

## **COVER PAGE**

**Title of document:** Randomized Controlled Study of Intraincisional Infiltration Versus Intraperitoneal Instillation of Standardized Dose of Ropivacaine 0.2% in Post-Laparoscopic Cholecystectomy Pain

**NCT Number** – Not Available

**Document Date** – 01/04/2014

## **AIMS AND OBJECTIVES**

The study was designed as a prospective randomized case control study involving patients who were subjected to laparoscopic cholecystectomy in Unit I in the Department of Surgery, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh. The duration of study was 36 months.

The primary objective of this study was to study and assess the effect and impact of using the local anesthetic ropivacaine, over controls, on the intensity of post-operative pain in patients undergoing laparoscopic cholecystectomy; and to compare and assess the optimal site i.e. intraincisional v/s intraperitoneal of using local anesthetic (ropivacaine) for better post-laparoscopic cholecystectomy pain relief.

The secondary objectives of this study included

1. To identify the component of pain that is dominant after laparoscopic cholecystectomy.
2. To strive for making laparoscopic cholecystectomy a truly day case procedure in the public setup of developing countries like ours using this cheap drug i.e. ropivacaine.
3. To appreciate any emerging new trends in the epidemiology of cholelithiasis in North India.

## **MATERIALS AND METHODS**

The study was designed as a prospective randomized case control study involving patients who were subjected to LC in a single unit by a single surgeon in the Department of Surgery of a tertiary teaching government institute over a period of 36 months. Ethical approval was provided by the Ethical Committee of the University and was conducted in accordance with guidelines of 'Good Clinical Practice' and the 'Declaration of Helsinki'. Written informed consent was taken from all patients. The drug used for the study was 'Ropivacaine 0.2%' (Injection Ropin 0.2 %, Neon Laboratories Ltd., Mumbai, India) which is dispensed as a 20 ml ampoule. Ropivacaine is a United States-Food and Drug Administration (US-FDA) approved drug [FDA Application No. – (NDA) 020533] approved on 24/09/1996 [14] and has increasingly been used for infiltration anesthesia.

### **Inclusion Criteria**

All patients in the age group of 15-80 years conferring to Grade I or II of American Society of Anesthesiologists (ASA) physical status classification system, undergoing elective LC for symptomatic cholelithiasis by a single surgeon, were included in this study.

### **Exclusion Criteria**

Patients with known allergic reactions to LAs; cases that were converted to open cholecystectomy, as well as patients with major intra-operative complications; patients suffering from acute cholecystitis, empyema or malignancy of gall bladder, having history of chronic pain or those taking frequent analgesics or opioids preoperatively; patients with peptic ulceration, bleeding disorders, impaired renal and/or hepatic function, and sensitivity to NSAIDs or opioids. patients in whom gall bladder (GB) stones are found incidentally on ultrasonography (USG) (asymptomatic cholelithiasis); patients suffering from severe chronic

medical diseases and morbid obesity and patients unable to comprehend instructions or having communication problems were excluded from the study.

### **Study Design and Study Groups**

It was a prospective randomized case control triple blind study in which neither the patient nor the investigator i.e. myself, nor the operating surgeon knew whether the drug would be used or not; and if the drug is going to be used, what would be its location. Patients were, thus, divided into 3 groups – Controls: those who did not receive any drug but received normal saline (NS) at both sites, that is, intraperitoneally as well as intraincisionally; Intraperitoneal Ropivacaine group (IPR group): those who were given ropivacaine intraperitoneally and NS intraincisionally; and Intraincisional Ropivacaine group (IIR group): those who were given ropivacaine by infiltrating it locally at the skin incision site and given NS intraperitoneally.

### **Methodology**

During initial outpatient visits, the patients were fully assessed and a confirmed diagnosis was made on the basis of USG abdomen. In patients identified to having a recent episode of acute cholecystitis, an interval laparoscopic cholecystectomy after at least 6 weeks or later was done. Upon admission, patients were explained about the study and an informed consent was taken for participation in the study. Pain was assessed at 5 points of time in the post-operative period, that is, at 30 minutes (0.5 hour), 4 hour, 8 hour, 12 hour and 24 hour. Pain was assessed by both objective and subjective methods. The frequency of extra doses of analgesics (rescue analgesia) given over and above the standard analgesia was also noted. The different pain scales used were-

#### *A. Subjective Scales*

1. Visual Analog Scale (VAS) – A 10 cm line was used and patient was told to mark on it using a pen regarding the pain perceived by him/her.
2. 11 Point Numeric Rating Scale (NRS-11/NRS) – Patient was asked to assign a number to pain, what he/she think was appropriate to describe the pain.

**0-None; 1, 2, 3-Mild; 4, 5, 6-Moderate; 7, 8, 9, 10-Severe**

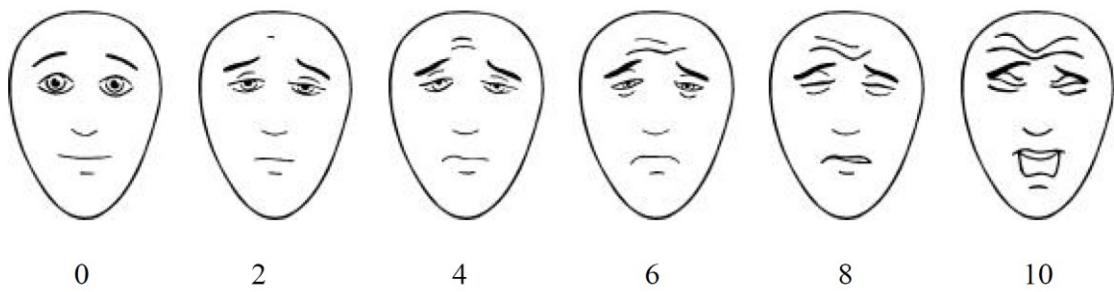
3. Visual Descriptor Scale (VDS) – A 7 point subjective scale in which patient was told to indicate it verbally about the perception of pain as experienced.

**No Pain / Slight Pain / Mild Pain / Moderate Pain / Severe Pain / Extreme Pain /  
The Most Intense Pain Imaginable**

कोई दर्द नहीं / बिल्कुल कम दर्द / कम दर्द / ठीक ठाक दर्द / तेज़ दर्द / बहुत तेज़ दर्द / असहनीय दर्द (in Hindi dialect)

#### *B. Objective Scales*

1. Faces Pain Scale – Revised (FPS-R) – This is an objective method of pain assessment in which facial expressions of the patient are assessed by the investigator, as depicted in the Figure 1 and scored accordingly.



2. Activity Tolerance Scale (ATS) – This is a combined objective and subjective method in which patient was asked subjectively for the below mentioned 5 grades of activity and the criterion told by patient was further objectively assessed by the investigator. By convention, this scale was not used to assess the patient at 30 minutes post-operative hour as all the patients remained in the recovery room at that time on the stretcher.

**No Pain / Can Be Ignored / Interferes With Task / Interferes With Concentration /  
Interferes With Basic Needs / Complete Bed Rest Required**

Patients were explained about the usage of the subjective pain scales and how to convey them to investigator. The objective pain scales were assessed by the investigator.

After routine standardized pre-operative evaluation, patients were shifted to operating room (OR) where they were made to choose from 3 pre-formed envelopes. These contained the information as to in what study group, the patients would belong to. The chosen envelope was then given to an independent OR attendant from a different OR, who then prepared one 20 ml and one 5 ml syringe. The 20 ml syringe either contained 20 ml of undiluted drug or 20 ml of NS depending upon the group. Similarly, the 5 ml syringe either contained 5 ml of undiluted drug or 5 ml of NS, again depending upon the group. Thus for control group, both syringes contained NS. For IPR group, 20 ml syringe contained the drug while 5 ml syringe contained NS. In IIR group, the 20 ml syringe contained NS while 5 ml syringe contained the drug. Thus all patients received intraperitoneal instillation as well as intraincisional infiltration at all points of time but nobody in the OR knew what is being given. Patient's name was written on the envelope and it was put in a locker. The envelopes were opened only after completion of study.

**Anesthetic Technique Protocol**

All patients received the same anesthetic technique. Anesthesia was induced with intravenous (IV) fentanyl  $1.5 \mu\text{g}/\text{kg}$ , propofol  $2 \text{ mg}/\text{kg}$ , and atracurium  $0.6 \text{ mg}/\text{kg}$ . Fentanyl was used for pain relief because it has a duration of analgesic action of 30 – 60 minutes [15] so it was not likely to affect the post-operative assessment of pain. After tracheal intubation, patient's lungs were mechanically ventilated and anesthesia was maintained with 60% nitrous oxide, oxygen, and one minimum alveolar concentration (MAC) isoflurane. A further bolus of fentanyl  $50 \mu\text{g}$  was given after 45 min of the initial dose or earlier if heart rate or BP increased by more than

20% of baseline value after incision. At the end of the surgery, residual neuromuscular blockade was antagonized with IV neostigmine 2.5 mg and glycopyrrolate 0.5 mg.

### **Operative Technique Protocol**

All the operations were performed by a single surgeon so the basic operative technique was similar in all the patients. A standard 4 port laparoscopic cholecystectomy (LC) was performed in all patients. A 10 mm horizontal skin incision was made at the superior aspect of the umbilicus and then deepened through the subcutaneous fat to the anterior rectus sheath. The infra-umbilical skin was pinched up with the left hand along with the underlying soft tissue (to avoid injury to viscera and bowel especially in case of any adhesions). A veress needle was inserted through the incision with the right hand, directed towards the midline. The veress needle was connected to the insufflator. Carbon dioxide (CO2) was insufflated into peritoneal cavity at the rate of 2 litres/min, upto a pressure of 10 mm of Hg. Veress needle was then removed. A 10 mm bladed trocar with sheath was placed at the umbilical port. The trocar was removed keeping the sheath in place. Insufflation of CO2 was initiated at the rate of 2 litres/min, upto a maximum pressure of 12-14 mm Hg. The gas flow rate was then kept at 6 litres/min during the procedure. The 10 mm epigastric port incision and the 5 mm right midclavicular and right anterior axillary incisions were given under vision.

At the end of procedure, intraperitoneal instillation was done using the irrigation apparatus under the right hemi-dome of diaphragm and in the GB fossa. The amount of intraperitoneal instillation was kept at 1ml/cm of length for uniformity of comparison at the 2 locations. Cassart et al., 1997 in their study calculated the total length of diaphragm ( $L_{di}$ ) at total lung capacity (TLC) to be  $44.1 \pm 1.6$  cm (right > left) and length of dome of diaphragm ( $L_{do}$ ) at TLC to be  $32.6 \pm 0.7$  (right > left) in control subjects. He also found out that  $L_{do}$  does not change in patients of COPD significantly; however  $L_{di}$  decreases significantly in patients suffering from

COPD. Taking a rough estimate of the length of dome of diaphragm at TLC, and since right hemi-dome is larger than the left, we took the length of right hemi-dome to be roughly 16 cm and thus used 16 ml intraperitoneal instillation along the right hemi dome. We also used 4 ml of solution in the GB fossa.

If a patient needed to be inserted a drain, a suction drain no. 12 was inserted through the lateral 5 mm port and it had to be blocked for half an hour to prevent the escape of solution into the drain. In such patients, thus, drain was opened only at the time when first observation was made. All of the skin incisions were closed with 3-0 non-absorbable monofilament nylon suture on cutting needle, followed by aseptic dressing. Intraincisional infiltration was done using the standardized amount i.e. 1ml/cm of length of incision. For this, length of the incision site was measured using a scale and the drug was infiltrated accordingly. Thus, if a port had to be increased to 12 mm for some reason, 1.2 ml of intraincisional infiltration was used. This ensured the uniformity of drug dosage used in the IPR and IIR groups. Duration of surgery was measured from the time of first incision to the final stitch taken at port sites.

### **Post-operative Pain Control Protocol**

Pain control in post-operative patients was in 2 forms:

1. Standard Pain Control: Injection (Inj.) Diclofenac Sodium 75mg/1ml (aqueous) IV 12 hourly was used as standard analgesia in all the patients irrespective of what study group patient belonged to.
2. Rescue Analgesia (RA): Inj. Tramadol 100 mg IV stat was used for providing analgesia at any point of time for those patients who demanded for additional pain relief, in case the pain was very distressing to them. Moreover, all the patients who had a VAS and/or NRS >6 or agonizing pain at any point of time, were offered rescue analgesic, especially at the

0.5<sup>th</sup> hour when the pain is usually higher. Some patients might still need additional analgesia beyond this point. But the dose of Inj. Tramadol cannot be repeated for the next 6-8 hours due to possibility of drug accumulation/toxicity. So, a dermal patch of Diclofenac Diethyl Amine (Nupatch 100mg/50cm<sup>2</sup>; Zydus Cadila, Ahmedabad, India) which is a slow release drug delivery system, was used as a second line of RA. It was offered to all the patients who had already been given Inj. Tramadol and even after 2 hours of its administration as timing of peak effect of Tramadol  $\approx$  2 hours, either the patient had a VAS and/or NRS  $>6$ ; or patient had agonizing pain; or if the patient still asked for additional pain relief.