. Related retrospective studies have shown that most jaw cysts occur in the anterior maxilla and molar areas of the mandible, and odontogenic jaw cysts are common in the mandibula[6]. When the cyst lesion involves the mandibular branch, due to the high anatomical position, the surgeon cannot observe the full scope of the lesion under direct vision, and it is difficult to accurately locate the lesion boundary, which will increase the risk of residual lesion and postoperative recurrence, and bring difficulty and challenge to the operation. In addition, the inferior alveolar nerve passes through here, and if the location relationship between the nerve and the lesion is not clear, the risk of nerve injury will be greatly increased. When odontogenic maxillary cysts involving mandibular branches cannot be completely observed under direct vision, endoscopic techniques enable the surgeon to obtain sufficient visual field through small incisations, better understand the characteristics of the lesions, protect the inferior alveolar neurovascular bundles, prevent intraoperative pathological fractures and shorten the operation time [8-10].

Although endoscope can help surgeons to clearly observe lesions and nerves, it cannot standard determine the anatomical position of each bone in maxillofacial region, the boundary of lesions and the anatomical relationship between lesions and nerves. Navigation technology provides a solution to this problem. In order to apply navigation technology in the operation, it is necessary to collect the data of the patient's lesion site before surgery, conduct 3D simulation and establish a model to clarify the anatomic relationship between the lesion and the surrounding tissue[11]. During the operation, the reference frame should be fixed in the mandible, and the anatomical position of each bone in the maxillofacial region and the boundary of the lesion should be accurately located by the locator and probe, and the area reached by the probe or surgical instrument should be reflected in real time, so that the surgeon can accurately judge each orientation of the sac cavity [12-14], and play a role in guiding the surgical route.

However, there are few studies on endoscopy combined with intraoperative navigation-assisted treatment of giant mandibular bone cysts. In this study, an innovative surgical scheme will be proposed to integrate endoscopy and navigation through the adapter, so that endoscopy can not only play the role of obtaining a clear vision but also play the function of real-time positioning, so as to achieve accurate surgery, aiming at reducing the postoperative nerve injury rate and postoperative recurrence rate of odontogenic jaw cyst, so as to obtain better clinical efficacy.

2.2 Risk/benefit evaluation

2.2.1 Known potential risks

(1) Accidental risk of general anesthesia: After patients receive general anesthesia, due to individual differences of patients, abnormal response to drugs may lead to severe suppression of respiratory and circulatory functions and malignant hyperthermia, etc., which can be life-threatening in severe cases. During anesthesia, various adverse reflexes may induce cardio-cerebrovascular accidents or cardiac and

respiratory arrest, leading to death. In the event of anaesthesia related adverse reactions, clinical treatment should be performed as a complication of normal surgery, while the patient's medical record is detailed and the possibility of continuing the clinical trial should be evaluated.
(2) Risk of tearing the inferior alveolar neurovascular bundle: When cystic lesions are severely attached to the nerve, there is a risk of nerve tearing when separating the mass, resulting in postoperative damage to the inferior alveolar nerve and numbness of the lower lip. When intraoperative nerve tears occur, intraoperative neuroanastomosis should be performed to preserve nerve function as much as possible.
(3) Risk of serious infection after surgery: When the scope of cystic lesions is too large, the risk of postoperative infection increases, and the wound in the operative area may not heal in one stage. In severe cases, it may spread to neighboring tissues, resulting in infection of the maxillofacial space. In the case of severe infection, anti-infection treatment should be actively applied. In the case of infection of maxillofacial space or severe edema of surrounding tissue, the existence of indications for incision and discharge of pus should be considered, and the vital signs of patients should be closely monitored.
(4) In this study, for patients with serious complications of anesthesia during perioperative period, severe postoperative infection or bleeding, respiratory distress caused by severe edema of surrounding tissues, and failure to reanastomosis of nerve tear, etc., the study intervention should be suspended and withdrawn from the study, clinical treatment of corresponding complications should be carried out, and patients should be actively treated. Specific measures should be the treatment plan mentioned in the above complications. The safety of the surgical method of the study protocol was discussed, and the follow-up was determined whether to adjust the study surgical protocol, and follow-up records of the original subjects were maintained during the suspension of the study. In the case of clear withdrawal, the investigator may continue to complete the follow-up without the study intervention.

2.2.2 Known potential benefits

The potential benefits of this study include safer and more effective surgery, complete curettage of cystic lesions and protection of the associated normal anatomical structure. It can better protect lower alveolar neurovascular bundle, prevent intraoperative pathological fracture and shorten operative time. The operation is minimally invasive and the patients recover faster after operation. Subjects entering this clinical study can reduce the surgical cost of endoscopic technology, gain more attention from researchers and timely treatment of disease changes, which is conducive to the treatment of subjects' diseases.

2.2.3 Potential risk and benefit evaluation

In this study, endoscopy combined with intraoperative navigation assisted treatment of giant mandibular bone cysts was adopted. Endoscopy technology provided surgeons with a clearer and more complete surgical field of view, while

navigation technology could reflect the relationship and position between surgical instruments and the patient's anatomical structure in real time, allowing surgeons to obtain clear and objective anatomical recognition during surgery. Preoperative computer simulation combined with intraoperative navigation has been proven to be an effective way to improve surgical outcomes. In this study, endoscopic techniques combined with intraoperative navigation techniques were used to treat large odontogenic maxillary cysts involving mandibular branches, which were not only safe and effective, but also able to completely curettage cystic lesions during the operation and protect the associated normal anatomical structures. It can better protect the lower alveolar neurovascular bundle, prevent intraoperative pathological fracture and shorten the operation time. This procedure is minimally invasive and patients recover faster after surgery. As a result, patients have a lower risk of developing nerve tears during surgery. In addition, each patient will undergo various basic examinations before surgery to strictly evaluate whether they can tolerate general anesthesia surgery and reduce the risk of anesthesia accidents. In future studies, researchers will pay more attention to the subjects' systemic conditions and tumor treatment, and the subjects will also obtain certain clinical benefits in this study.

III. Purpose and endpoint of the study

3.1 Purpose

3.1.1 Main purpose

The main objective of this study was to investigate the rate of lower alveolar nerve injury 1 month after endoscopy combined with intraoperative navigation-assisted treatment of giant mandibular cyst.

3.1.2 Secondary Purpose

The secondary objective of this study was to investigate the recurrence rate 1 year after endoscopy combined with intraoperative navigation-assisted treatment of giant mandibular bone cysts.

3.1.3 Exploratory purpose

The exploratory objective of this study was to evaluate the postoperative efficacy of endoscopy combined with intraoperative navigation-assisted treatment of giant mandibular bone cysts

3.2. Research indicators

3.2.1 Main Indicators and Definitions

Rate of inferior alveolar nerve injury 1 month after surgery: For patients who received endoscopic combined with intraoperative navigational assistance in the treatment of giant mandibular cyst, inferior alveolar nerve function was detected before surgery and 1 month after surgery to determine whether postoperative inferior alveolar nerve injury existed. Detailed detection methods are shown below.

3.2.2 Secondary indicators and definitions

Recurrence rate 1 year after surgery: The number of patients who received endoscopy combined with intraoperative navigation-assisted treatment for giant mandibular bone cysts who had cyst recurrence 1 year after surgery.

3.2.3 Security Specifications

The subjects' vital signs, blood routine, liver function, heart function, blood biochemistry, urine routine, stool routine, coagulation function, electrocardiogram, chest film, maxillofacial imaging data and other safety indicators were all interpreted by the researcher team based on the test results before the subjects were enrolled.

IV. Study the population

4.1 Inclusion criteria

(1) Aged between 18 and 75 years old

(2) Imaging and puncture pathology showed dental cystic lesions of the mandible

(3) Cystic lesions greater than or equal to 2cm in diameter and affecting the inferior alveolar nerve

(4) Lesions of new or recurrent cysts, or odontogenic cystic lesions that are still greater than or equal to 2cm after other treatments such as fenestration and affecting the lower alveolar nerve

(5) No serious systemic diseases, can tolerate general anesthesia

(6) Patients who intend to undergo surgical treatment for mandibular bone cysts under general anesthesia

(7) There was no inferior alveolar nerve injury before operation

(8) Did not participate in other clinical trials within the past 30 days

(9) Patients who voluntarily participate in the project and sign informed consent

4.2 Exclusion Criteria

(1) The patient has serious systemic disease or pregnancy, and after the research team and multidisciplinary consultation and evaluation, it is determined that she cannot tolerate the clinical study process and general anesthesia

(2) Unable to complete the entire clinical research process due to personal, social and economic reasons

(3) Patients suffering from mental diseases or unable to perceive and communicate normally, such as schizophrenia, claustrophobia, etc., are unable to complete the examination and cooperate with the entire clinical study process

4.3 Lifestyle considerations

After entering the clinical study, the subjects should have a light diet, abstain from tobacco and alcohol, and prohibit strenuous exercise. If the subjects need to use drugs, treatments or operations unrelated to the study in the clinical study, the researchers should evaluate whether the reasons for the need for such drugs, treatments and surgical treatments are adverse events caused by the study. If the subject needs additional treatment due to accident or other reasons, whether the

treatment has an impact on the progress of the study will be considered. If the impact is too large, it is recommended that the subject withdraw from the conventional treatment and seal the subject's data.

4.4 Filtering Failure

Patients will be screened after signing the informed consent for this study, and those who fail the screening will be excluded from the study. Based on the results of the multidisciplinary consultation, the study will inform the failed patients and give the optimal treatment recommendations.

4.5 Recruitment and retention strategies

This study will recruit subjects mainly offline and combine both online and offline. The main offline location will be the Oral and maxillofacial Surgery Department of Sun Yat-sen Memorial Hospital, including but not limited to posters, leaflets, information sessions and other forms to attract more subjects. Every interested patient will register on the spot, leave his contact information and continue to have one-to-one explanation program. If the subject has financial difficulties, the researcher team will assist the subject to apply for public welfare fund to help reduce the financial burden of the subjects.

V. Research design

5.1 Overall Design

This study hypothesized that endoscopy combined with intraoperative navigation-assisted treatment of giant mandibular bone cysts was more effective than the traditional surgical method of removal and curettage. In this study, a prospective, single-arm, Phase II clinical study was used to design the protocol, and the estimated rate of postoperative nerve injury was reduced by about 12% from 32% to 20% compared with traditional surgery.

5.2 Research and design process

5.2.1 Study the specific implementation process

This study started from the recruitment of subjects, oral panoramic film, maxillofacial CT and other imaging examinations were performed to confirm the diagnosis. After preliminary screening according to the inclusion and exclusion criteria, patients were enrolled after signing the informed consent letter. Endoscopic and navigational techniques were used for surgical treatment. This study referred to A prospective study by Abdullah Hanfesh15 et al to evaluate the function of the inferior alveolar nerve: the bilateral mandibular and lower lip were divided into four areas: area A, area B, area C, and area D. The four areas will be lightly touched, acupuncture, cold and hot stimulation, and two-point discrimination detection four times respectively. The detection situation of each area will be recorded. The scoring criteria for each test are as follows.

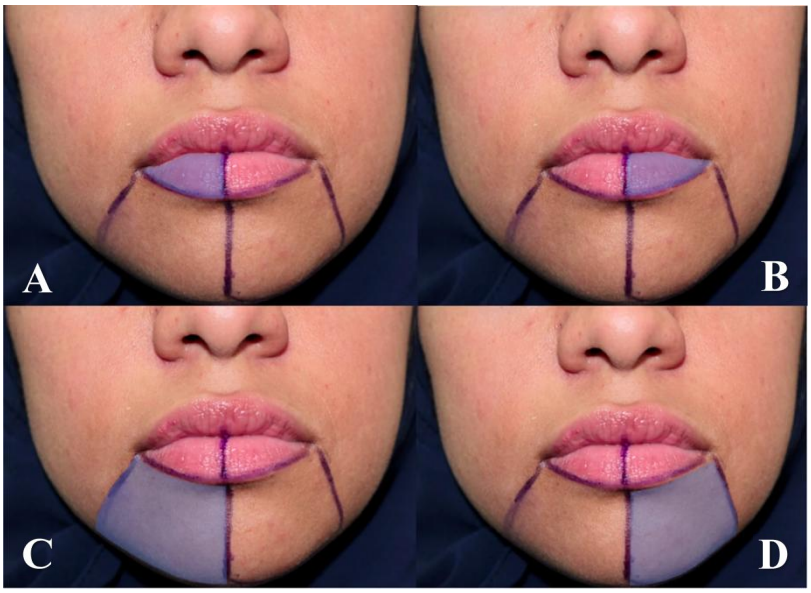


Figure 1. Area diagram[15]
A: Upper right lip B: Upper left lip C: Right jaw D: Left mandible

Light touch: Cotton wool is used for light touch detection. The score range is 0-4, with 4 indicating no nerve damage.

Table 1 Light touch stimulus rating table

Sign	Score
Completely unresponsive to stimuli	0
Severe loss of perception	1
Mild irritation is almost imperceptible	2
Compared with pre-operation slight stimulation can still be perceived	3
Compared with pre-operation there was no difference, normal perception of mild stimulation	4

Acupuncture: Detection is performed using dental probe stimulation on a scale of 0-1, with 1 indicating no nerve damage.

Table 2. Acupuncture stimulation rating table

Sign	Score
Completely unresponsive to stimuli	0
Produces a sharp tingling sensation to stimuli	1

Figure 2 Lower alveolar nerve function measured by cotton wool[15]

Figure 3. The function of inferior alveolar nerve was detected by acupuncture[15]

Hot and cold stimulation: Test tubes filled with hot water (45-50 ° C) and filled with ice water were used to detect hot and cold stimulation, respectively. The score range was 0-1, with 1 indicating no nerve damage.

Table 3. Cold and heat stimulation rating table

Sign	Score
Completely unresponsive to stimuli	0
Develop a cold/hot sensation to stimuli	1

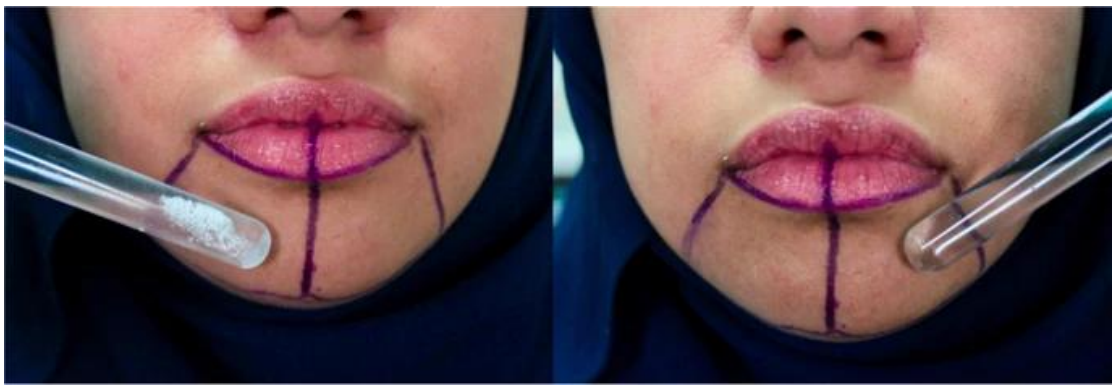


Figure 4. The function of inferior alveolar nerve was measured by heat and cold stimulation[15]

Two-point discrimination test: The distance between two points can be distinguished using a vernier caliper. The score ranges from 0 to 5, with 5 indicating no nerve damage.

Table 4: Two-point discrimination measurement rating table

Sign	Score
The distance between the two ends of the vernier caliper is > 15mm	0
The distance between the ends of the vernier caliper is 10-15mm	1
The distance between the ends of the vernier caliper is 9-10mm	2
The distance between the ends of the vernier caliper is 7-9mm	3
The distance between the ends of the vernier caliper is 5-7mm	4
The distance between both ends of the vernier caliper is less than 5mm	5

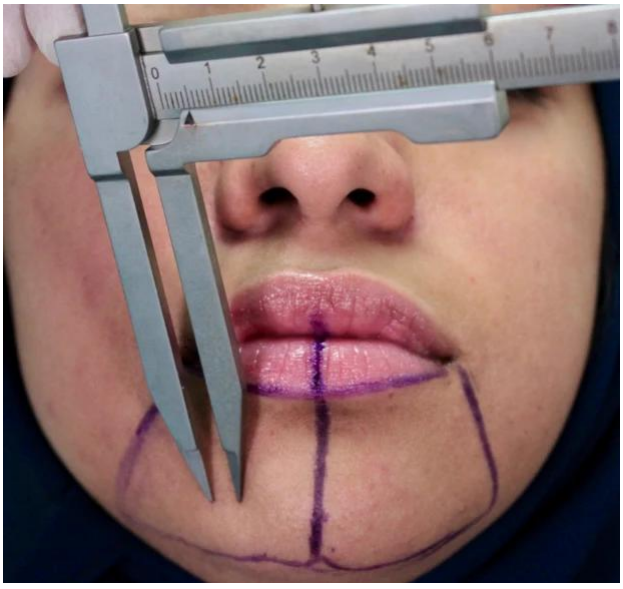
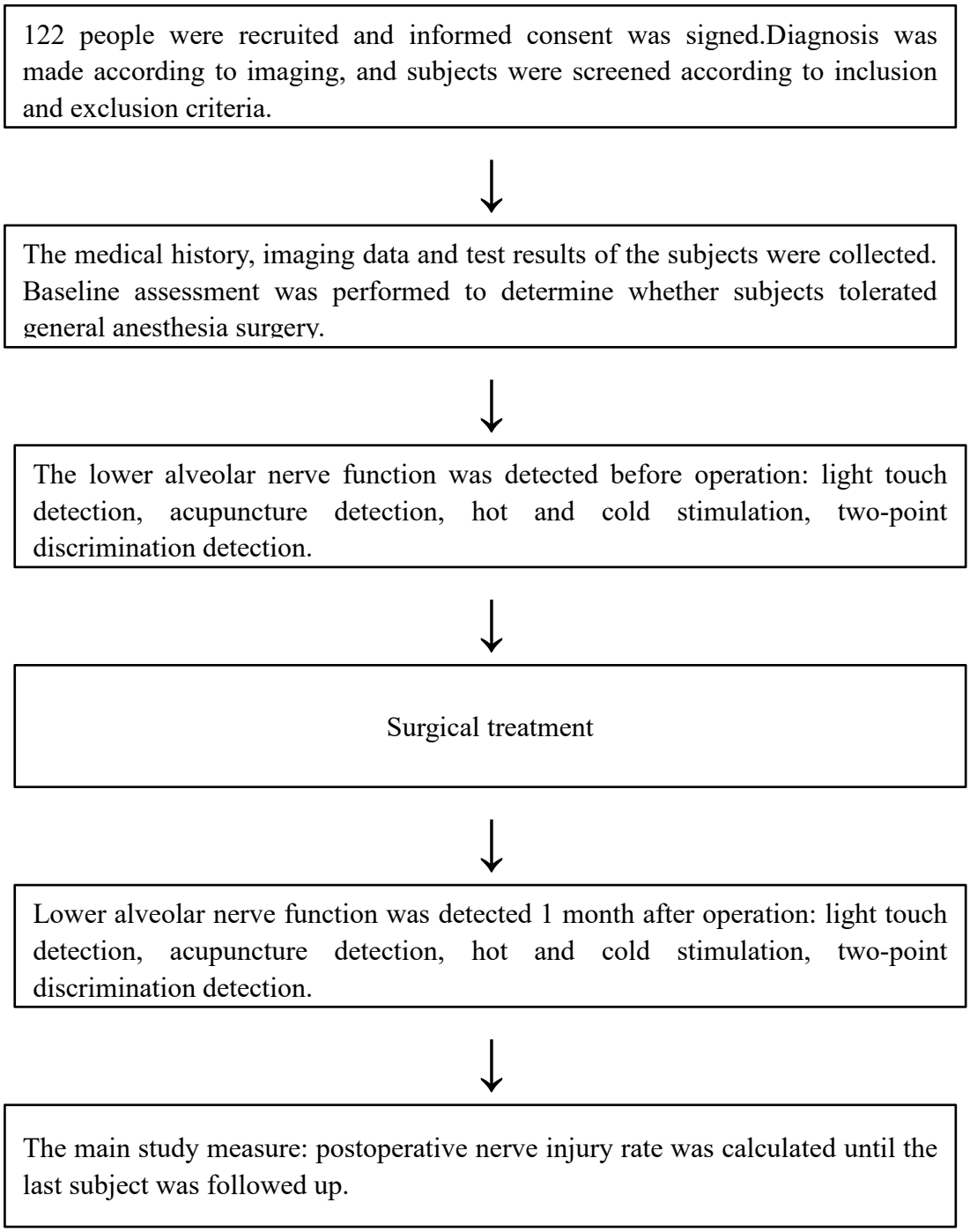


Figure 5 Vernier calipers measure the distance between two points[15]

Inferior alveolar nerve function was detected before and 1 month after surgery. Light touch detection 4 points, acupuncture detection 1 point, hot and cold stimulation 1 point, two-point discrimination detection 5 points showed no nerve damage. Any other score for any of the above is considered to be nerve damage.

5.2.2 Study flow charts



5.2.3 Research schedule

Interview	Screening period	Before operation	Operation	Follow-up visit			
	V1	V2	V3	V4	V5	V6	V7
Follow-up time	1 day before enrollment	Enrollment day	Day after V2	1 week after surgery	One month after surgery	Three months after surgery	1 year after surgery
Sign informed consent	√						
Inclusion/exclusion criteria	√						
Demographic data	√						
Medical history	√						
Neural test score		√			√		
Physical examination	√	√	√	√	√	√	√
Vital sign	√	√	√	√	√	√	√
Electrocardiogram	√						
Blood routine examination	√						
Blood biochemistry	√						
Liver function	√						
Coagulation function	√						
Imaging examination	√				√		√
Pathological examination			√				
Epidemiological examination	√						
Adverse event evaluation			√	√	√	√	√

5.3 Definition of study end

The end of the study was defined as the last subject to complete the last follow-up or loss of follow-up or death.

5.4 Statistical Analysis

5.4.1 Sample size and calculation basis

The main efficacy index of this study was the postoperative nerve injury rate of endoscopic combined with intraoperative navigation-assisted treatment of giant mandibular bone cysts. The hypothesis of this study is that the postoperative nerve injury rate of endoscopy combined with intraoperative navigation-assisted treatment of giant mandibular cyst is lower than that of traditional excision and curettage. Research parameters were set as follows: α=0.025 (unilateral) and Power=80%. According to the results of previous studies or pre-trials, the postoperative nerve injury rate in the endoscopic navigation group was reduced by about 20% to 12%. 109 cases were calculated using PASS 15.0 software, and 122 subjects were included considering the 10% shedding rate.

5.4.2 Data Analysis Set

Statistical analysis will be performed using SAS statistical analysis software (V.9.4, SAS Institute). If there is no special explanation, unilateral test will be used for the main index, and the control error α is 0.025; bilateral test will be used for the other indicators, and the error α is =0.05. If you need to calculate confidence intervals, calculate bilateral 95% confidence intervals unless otherwise specified.

(1) full analysis set (FAS) : comprised of all subjects who underwent surgical treatment and were evaluated for efficacy. The data set is derived from all subjects by eliminating subjects in a minimal and reasonable way.

(2) safety analysis set (SS) : A group of people who have received surgical treatment and have safety evaluation data. In the safety analysis, all patients will be analyzed according to the actual surgical group received.

(3) per-protocal set (PPS) : all subjects who met the protocol and did not use concomitant drugs that affected the effectiveness evaluation, had good medication compliance (between 80% and 120%), and excluded subjects who had a major protocol violation and were judged to have a significant impact on the results. All trial protocol deviations that result in subjects being excluded from the conformance protocol set will be detailed in the Statistical Analysis Plan (SAP) and completed prior to data locking.

5.4.3 Statistical Analysis Plan

Data description of statistical analysis, analysis methods of primary/secondary indicators/safety indicators, statistical correction methods, bias control, stratification/subgroup/sensitivity analysis, etc.

Demographic and other baseline characteristics: Based on FAS set, demographic data, medical history, vital signs and other baseline data were statistically described. The mean, standard deviation, minimum, maximum and median values were given for measurement data (age, BMI, body weight, blood pressure, etc.). Counting data (gender, tobacco and alcohol history, etc.) give the frequency and corresponding percentage.

Analysis of efficacy index: The main evaluation index (postoperative nerve injury rate) was estimated by point and the bilateral 95% confidence interval was estimated by Clopper-Pearso exact probability method. If the lower limit of the 97.5%

confidence interval is lower than the postoperative nerve injury rate of the historical control, it is considered that the efficacy of the navigational endoscopy group is better than the historical control. Secondary efficacy indicators were analyzed using FAS and PPS analysis sets. For postoperative recurrence indicators, the median postoperative recurrence time and bilateral 95% confidence interval were calculated. For the rates of each index, point estimation was performed and the Clopper-Pearson accurate probability method was used to estimate the bilateral 95% confidence interval. For the continuity index, if it conforms to the normal distribution, its mean and bilateral 95% confidence interval are calculated based on the normal distribution method, otherwise based on hundreds.The quantile method calculates the median and bilateral 95% confidence intervals.

Analysis of safety indicators: SS sets were used to make statistical descriptions of the incidence of adverse events/serious adverse events, adverse reactions and other safety indicators, and to list and describe the details of each adverse event for each subject, including the type and severity of adverse events. Laboratory indicators, vital signs, electrocardiogram and other safety-related indicators were compared and evaluated before and after treatment, and clinical evaluation (normal, abnormal no clinical significance, abnormal clinical significance, no investigation) was given before and after treatment for statistical description.

The processing principle of missing/deleted/lost data: LOCF (last observation carried forward) method was adopted to fill in the analysis of main indicators, that is, the last observed data was used to fill in the data that failed to observe the main indicators. Secondary indicators and security indicators are not filled.

VI. Research and intervention

6.1 Study intervention content

All enrolled patients underwent blood routine, liver function, heart function, blood biochemistry, urine routine, stool routine, coagulation function, electrocardiogram, chest film, maxillofacial imaging and other related examinations to ensure the safety of general anesthesia. Preoperative copies of the patient's maxillofacial imaging data were digitally designed, professional software was used to segment cystic lesions and segment the inferior alveolar nerve together, and then the data was imported into the navigation system. After general anesthesia, gingival trapezoidal incision or modified trapezoidal incision was made in the area of the cyst, and the flap was turned to expose the bone surface. The bone window was opened with electric grinding and drilling system, and the lesions were initially cureted with curette immediately after the window opening. The occlusal surface and the internal and external sides were mainly treated. The surgeon placed the mandibular reference frame in the mandibular anterior tooth area, and used the navigation probe under the guidance of navigation to accurately locate the anterior cavity of the capsule, the apex of the root of the tooth and the ascending branch of the mandible. After accurate positioning was obtained, the navigation adapter was loaded onto the endoscope to locate the lesions in all directions and the inferior alveolar nerve under visual

conditions, and further precisely curettage the lesions in the cystic cavity with the assistance of the adapter.

6.2 Preparation/handling/storage/Responsibilities

Any drug use or adverse reactions must be recorded in the patient's medical record and recorded at the appropriate location in the CRF.

6.3 Study intervention compliance

The subjects were asked to return to the research center one month after surgery for lower alveolar nerve function detection. The subjects were required to return to the research center for maxillofacial imaging examination at 1 month, 3 months, 6 months, 1 year and 2 years after surgery to determine whether the cyst recurred and whether there was new bone formation in the cystic cavity. During the same period of follow-up, whether the oral wound healed in one stage, whether there was fluid seepage or suppuration. The compliance of the study can be verified according to the review status of the subjects. In the later follow-up, members of the research team must conduct telephone follow-up communication with the subjects and reasonably arrange the time of the subjects' review and visit.

6.4 Combination Therapy

Subjects with diseases requiring long-term drug control, such as hypertension, diabetes, and coronary heart disease, should be evaluated by investigators and relevant specialists to determine the impact of the disease and related research protocols and determine the dosage and duration of adjuvant medication.

6.4.1 Rescue

The life risk of the subjects during the implementation of the clinical study protocol should be implemented according to the clinical rescue protocol, such as cardiopulmonary resuscitation, emergency airway management, and emergency surgical treatment. The relevant records during hospitalization should be recorded in the medical record system, and the occurrence after discharge should be recorded in the adverse event record table. Meanwhile, researchers should analyze the cause of rescue. As to whether it is related to the research and discussed, the discussion is recorded in the rescue record simultaneously.

VII. Study intervention discontinuation or Subject discontinuation and withdrawal

7.1 Study intervention discontinued

During the perioperative period of this study, if the number of patients with serious complications such as anesthesia, serious postoperative infection or bleeding, respiratory distress caused by severe edema of surrounding tissues, nerve lacerations and other serious complications reached 30% of the participants, the study should be

suspended, and the safety of surgical methods of the study protocol should be discussed to determine whether to adjust the study surgical protocol, and follow-up should be conducted during the suspension of the study. Follow-up records of the original subjects were maintained.

7.2 Subject discontinuation/withdrawal from study

When subjects suspend or withdraw from the study due to dissatisfaction with the therapeutic effect of the study program or their own financial reasons, they should communicate with them to encourage them to actively treat the treatment and help them apply for public welfare funds to complete the treatment. In the perioperative period, if serious complications of anesthesia, serious postoperative infection or bleeding, respiratory distress caused by severe edema of surrounding tissues, nerve tears and other serious complications reached 30% of the number of subjects, the study should be suspended, and the safety of the surgical method of the study protocol should be discussed to determine whether to adjust the study surgical protocol, and follow-up should be conducted during the suspension of the study. Follow-up records of the original subjects were maintained. In the case of clear withdrawal, the investigator may continue to complete the follow-up without the study intervention.

7.3 Loss of access (measures to reduce loss of access and data loss due to loss of access)

After the enrollment of subjects, the researchers should keep the contact information of multiple subjects and the contact information of subjects' families. After the subjects are discharged from hospital, the researchers should actively contact the subjects by phone, timely understand the condition of the subjects, and arrange the subjects to be admitted to the hospital for the next stage of treatment in advance.

VIII. Adverse Events and unexpected events

An adverse event (AE) is an adverse medical event that occurs after a subject receives treatment, but is not necessarily causally related to the treatment. An adverse event may be any adverse and unexpected sign (including abnormal laboratory findings), symptom, or disease associated with the use of the treatment, regardless of whether it is related to the treatment. It includes, but is not limited to:

(1) exacerbation of disease that existed before the study treatment was used;

(2) Increased frequency or severity of paroxysmal events that existed before the study treatment was used;

(3) abnormal changes detected or diagnosed after the study of treatment use, although such abnormal changes may have existed before treatment;

(4) Exacerbation of disease or symptoms that were already persistent before the study began.

Causal relationship between adverse events and treatment measures: In the trial, researchers should conduct comprehensive analysis according to the specific

circumstances of adverse events and subjects' past history, concomitant diseases and concomitant medication, etc., to determine the relationship between adverse events and treatment measures. The relationship between adverse events and treatment measures was classified as "definitely related, it may well be relevant, it may be relevant, it may not be relevant and it may not be relevant."

(1) Unrelated: Adverse events were not associated with treatment.

(2) May not be relevant: the occurrence of an adverse event is more likely to be related to other factors, such as co-medication or concomitant disease, or the timing of the event indicates that it is unlikely to be causally related to the treatment.

(3) May be related: The occurrence of adverse events may be caused by therapeutic measures. Cannot rule out whether other

Causes, such as: drug combination or concomitant disease. The occurrence of adverse events and treatment measures have a reasonable time sequence, and the causal relationship between the events and treatment measures cannot be ruled out.

(4) Likely related: The occurrence of adverse events may be caused by therapeutic measures. The occurrence and treatment measures are

Reasonable chronological order.

(5) Definitely relevant: the type of adverse event has been identified as a result of the treatment and cannot be otherwise justified

Explain, for example, drug combinations and concomitant diseases. The timing of the event strongly suggests causality. The criteria for judging the severity of adverse events can refer to the following criteria:

(1) Mild: mild symptoms or signs but tolerable.

(2) Moderate; Symptoms are significant enough to interfere with normal life.

(3) Severe: severe symptoms, has been unable to carry out normal activities.

All information about adverse events, whether referred to by the patient, discovered by the investigator, or discovered by physical examination, laboratory examination, etc., should be recorded in the study medical record and case report form. During the trial, the occurrence time, duration, symptoms, signs and severity, measures taken and outcome of adverse events should be carefully observed and recorded

And the relationship with treatment measures should be assessed, and appropriate follow-up should be conducted. Possible adverse events include:

(5) Accidental risk of general anesthesia: After patients receive general anesthesia, due to individual differences of patients, abnormal response to drugs may lead to severe suppression of respiratory and circulatory functions and malignant hyperthermia, etc., which can be life-threatening in severe cases. During anesthesia, various adverse reflexes may induce cardio-cerebrovascular accidents or cardiac and respiratory arrest, leading to death. In the event of anaesthesia related adverse reactions, clinical treatment should be performed as a complication of normal surgery, while the patient's medical record is detailed and the possibility of continuing the clinical trial should be evaluated.

(6) Risk of tearing the inferior alveolar neurovascular bundle: When cystic lesions are severely attached to the nerve, there is a risk of nerve tearing when separating the mass, resulting in postoperative damage to the inferior alveolar nerve and numbness

of the lower lip. When intraoperative nerve tears occur, intraoperative neuroanastomosis should be performed to preserve nerve function as much as possible.
(7) Risk of serious infection after surgery: When the scope of cystic lesions is too large, the risk of postoperative infection increases, and the wound in the operative area may not heal in one stage. In severe cases, it may spread to neighboring tissues, resulting in infection of the maxillofacial space. In the case of severe infection, anti-infection treatment should be actively applied. In the case of infection of maxillofacial space or severe edema of surrounding tissue, the existence of indications for incision and discharge of pus should be considered, and the vital signs of patients should be closely monitored.

IX. Data collection and management

9.1 Case report form/electronic data record

Before the study began, the Redcap electronic database /EDC database was established according to the contents of the paper case report form.

9.2 Data Management

The original data are uniformly recorded in the study medical records. According to the contents of the study medical records, the researchers themselves or designated/authorized trained personnel can complete the case report form and data entry in the electronic database to ensure the integrity and accuracy of the information. In order to ensure the accuracy of the data, the researchers conducted self-checks no less than twice a year, regularly dispatched personnel to the sub-center to conduct project quality control, and accepted the inspection of the hospital and school management departments. If it is found that the data registered in the case report form/electronic database is inconsistent with the original record (study medical record), the researcher shall organize timely verification of the data, modify the incorrect part as required, and make corresponding explanations if necessary.

X. Ethical requirements

This study complies with the provisions of the "Medical Device Clinical Trial Quality Management Practice" and the "Administrative Measures for Conducting investigator-initiated Clinical Studies in Medical and Health Institutions" (Trial) and the Declaration of Helsinki. This study can only be carried out after the protocol is approved by the Ethics Committee of our hospital before the trial starts. During the study, if a protocol revision is necessary, the revised protocol must be re-submitted to the Ethics Committee for review, and the researcher must wait until the Ethics Committee agrees before implementing the new protocol.

Each enrolled patient must sign an informed consent form. A copy of the

informed consent form and contact information for the investigator and the ethics committee must be provided to the patient upon request. This study will collect clinical data and personal information of research subjects for scientific research, which will involve the privacy rights of patients. Participants in this study and data analysts signed confidentiality agreements, not to disclose patients' personal information and disease-related information to any individuals and institutions unrelated to this study. The collected patient data shall be managed in a unified manner to prevent the leakage of personal privacy.

XI. References

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