Effect of Low-pressure Pneumoperitoneum on Pain and Inflammation Post Laparoscopic Cholecystectomy: A Randomized, Double-blinded, Controlled, Clinical Trial.

ClinicalTrials.gov Identifier: **not yet assigned**

Date protocol accepted by IRB at the University of Jordan: **15th January 2020**

Study Summary:

In the era of laparoscopic abdominal surgeries, pneumoperitoneum pressure is set to a point of 12-15 mmHg. The new generation of surgeon has been questioning if we could do laparoscopic surgeries with no compromise at a lower pneumoperitoneum pressure in the aim of improving the quality of patients' lives postoperatively and efficacy of health care system. In reviewing the literature, such intervention has showed benefit in terms of decreasing postoperative pain (1) and rise of inflammatory markers (2). This study is designed as a randomized double- blinded controlled clinical trial to challenge such hypothesis. The study shall be conducted on patients at The University of Jordan hospital booked electively for laparoscopic cholecystectomy then randomized into two groups operated at either standard or low pneumoperitoneum pressure then assessed post operatively for pain and rise of inflammatory markers.

Research design:

It is a clinical trial, designed to look for a statistical difference in pain and rise of inflammatory markers post operatively between interventional group which is operated at a low-pressure pneumoperitoneum of 8-10 mmHg compared to the standard of care of pneumoperitoneum set at a pressure of 12-14 mmHg.

further to increase validity of results and strengthen the study design, the study participants are randomized, the groups are masked, and the data is blinded to investigators, analyst, and participants.

Research subjects:

All patients admitted to surgery ward through clinic with the diagnosis of multiple gallbladder stones undergoing laparoscopic cholecystectomy are to be considered for enrollment in this study.

Inclusion criteria:

- Elective admission for laparoscopic cholecystectomy
- Minimum age of 12 years
- American Society of Anesthesiologists (ASA) score 1 or 2

Exclusion criteria:

- Current or previous diagnosis of acute cholecystitis confirmed by ultrasound.
- previous GI surgeries, except bariatric and anti-reflux surgeries
- Currently on immunosuppressant agents
- Pregnancy
- Breastfeeding
- Currently diagnosed with drug addiction
- American Society of Anesthesiologists (ASA) score 3, 4, 5, or emergency surgery

Allocation to groups:

participants are to be given numbers in study and be labeled with it. A preset computer-generated list is to be used to divide patients between two study arms into either of masked groups. Allocation to groups is random according to the computer-generated randomized list.

Masking (blinding) method:

The two study arms are to be color coded. The codes are to be used for randomization, data entry and analysis. None of the participants, investigators and analyst are to be informed of color code reference. the principal investigator, operating surgeon and circulating nurse during operation are to be informed of the color code meaning. After closure of the study, the color codes can be disclosed to the public.

Criteria to discontinuation:

Any participant withdrawing consent during any time of the study.

Patients found to have intra operative adhesions and evidence of previous inflammation are not to be discontinued from the study.

Sample size:

A convenient sample of 100 participants is decided, divided into 50 for each study group.

Intervention:

Interventional group is to be operated at low-pressure pneumoperitoneum which is set at 8-10. Control group is to be operated at standard-pressure pneumoperitoneum which is set at 12-14. The pressure set point is to be determined at the beginning of surgery, any change to pressure after initial insufflation is not to change the participants study arm grouping.

Observations:

Pre-operative demographics are to be collected for each patient, including patient name, medical record number (MRM), age, gender, weight, height, ASA score, medical history, surgical history, current medications, marital status, smoking status, operation date.

During operation, the following are to be observed and recorded: time of surgery start, time of surgery end, total time of insufflation, method of insufflation (open, closed), operator level of experience, intraoperative findings (adhesions, inflammation, perforation, bile leak), difficulty of surgery subjectively assessed by operator (easy, moderate, difficult), estimated blood loss, change of pneumoperitoneum pressure set point, intraoperative mortality, intraoperative complications.

Post-operative during hospital-stay the following are to be collected: pain score out of 10 according to patient perception recorded at 6hr, 12hr and 24hr post-op, hospital stay length in days, total analgesia given post-op (number of dosage and type).

Post-operative after hospital discharge the following are to be collected: pain score out of 10 according to patient perception recorded on 7^{th} day post-op and to be collected via phone call, post-operative complications up to day 30 (readmission, CBD stone, pancreatitis, cholangitis, ..etc.), and histopathology result.

The following inflammatory markers are to be investigated: white blood cell count, platelet count, erythrocyte sedimentation rate, C reactive protein level, albumin level, free serum cortisol level, interlukein-6 level, interlukein-17 level, interlukein-1 beta level, tumor necrosis factor alpha level.

Flow of study work:

After ensuring patients eligibility for study and obtaining informed consent, they are to be allocated to one of study arms randomly. Observations are to be taken and entered to on-line excel. After discharge patients are to be followed on day 7 post-op to collect pain score via phone call, complications are to be followed up to day 30 post-op from electronic records.

Regarding inflammatory markers, the tests are to be performed at Jordan University Hospital laboratories, the blood samples are to be collected safely by study assistants and delivered to the lab labeled with patient name, MRM, date, and time of collection. The runoff tests are done as standardizes by hospital laboratory policies.

Specifications to operation:

Patients enrolled in the study are to undergo laparoscopic cholecystectomy as per the following protocol:

- Regarding general anesthesia, the use of dexamethasone during induction is to be avoided
- Regarding creation of pneumoperitoneum, the choice is given to operating surgeon to choose either open, closed, or optical technique
- Regarding number and site of trocars, the choice is given to operating surgeon to perform as per trained
- Cholecystectomy is to be performed as standardized, after establishment of critical view of safety, the operating surgeon is to carry on steps to establish hemostasis, clipping of cystic duct, and dissection of gallbladder from its liver bed
- Retrieval of specimen is to be done through umbilical port
- The use of endoclose device for closure of fascia is to be avoided
- The infiltration of local anesthesia at site of trocars is to be avoided
- Regarding skin closure, the choice is given to operating surgeon to perform as per trained

Data management and analysis:

The principal investigator is to ensure adherence to protocol and data validity. To ensure this, data will be reviewed each end of month, and a progress summary is to be written and provided to study regulatory every six months.

Analysis is to be conducted using SPSS version 1.0.0.1406. analysis plan is attached in separate file.

Ethical considerations:

No data to be collected without obtaining patient informed consent, the signed paper is to be kept for a minimum of two years

Funding:

The study is funded by a grant through the University of Jordan scientific research deanship.

References:

1- Gurusamy KS, Vaughan J, Davidson BR. Low pressure versus standard pressure pneumoperitoneum in laparoscopic cholecystectomy. *Cochrane Database of Systematic Reviews* 2014, Issue 3. Art. No.: CD006930. DOI: 10.1002/14651858.CD006930.pub3.
2- Agarwal BB, Nanavati JD, Agarwal N, et al. Biomolecular inflammatory response to surgical energy usage in laparoscopic surgery: results of a randomized study. *Surg Endosc Other Interv Tech.* 2016;30(5). doi:10.1007/s00464-015-4408-2.