



## Multimodal Preincisional Premedication to Prevent Acute Pain After Cholecystectomy

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### ABSTRACT

**Introduction:** Postoperative pain as an important medical concern is usually treated by opioids which also are of various inevitable side effects. The aim of this study was to assess the efficacy of multimodal preincisional premedication on preventing post-cholecystectomy acute pain. **Methods:** In a randomized clinical trial, sixty patients undergoing open cholecystectomy were randomized into two groups. Before anesthesia induction, Diclofenac suppository (100 mg) and oral Clonidine (0.2 mg) were administered in the first group. Immediately before operation, patients received Ketamine (1 mg/kg IV) while the control group received placebo. The site of incision was infiltrated by the surgeon with 20 mL Bupivacaine 0.25% in both groups. Anesthesia induction and maintenance were similar in both groups. The severity of pain was recorded 2, 4, 6, 12, 24 and 48 hours after operation according to Visual Analogue Scale. **Results:** The severity of pain at two defined stages (6 and 12 hours later) was significantly less in the intervention group than the control group ( $P < 0.005$ ). The average pain severity score was less than the control group ( $P < 0.005$ ). **Conclusion:** In our study, the administration of Clonidine, Diclofenac and Ketamine and bupivacaine infiltration to the site of incision, altogether was associated with a significant decrease in pain score and opioid requirement after cholecystectomy in comparison to bupivacaine infiltration to the site of incision.

### Introduction

Post-operative pain can be derived from the anesthesia techniques used for the surgery, for instances the back pain caused following spinal anesthesia or the surgical process solely.<sup>1,2</sup> Surgical procedures are associated with tissue injury and its consequent release of inflammatory mediators i.e. histamine etc. which in turn activates peripheral nociceptors transmitting stimuli to the central nervous system (CNS). Peripheral functional nociceptors are sensitized by the continuous release of inflammatory mediators which is associated with a decreased activation threshold and increased rates of activation and basal (spontaneous) discharge.<sup>3</sup> Poorly-controlled postoperative pain would result in undesirable acute and chronic effects including delayed long-term recovery and chronic pain. Furthermore, uncontrolled postoperative pain activates the sympathetic nervous system; hence contributing to increased morbidity and mortality rates.<sup>2,3</sup> Central

sensitization has been suggested to be prevented by preemptive analgesia reducing acute and chronic pain. However, very few studies support the efficacy of preemptive analgesia.<sup>1,3</sup>

The term "preemptive analgesia" is considered as a controversial one, being questioned for its clinical relevance.<sup>3</sup> Multimodal analgesic regimens, i.e. administration of non-opioid analgesics for minimizing the postoperative opioid requirement, would allow more prompt post-operative recovery and therefore retaining normal daily activities.<sup>3,4</sup>

Due to the existing ambiguity in terms of the preemptive analgesia value, we decided to evaluate the effect of quadruple premedication for preemptive analgesia in open cholecystectomy operation. Our suggested quadruple premedication regimen for reducing the postoperative pain of the patients undergoing open cholecystectomy consisted of a single dose of diclofenac (100 mg suppository),

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clonidine 0.2 mg PO, Ketamine 1 mg/kg IV, and a local anesthetic wound infiltration using Bupivacaine.

### Materials and methods

The present study has been approved by Local Ethics Committee of Tabriz University of Medical Sciences with the approval number of 87/1-2/10 published in the letter number 5/4/174 in 12/ 30/ 2008. All medications used in this study are FDA approved. Written informed consents were obtained from all patients before entering the study. Our research is a randomized placebo-controlled clinical parallel trial in which 60 patients over 18 years old participated from 2009-2010. The patients were hospitalized in Imam Reza hospital, Tabriz, East Azerbaijan, Iran and scheduled to undergo open cholecystectomy via Kocher incision. Inclusion criteria were as follows: Age over 18, filling out the informed consent form, being operated by open Cholecystectomy via Kocher incision.

Exclusion criteria were as follows: Patient's refusal for participation, uncontrolled and complicated underlying disease, addiction to opiate or alcohol, ingestion and usage of antipsychotic drugs, history of drug reactions and addiction, having coagulopathies and analgesic consumption. Patients were divided into two 30 unit groups, based on their order of entrance to the operating room (experiment group receiving premedication and the control group receiving placebo). This selection was done by casual transposition and the programs on <http://www.randomization.com/> website. The first anesthesiologist who was unaware of the rest of the trial performed this randomization. A 2sheet paper form was allocated for collecting data. The first sheet included the information of patient such as name, surname, age, gender, and operation date and type (emergent or elective). File number of admission was coded as form number. The second sheet was coded as the same number in the operating room and inserted to patients file by the second anesthesiologist who at the meantime conducted the anesthesia. The 2nd sheet contained the pain scoring and analgesic use tables and the code number which was fulfilled in the ward by a colleague who was unaware of patients order and evaluated the patient with a code number. Thirty minutes before the operation, case group was given one Clonidine tablet (0.2 mg) & one Diclofenac suppository (100 mg). For anesthesia induction, Atracurium 0.5 mg kg<sup>-1</sup>, Ketamine IV (1 mg kg<sup>-1</sup>), Remifentanyl 1μgkg<sup>-1</sup> and Propofol (1- 2.5 mg kg<sup>-1</sup>) were administered. Total Intra Venus Anesthesia (TIVA) was administered for maintenance of anesthesia using Propofol 50-150μg/kg/h and Remifentanyl 1μg/kg/min. The site of incision was infiltrated by the surgeon with 20 mL Bupivacaine 0.25% before starting operation. At the end of operation, the muscle relaxation was reversed by 2.5 mg Neostigmine and 1.5 mg Atropine. In the ward, the pain score of patients were measured using Visual Analogue Scale & Numerical Verbal Rating Score in 2nd, 4th, 6th, 12th, 24th

and 48th hours post-operation. For control group, no premedication was administered and instead of Clonidine, Diclofenac and Ketamine, the patients received placebo. Similarly, we administered Total Intra Venus Anesthesia and surgery site infiltration by Bupivacaine for the control patients. Scaling pain score was also the same as treatment group and all patients in both groups received analgesics (Pethidine Intra Muscular 25 mg injection immediately for post operative pain and Diclofenac suppository 100 mg after 24 hours PRN) in the ward if the pain intensity exceeded 4 VAS scores.

In the ward each patient received analgesics including Diclofenac suppository 100 mg or Pethidine Intra Muscular injection 25 mg if needed. Patients, the nurses caring for them, the colleague who recorded all the data and the surgeon were blinded so the conduct of anesthesia and to minimize any possible bias, analgesia was controlled based on a protocol.

### Statistical methods

The obtained data were analyzed by the statistical program SPSS 16 (SPSS Inc., Chicago, IL, USA). Quantitative data were explained as median and standard deviation. Qualitative data also were presented by frequencies. For comparison of quantitative and qualitative data (with normal distribution) Chi-squared test and t-test were used. Significant level for *P* value was estimated to be less than 0.05.

### Results

The mean age of the patients was 58.98 ±16.39 years with the range of 19 to 85 years. In treatment group (23 females, 7 males), the mean age was 58.55 ±16.27 years old. In control group (25 females, 5 males), the mean age was 50.4 ±16.77 years old. Chi-squared test showed there was no significant difference in sex distribution in both groups. ( $P=0.748$ ,  $df=1$ ,  $\chi^2=0.418$ ). T-test revealed that there was no significant difference between mean ages of 2 groups. [ $P=0.845$ ,  $f(0,197)=57$ ].

Among 60 patients, 6 (10%) were operated emergently while the rest (90%) were operated electively. 3 of the emergently operated patients were female (50%) and 3 were male (50%). 45 of the elective patients were female (83.33%) and 9 were male (16.66%). Chi-squared test revealed no significant relation of sex distribution in electively or emergently operated patients. ( $P=0.088$ ,  $df=1$ ,  $\chi^2=3.750$ ). In all 60 patients, the most severe pain was experienced within 6th and 12th hour post-operation. Table 1 demonstrates the difference in pain expressing in 2 groups of patients. The mean overall score of pain in treatment and control groups was 3.6± 0.88 and 5.07 ±0.92 respectively.

Analysis performed by t-test showed significant difference both groups and the treatment group expressed less pain than the control group ( $P<0.005$ ). The need for Pethidine increased until the 12th hour (highest score was in 6th and 12th hours) then decreased by 24th and 48th hour.

Comparison of the mean pain score in patients of

intervention and control group by t-test revealed that there was a significant difference between the pain score of these 2 groups. Consequently, the patients in treatment group having received premedication of quadruplet drugs (Ketamine, Clonidine, Diclofenac and Bupivacaine infiltration) complained from less pain than the control group. Analysis performed by chi-squared test shows that among all post operation hours, the pain score of the treatment group was more significantly less than the control group in 6th and 12th hours after operation. Therefore, the required dosage of Pethidine in these 2 hours (6 and 12) was significantly less in treatment group than the control group. In conclusion, our study demonstrated that quadruple therapy with Diclofenac suppository 100 mg, Clonidine 0.2 mg per oral before operation, Ketamine 1 mg/kg IV during induction, and a local anesthetic field block with Bupivacaine 0/25% 20 mL, administered before open Cholecystectomy is associated with reduced pain scores and Pethidine use in the first 6th and 12th hours after surgery. The usage of postoperative NSAID (Diclofenac) however was not significantly influenced. Need for Pethidine in different hours post operation is shown in Table 2. Need for Diclofenac in different hours post operation is shown in Table 3. No complication or adverse reactions to the administered medications were observed.

## Discussion

The results of the present study show that quadruple therapy with diclofenac 100 mg Trans-rectal, Clonidine 0.2 mg oral, Ketamine 1 mg/kg Intravenous for induction, and a local anesthetic wound infiltration with bupivacaine administered before open cholecystectomy reduces pain scores and analgesic use in the first 6th and 12th h after surgery. Postoperative pain is proven to be reduced by each of the four afore-mentioned treatment modalities through different mechanisms.<sup>5-12</sup> Therefore, we hypothesized that combining all four modality would be associated with the maximum benefit through different mechanisms for preemptive analgesia.

The advantages of local anesthetic field block prior to hernia surgery have previously been studied in two different studies by Beaussier *et al.*, and also by Lowenstein *et al.* for abdominal hysterectomy. Local infiltration of anesthetics blocks C-fiber input to the dorsal horn of the spine which in turn inhibits central sensitization via blocking nociceptive impulses from reaching the CNS and suppressing the sustained state of hyper excitability responsible for intense postoperative pain. This, seemingly inadequate for pain control, is preferred by most surgeons.<sup>5,6</sup>

Preemptive administration of Levobupivacaine in Gurbet *et al.* research showed that administration of Levobupivacaine in the early postoperative period is significantly associated with less pain experience compared with patients who received no local anesthetics.<sup>7</sup> Persec *et al.* showed that post incisional treatment with

**Table 1.** The difference in pain expressing (by NVRS and VAS) during post operation hours in ward, compared by P value

Hours post operation	2	4	6	12	24	48
Pain score of treatment group	3.66	3.46	3.86	3.93	3.73	2.65
Pain score of control group	4.53	5	6.1	6.27	5.1	3.79
P value	0.003	<0.005	<0.005	<0.005	0.001	0.003

**Table 2.** Amount of used Pethidine (25 mg IM) in different hours post operation gathered in patients

Hours post operation	2	4	6	12	24	48
Pethidine (25 mg IM) used in experimental group	1	1	7	10	6	1
Pethidine (25 mg IM) used in control group	1	5	15	18	5	1
P value	<0.754	<0.097	<0.03	<0.035	<0.50	<0.754

**Table 3.** Amount of used Diclofenac (100 mg Supp) in different hours post operation gathered in patients of 2 groups

Hours post operation	2	4	6	12	24	48
Diclofenac (100 mg Supp) used in experimental group	1	1	7	5	10	1
Diclofenac (100 mg Supp) used in control group	1	3	10	9	12	1
P value	<0.754	<0.306	<0.284	<0.180	<0.395	<0.754

$\alpha$ 2-adrenoreceptor agonist Clonidine is associated with reduced analgesic requirements.<sup>8</sup> Flacke and colleagues proposed that narcotic requirement reduced following the usage of Clonidine in patients undergoing coronary surgery which was in line with the findings of Mikawa *et al.* study carried out on children by oral premedication with Clonidine.<sup>9,10</sup> Based on the results obtained from above mentioned studies we added Clonidine to our regimen as one of the elements of our premedication.

In two similar studies, the role of single dose Diclofenac suppository in reduction of post cesarean section pain was emphasized<sup>11</sup> in which patients used a single Diclofenac suppository preoperatively; however the need for Diclofenac was not significantly different postoperatively which could have been due to Pethidine usage difference. In a study similar to ours, without the usage of clonidine, Pavlin *et al.* introduced a tri-modal premedication consisting of Rofecoxib, preincisional Ketamine, and local anesthetic infiltration (Lidocaine and Bupivacaine) with longer follow up period of a week that ultimately resulted in reduced pain scores and analgesic requirement just in the first 24 hours after surgery, with no significant effect on later hours.<sup>3,12</sup> Patients in our study however were followed up until 48 hours post operation. And pain significantly reduced as previously described.

## Conclusion

Administration of multimodal preincisional premedication consisting of Clonidine, Diclofenac, Ketamine and bupivacaine infiltration to the site of incision, could lead to

bupivacaine infiltration to the site of incision, could lead to a significant decrease in pain score and opioid requirement after cholecystectomy in comparison to bupivacaine infiltration to the site of incision.

*Conflict of interests:* The authors declare no conflicts of interest.

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