

STUDY PROTOCOL (NCT:1/134)

10 December 2019

NAME OF THE STUDY

Effect Of Early Versus Delayed Laparoscopic Cholecystectomy On Postoperative Mortality, Morbidity and Difficult Cholecystectomy In Patients With Grade II Cholecystitis According To Tokyo 2018 Guidelines

1. SUMMARY OF THE STUDY

According to the Tokyo 2018 acute cholecystitis diagnosis and treatment guideline, there is currently no definite conclusion about when patients diagnosed with Grade II acute cholecystitis should be operated on. In this study, two different treatment methods, which have been applied before in the literature and whose superiority has not been clearly proven, will be compared. The patients will be operated in the early (first 7 days) and late (>6 weeks) periods and the difference between the two groups in terms of difficult cholecystectomy, mortality and morbidity will be compared.

2. PURPOSE OF THE STUDY

Acute cholecystitis is a gallbladder pathology that can lead to serious complications, and Tokyo 2013 and 2018 acute cholecystitis and acute cholangitis diagnosis and treatment guidelines have been published in order to be applied in the diagnosis phase. In these guidelines, patients were divided into three groups based on clinical findings, laboratory findings, and imaging findings, and these groups were named as Grade I, Grade II, and Grade III. While early cholecystectomy is recommended in Grade I patients, treatment options such as early cholecystectomy, late cholecystectomy after antibiotic therapy, and late cholecystectomy after cholecystostomy are left to the discretion of clinicians in Grade II high-risk and Grade III patients, depending on the clinical condition of the patient. Although there is no definite opinion about which treatment is superior today, the studies included patients in all three stages. In addition, most of the studies in the literature have been carried out retrospectively, and the number of prospective studies is very few. In this study, we will examine whether there is a significant difference in terms of difficult cholecystectomy, mortality and morbidity between early and late cholecystectomy in Grade II patients who are most difficult in the decision stage.

Koetsu Inoue et al. reported that there are fewer technical difficulties in cholecystectomies performed within the first 96 hours after admission with the diagnosis of acute cholecystitis (1).

In contrast, Yun-Xiao Lyu et al. showed that there is a significant difference between cholecystectomy performed at the first admission and cholecystectomy performed in the late period, only in terms of length of hospital stay (2). Ismael Mora-Guzmán et al. also reported in their study that there was no significant difference in complications between early and late cholecystectomy(3). Again, Vinoban Amirthalingam et al. It has been reported that early period cholecystectomy can be performed safely in Grade II and III patients (4). In all these studies, no clear distinction was made for early and late cholecystectomy, and both techniques were shown to be applicable.

3. EXPECTED BENEFITS AND RISKS FROM THE RESEARCH

In this study, there is no expected risk since a different treatment method and medication will not be tried in previous similar studies. As a result of this study, if there is a difference between the research groups, new data will be obtained in terms of the approach to Grade II acute cholecystitis in the literature. Due to the limited number of prospective studies on this subject, the data to be obtained may change the treatment scheme to be applied in the future for the patient population in the research group and may benefit from reducing the complication rates.

4. TYPE, SCOPE, DESIGN AND THE DATA TO BE OBTAINED AFTER THE RESEARCH STATISTICAL TO BE USED IN THE EVALUATION METHODS

The research was planned as a prospective study. The study is single-centered and the patient group graded as Grade II according to the Tokyo 2018 guideline acute cholecystitis diagnostic criteria will be included in the study. Grade I and III patients, patients with accompanying choledocholithiasis, patients who are pregnant or likely to become pregnant, patients who cannot comply with the treatment due to their mental status and who cannot sign their own consent for treatment will not be included in the study. Patients classified as Grade II acute cholecystitis will be informed about the treatment options and possible complications after hospitalization. Patients will decide on the treatment method to be applied with their consent. The patients will be divided into two groups as those operated in the early period (first 7 days) and those operated in the late period (>6 weeks). The parameters to be compared were the rate of conversion from laparoscopic to open, bile duct injury and bile leakage rate, grade II-III complication rate in the Clavien Dindo complication scoring system, morbidity rate in the first 30 days postoperatively, and difficult cholecystectomy rate based on intraoperative imaging findings according to the Parkland scoring system. The research will be terminated when the number of 120 patients determined by the power analysis result is reached.

Chi-square and Student's t test will be used for the statistical evaluation of the results of the patients, respectively, for quantitative and continuous variables, and Mann-Whitney U test (two samples) or Kruskal-Wallis test (more than two samples) will be used for the analysis of abnormally distributed variables.

5. THE NUMBER OF PATIENTS AND VOLUNTEERS TO BE INCLUDED IN THE RESEARCH QUALITY AND JUSTIFICATION OF SELECTION (AGE RANGE, GENDER ETC.).

The research population was determined as 120 patients as a result of the power analysis results. The number of volunteers will be 120, and the patient group graded as Grade II according to the Tokyo 2018 guideline acute cholecystitis diagnostic criteria will be included in the study, regardless of gender group over the age of 18.

6. PARAMETERS TO LOOK AT AND WHERE TO LOOK AT THE PARAMETERS AND BY WHOM

Parameters to be checked: Age, gender, comorbid diseases, previous abdominal operations, drug allergy, ASA score, Parkland score, length of hospital stay, duration of operation, amount of bleeding during the operation, type of operation, biliary tract complication, Clavien Dindo complication score, postoperative mortality and morbidity. The parameters will be checked and recorded by the principal investigator during the application and follow-up.

7. WHICH PARAMETERS TO BE USED IN THE RESEARCH ARE ROUTINE FOR THAT DISEASE GROUP AND WHICH ARE SPECIALLY REQUESTED FOR THE RESEARCH

Among the parameters and tests used in the research, there are no specific ones used for the research, and all of them are recorded and requested during the routine follow-up of the disease.

8. PROJECTED WORKING TIME, START AND END DATES

The duration of the study was planned as 18 months, and the study date range was determined as 14.12.2019-14.06.2021.

9. WITHDRAWAL AND TERMINATION CRITERIA

When patients want to leave the study, they can leave the study provided that they inform the principal investigator. The research doctor, who is also the coordinator of the study, may remove the patient from the study without informing the patient due to my negligence in fulfilling the requirements of the study program or in order to improve the quality of the medical care I am receiving.

The research will be terminated if the determined population (even earlier than the determined date) is reached.

10. REFERENCES

1. Koetsu Inoue, Tatsuya Ueno, Daisuke Douchi, Kentaro Shima, Shinji Goto, Michinaga Takahashi, Takanori Morikawa, Takeshi Naitoh, Chikashi Shibata and Hiroo Naito. Risk factors for difficulty of laparoscopic cholecystectomy in grade II acute cholecystitis according to the Tokyo guidelines 2013. Inoue et al. BMC Surgery (2017) 17:114

2. Yun-Xiao Lyu , Yun-Xiao Cheng, Hang-Fei Jin, Xin Jin, Bin Cheng and Dian Lu. Same-admission versus delayed cholecystectomy for mild acute biliary pancreatitis: a systematic

review and metaanalysis. Lyu et al. BMC Surgery (2018) 18:111

3. Ismael Mora-Guzmán, Marcello Di Martino, Alvaro Gancedo Quintana, Elena Martin-Perez. Laparoscopic Cholecystectomy for Acute Cholecystitis: Is the Surgery Still Safe beyond the 7-Day Barrier? Journal of Gastrointestinal Surgery. <https://doi.org/10.1007/s11605-019-04335-5>

4. Vinoban Amirthalingam, Jee Keem Low, Winston Woon, Vishalkumar Shelat. Tokyo Guidelines 2013 may be too restrictive and patients with moderate and severe acute cholecystitis can be managed by early cholecystectomy too. Surg Endosc. DOI 10.1007/s00464-016-5300-4

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PATIENT INFORMED CONSENT FORM

1. INFORMATION ABOUT THE RESEARCH

Name of the Study: Comparison of early and late stage difficult cholecystectomy, mortality and morbidity rates in patients with Grade II acute cholecystitis according to Tokyo 2018 acute cholecystitis diagnostic criteria.

Content of the Study: Currently, there is no definite conclusion about when patients with gallbladder inflammation (acute cholecystitis) should be operated on. In the above-mentioned study, two different treatment methods, which have been previously applied in the literature and whose superiority has not been clearly proven, will be compared. Patients classified as Grade II acute cholecystitis in the Tokyo 2018 acute cholecystitis diagnosis and treatment guideline will be informed about the treatment options and possible complications after their hospitalization. Patients will decide on the treatment method to be applied with their own consent. The treatments to be applied are divided into two as surgical removal of the gallbladder in the early period or removal of the gallbladder with the gallbladder surgery to be performed 6 weeks after the antibiotic treatment. As a result of the research, it is planned to obtain results related to the superiority and reliability of these two treatment methods applied today.

Purpose of the Study: Comparison of the complications that may occur between the patients after the treatment of the patients whose diagnosis was made in accordance with the data in the Tokyo 2018 acute cholecystitis diagnosis and treatment guideline with two different treatment modalities specified in the same guideline, and thus to compare the complications that may occur between the patients, which are relatively less and have better results. is to encourage the implementation of the treatment scheme.

Projected Duration of the Study: 18 months

Number of Volunteers Expected to Participate in the Study: 120

Practices and Treatment to be Followed in the Study: Patients classified as Grade II acute cholecystitis will be informed about the treatment options and possible complications after their hospitalization. Patients will decide on the treatment method to be applied with their own consent. One group of patients will be operated on as an emergency within the first 7 days of admission, and the treatment of the patients in the other group will begin with antibiotic therapy. Patients whose antibiotic therapy is completed will be taken into surgery after completing their anesthesia preparations at the end of the 6-week waiting period. Both patient groups will be monitored for complications for 30 days after surgery.

2. POSSIBLE BENEFIT(S) EXPECTED FROM PARTICIPATION IN THE RESEARCH

Both mentioned treatment methods have applicability within the guidelines. Patients will decide on the treatment method to be applied with their own consent. Both treatment methods to be applied are currently being applied and one has not been proven to be superior to the other.

3. RISKS AND DISEASES THAT THE VOLUNTEER MAY ENCOUNTER DURING THE APPLICATION

Gallbladder surgery can be performed with open or closed (laparoscopic) methods. As a standard, closed surgery is recommended for all patients. However, open surgery can also be performed due to previous surgeries, anomalies related to the abdominal wall, and diseases of the patient's other organs such as lungs and heart. Even in patients who are suitable for closed surgery, with a probability of up to 5%, due to the disease and the characteristics of the patient, even if the surgery started closed, it can be ended openly. Any intervention other than the planned diagnosis/treatment/intervention can only be applied to prevent serious harm to your health and save your life. Complications that may be encountered in this surgery are injuries that may occur in the bile ducts, bleeding that may occur during the operation due to the neighborhood of the gallbladder with the liver.

After surgery, there may be bile leakage from the liver bed of the gallbladder or the ligated gallbladder bile duct, leading to peritonitis (inflammation of the peritoneum) and/or fistulas (leakage of bile from the abdomen to the skin). This condition can be life-threatening, require repeat surgery, require intensive care treatment, and may result in death. With the opening of the ligated gallbladder vein, bleeding may occur and may require surgery again. Jaundice, cholangitis (inflammation of the bile ducts) and pancreatitis (inflammation of the pancreas) may develop as a result of the stones in the gallbladder falling into the bile duct while removing the gallbladder. During surgery, the main bile duct, where the gallbladder duct is opened, can be tied or cut. Depending on this, jaundice may develop and require repeat surgery. In this case, bile duct strictures may develop.

During the operation, the sac is punctured and stones and bile can be poured into the abdominal cavity, which may lead to intra-abdominal abscesses in the future. After the surgery, the intestines may work late and the patient's initiation of oral feeding may be delayed. Postcholecystectomy syndrome, characterized by indigestion and pain after fatty meals, may develop. During the surgery, organ injuries such as liver, duodenum (duodenum), large intestine may be injured and additional interventions may be required. After the operation, there may be separation of the surgical wound on the abdominal wall and re-operation may be required to close it. Even if there is no healing problem in the beginning, a hernia may develop at the incision site in the following years and may require surgery. Intestinal obstruction may develop in the early postoperative period or sometimes years later, due to adhesions between the intestines or between the intestines and the abdominal wall. This may require re-operation.

In the postoperative service follow-ups, complications related to your previous diseases (eg, hypertension, high blood sugar, respiratory distress), complications related to anesthesia taken during the operation, and allergic complications that you did not know before may develop due to the antibiotics and drugs to be applied.

4. EXPECTED MEDICAL BENEFIT FROM THE RESEARCH FOR VOLUNTEERS

Symptoms due to gallbladder inflammation will disappear, and the risks of possible complications will be eliminated.

If there is a difference in favor of any of the treatment methods applied in this study in terms of complications, this study will guide the general surgeons for the treatment to be applied to the patients after you.

5. PREGNANCY

Pregnant women are out of the scope of the study.

6. INFORMATION ABOUT INTERVENTIONS OR TREATMENTS THAT ARE OPTIONAL TO RESEARCH

The standard treatment for the disease is surgery. For patients with gallbladder inflammation, surgery in the early period and operation in the late period after antibiotic therapy are nowadays preferred by the surgeon. Apart from these methods, in high-risk patients with multiple comorbidities, the bile and the inflammation in the gallbladder can be drained by placing a catheter in the gallbladder. Although it is another method, recurrent gallbladder inflammation attacks have been reported in publications after this treatment method. For this reason, gallbladder surgery is mostly performed in the late period in patients whose inflammation is drained. Removing the gallbladder inflammation with a drainage procedure to be performed under ultrasound guidance is another treatment method that can be applied, but it will not be applied in the patient groups we included in the study due to the lack of high risk factors.

I learned that there are other suitable methods for my disease apart from the examination and treatment interventions to be applied in the research above, but they will not be applied in this research. I am aware that I have the right to receive the other treatments mentioned if I do not agree to participate in the above study.

7. EXCLUSIONS

If you do not fulfill the requirements of the applied treatment scheme, interrupt the study schedule, become pregnant or suffer a side effect related to the study drug, or increase the effectiveness of the treatment, etc. For reasons, your doctor may exclude you from the study without your consent.

8. MEETING THE EXPENSES WITHIN THE SCOPE OF THE RESEARCH

Any examination, physical examination and other research costs will not be paid to you or any official or private institution or organization that you are under the guarantee of.

9. WILL ANY PAYMENT BE MADE FOR PARTICIPATION IN THE RESEARCH?

You will not be paid for your participation in this research.

10. CONTACT FOR PROBLEMS THAT MAY OCCUR DURING THE RESEARCH

During the application period, you can contact the doctor below to get additional information about the study or if you have any problems, unwanted effects or other discomforts related to the study, or if you have to take a non-study drug.

1. Telephone... 05365652310 2. Phone:

11. MEASUREMENT OF DAMAGES:

I have been informed that if I am harmed by participating in this study, the necessary medical care will be provided by the principal investigator/physician, I am insured against any damage (including injury and death) that may occur due to the study drug or the procedure applied, and my expenses will be covered.

12. RIGHT TO VOLUNTEER, REJECT AND WITHDRAW THE TRIAL, WITHDRAWAL FROM THE TRIAL

- a. I voluntarily participate in the research without any pressure or coercion.
- b. I have been informed that I have the right to refuse to participate in the research.
- c. I am aware that I can withdraw from this study at any time without giving any reason, provided that I notify the principal investigator. I understand that I take no responsibility if I refuse to participate or subsequently withdraw from this study, and that this will not in any way affect the medical care I need now or in the future.
- d. The research doctor, who is the coordinator of the study, may exclude me from the study without my consent due to my negligence in fulfilling the requirements of the study program or in order to improve the quality of the medical care I am receiving.

13. PRIVACY:

The results of the study can be presented in scientific meetings or publications. However, in such cases, my identity will be kept strictly confidential.

14. CONSENT TO PARTICIPATE IN THE STUDY:

I have read the Informed Consent Form, which shows the information that should be given to the volunteer before the research, in my native language, or I have it read to me. The content and meaning of this information was explained in written and oral form. I was given the opportunity to ask all the questions that came to my mind and I received adequate answers to my questions.

In the event that I do not participate in the study or withdraw after participating, I will not have waived any of my legal rights. Under these conditions, I agree to participate in this research voluntarily without any pressure or coercion.

A signed copy of this form was given to me.

Volunteer's Name - Surname:

Age and Gender:

Signature:

Address (phone and/or fax number, if available):

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Date:

For those under custody or guardianship;

Name-Surname of Parent or Guardian:

Signature:

Address (phone and/or fax number, if available):

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Date:

Investigator-Doctor Who Made the Explanations

Name and surname:

Signature:

Date:

The establishment officer who witnessed the consent process from the beginning to the end.

Name and surname:

Signature:

Mission:

Date: