

# Diabetic Patients Develop Greater Intensity of Postoperative Pain than Non-Diabetics after Open Cholecystectomy: A Pilot Study

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## Abstract

**Background:** Pre-clinical and clinical studies have shown that inflammatory pain intensity is increased under diabetes condition. Open cholecystectomy (OC) is a surgical procedure with predictable postoperative pain. However, the comparison of postoperative pain due to open cholecystectomy in diabetic and non-diabetic patients remains unknown. The research question to answer was whether diabetic patients undergoing OC development greater intensity of postoperative pain than non-diabetic patients. **Methods:** The study was conducted between June 2016 and February 2018 at the Regional Hospital of High Specialty “Dr. Juan Graham Casasús” of Villahermosa, Tabasco, Mexico. Seventy patients in two groups of 35 patients each scheduled for OC under general anesthesia were studied. Pain was assessed using the 11-point numerical rating scale (NRS). The primary endpoint was to know NRS pain scores after awaking of general anesthesia. Secondary outcomes included the time of onset of pain and comparing NRS scores between diabetic and non-diabetic patients undergoing OC. **Results:** Diabetic patients reported significantly greater intensity pain than non-diabetic patients. The mean overall pain score in the diabetic and non-diabetic patients was  $7.2 \pm 0.3$  and  $5.3 \pm 0.3$  ( $P = 0.0002$ ), respectively. Furthermore, 60% of diabetic patients had severe pain ( $NRS \geq 8$ ) compared to 20% of non-diabetics ( $P = 0.006$ ). The time to onset postoperative pain was about 35 minutes in both groups ( $P = 0.876$ ). **Conclusions:** Diabetic patients undergoing OC have greater intensity postoperative pain and also more frequency of patients with severe pain

scores compared with non-diabetic patients. Therefore, analgesic treatment in those patients should consider this point in order to provide a satisfactory postoperative analgesia.

## Keywords

Postoperative Pain, Inflammatory Pain, Cholecystectomy, Diabetes, Observational Study

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## 1. Introduction

Diabetes is a chronic disease characterized mainly by hyperglycemia and there is experimental evidence that diabetes or hyperglycemia induces peripheral and central sensitization, which translates into greater sensitivity to a painful stimulus (hyperalgesia and allodynia) [1] [2] [3]. Putatively, this sensitization involves both the inflammatory and the neuropathic mechanisms [1] [4] [5]. Also, the analgesic efficacy and potency of different groups of analgesic drugs decrease in diabetic animals [5] [6] [7], and in diabetic patients [8], independently of the route of administration. Likewise, several reports show that diabetic patients report more intensity of postoperative pain after lumbar spine surgery or total abdominal hysterectomy than non-diabetic patients [8] [9]. Overall, the intensity of inflammatory pain or postoperative pain is greater both in experimental models of hyperglycemia or diabetes and in diabetic patients compared to non-diabetics. On the other hand, cholecystectomy is the surgical procedure for treatment symptomatic gallstones, also known as cholelithiasis. To date, laparoscopy cholecystectomy (LC) is the approach of choice for acute cholecystitis and has replaced open cholecystectomy (OC) [10], because LC reduces postoperative morbidity and hospital stay. However, OC is the current treatment of care for others [11]-[16] and OC has been associated with severe postoperative pain [17] [18]. However, the intensity of pain due to cholecystectomy in diabetic patients to date remains unknown. The research question to answer was whether diabetic patients undergoing OC development higher intensity postoperative pain than non-diabetic patients.

## 2. Material and Methods

This was a prospective, cross-sectional, observational study conducted from June 2016 to February 2018 (ACTRN12618000643279) and was led in accordance with the declaration of Helsinki. Seventy diabetic patients (5 males and 65 females), aged 18 - 65 years undergoing elective open cholecystectomy under general anesthesia were enrolled. The study was conducted at the Regional Hospital of High Specialty “Dr. Juan Graham Casasús” of Villahermosa, Tabasco, Mexico. All patients underwent a preoperative assessment before surgery. Inclusion criteria for this study were age > 18 yr, weight > 40 kg, and American Society of Anesthesiology physical status (ASA) I, II or III. Exclusion criteria were defined

as allergy to non-steroidal anti-inflammatory drugs, history of peptic ulcer disease, hemorrhagic diathesis, coronary heart disease, bronchial asthma, seizure disorders, pregnancy or any other contraindications.

Data from variables such as age, height, weight, BMI, glucose concentration, duration of surgery, time to onset postoperative pain were obtained from nursing records and the study data sheet. These data were collected by a researcher blinded to the study.

All patients received general anesthesia with standard monitoring. In brief, anesthesia was induced with propofol 2 - 3 mg/kg and fentanyl 5 µg/kg. Tracheal intubation was facilitated by vecuronium 0.1 mg/kg. Anesthesia was maintained with sevoflurane 1.5% and fentanyl 5 µg/kg. Patients also received diclofenac 75 mg i.v. once before the surgical incision. At the end of surgery, neuromuscular blockade was reversed with neostigmine 0.03 mg/kg and atropine 0.1 mg/kg. A continuous infusion of 0.9% saline was given at the rate of 5 - 8 ml/kg during surgery.

Hemodynamic variables were collected by chart review defined as hypotension (MAP < 60 mmHg), hypertension (MAP > 100 mmHg), bradycardia (heart rate < 40 beats/min) and tachycardia (heart rate > 90 beats/min) as well as blood glucose concentration. After completion of the surgical procedure (final suture) and emergence from anesthesia, patients were transferred to the recovery room. Duration of surgery was taken from the time of skin incision to completion of skin suturing. Onset of postoperative pain was defined as the time from end of anesthesia until presence of any postoperative pain score. Postoperative pain intensity was assessed by using a 0 - 10 numerical rating scale (NRS) (0 = no pain and 10 = worst pain imaginable) and were categorized in “no or mild pain” with NRS ≤ 3 and NRS > 3 corresponding to “moderate to severe” pain [19]. Postoperative pain management was carried out immediately after assessment according to institutional standards. Briefly, analgesic drugs that are routinely used for this type of surgery (diclofenac, 75 mg i.v.) or ketorolac (30 mg i.v.) were randomly administered.

### 3. Statistical Analysis

Data for continuous variables (age, height, weight, BMI, glucose concentration, duration of surgery, time to onset postoperative pain and NRS values) were analyzed using the Student *t* test for independent samples, as appropriate to determine between-group differences. About categorical data (sex, ASA, pain intensity), differences between two groups were analyzed using Chi-square test or Fisher exact test as required. All data are presented as means ± S.E.M. and categorical data are presented as number and frequencies (percentages). *P*-value < 0.05 was considered statistically significant. Data were recorded in and analyzed using GraphPad Prism 9.1.0 Software (San Diego, California, USA).

### 4. Results

Seventy patients who underwent open cholecystectomy were studied in two

groups of 35 patients each (**Table 1**). The two groups were comparable regarding sex, height, weight, BMI, but not ASA status (**Table 1**). Diabetic patients were significantly older than non-diabetic patients (**Table 1**). The mean duration of surgery in diabetic group was 81.7 minutes and in the non-diabetic group was 70.8 minutes, without difference between two groups (**Table 1**). Onset of postoperative pain was similar in both groups with about 35 minutes (**Table 2**).

Diabetic patients undergoing open cholecystectomy reported significantly higher pain intensity than non-diabetic patients. Regarding pain intensity, the results of this research show a lower frequency of diabetic patients with moderate pain. In contrast, diabetes patients (about 60%) reported severe pain compared to non-diabetics (about 20%) with severe pain (**Table 2**). Statistical analysis revealed difference between groups (**Table 2**). The intensity of postoperative pain measured with the NRS is shown in **Figure 1**. The mean overall pain score in the diabetic and non-diabetic patients was  $7.1 \pm 0.3$  (severe) and  $5.6 \pm 0.3$  (moderate), respectively (**Figure 1**).

## 5. Discussion

The present study was designed with the primary aim of examining acute

**Table 1.** Patient characteristics and physical status.

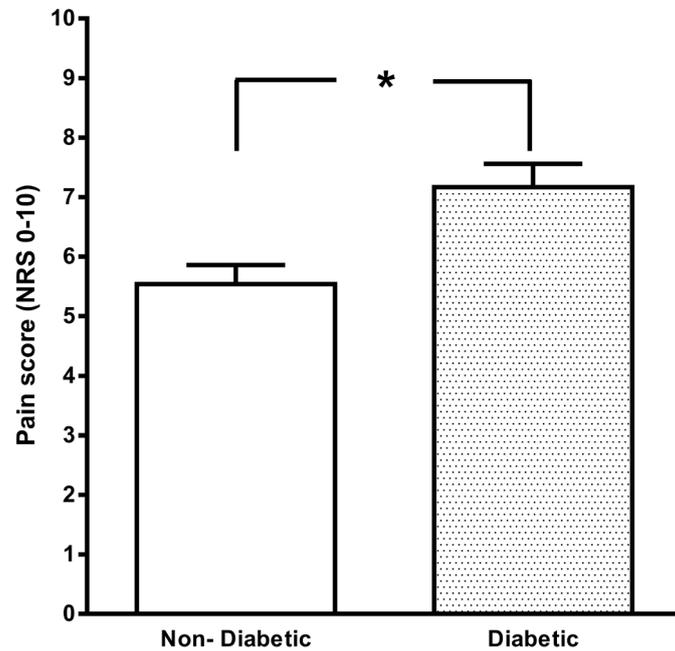
	Diabetic patients (n = 35)	Non-diabetic patients (n = 35)	P
Sex (Male/Female)	3/32	2/33	0.643
Age (yr)	65.6 $\pm$ 2.6	35.6 $\pm$ 2.3	0.001
BMI	29.2 $\pm$ 0.7	29.0 $\pm$ 0.8	0.876
ASA (I/II/III)	0/29/6	21/13/1	0.001
Heart rate (beats/min)	80.5 $\pm$ 1.9	76.1 $\pm$ 2.1	0.123
MAP (mmHg)	95.3 $\pm$ 1.7	93.3 $\pm$ 1.7	0.424
Glucose (mg/dL)	165.4 $\pm$ 10.6	95.0 $\pm$ 2.3	0.001
Duration of surgery (min)	81.7 $\pm$ 4.2	70.8 $\pm$ 6.3	0.158

BMI; Body Mass Index. MAP; Mean Arterial Pressure. Values are expressed as mean  $\pm$  standard error.

**Table 2.** Onset and postoperative pain intensity in diabetic and non-diabetic patients undergoing open cholecystectomy.

	Diabetic patients n = 35	Non-diabetic patients n = 35	P
Onset of postoperative pain (min)	34.4 $\pm$ 5.2*	35.4 $\pm$ 3.3*	0.876
Postoperative pain intensity (NRS)	n (%)	n (%)	
Mild (1 - 3)	3 (8.6)	5 (14.3)	
Moderate (4 - 7)	12 (34.3)	23 (65.7)	0.006
Severe (8 - 10)	20 (57.1)	7 (20.0)	

\*Values are expressed as mean  $\pm$  standard error.



**Figure 1.** Comparison of pain scores between non-diabetic and diabetic patients undergoing open cholecystectomy. Data are the mean  $\pm$  S.E.M. for 35 patients in each group. \*Differences between the groups were determined using Student t-test,  $p < 0.05$ .

postoperative pain intensity of diabetic patients after OC. Importantly, the findings of this study indicate that diabetic patients undergoing OC report having higher intensity postoperative pain compared to non-diabetic patients. The results of this research observed in non-diabetic patients agree with those described by other investigations that evaluated postoperative pain after open cholecystectomy. In this sense, demographic data and duration of surgery (about 80 min) and pain intensity was moderate to severe upon arrival to the recovery room or time zero [11] [12] [13] [20] [21] or 0.5 - 1 h later [14] [15]. About onset time of pain was about 35 minutes, this data was similar to about 40 minutes previously reported by others, for patients undergoing open cholecystectomy [16]. Interesting, in the present study, the onset of pain in diabetic and non-diabetic patients was similar, it could suggest that the development of postoperative pain, does not depend on the diabetic condition.

On the other hand, pain severity and the proportion of patients with mild, moderate or severe pain, it was diabetic patients who had the highest proportion with scores corresponding to severe pain. Patients with diabetes were older than non-diabetic patients (65 years *vs* 35 years), so it cannot be ruled out that they had peripheral neuropathy which is common in people with diabetes [22]. and that this could be associated with worsening postoperative pain. Additional to latter, data such as age may have an effect on intensity of postsurgical pain [17]. Our results are in line with those of Karci and co-workers 2004 [8], in which diabetic patients undergoing abdominal hysterectomy reported higher pain scores and also more patients required rescue analgesic than non-diabetic patients. Similarly, diabetic patients with knee osteoarthritis compared with non-diabetics

have higher pain intensity [23]. Also, the pain threshold measured in the oral mucosa, the tips of the fingers and toes was lower in diabetic than non-diabetic patients [24]. Furthermore, diabetic patients with glycosylated hemoglobin (HbA1c) greater than 6.5% have more incidence of inadequate analgesia in the early postoperative period [25] or higher analgesic requirements in the intra-operative period [26], suggesting that those patients have higher pain scores than non-diabetic patients with HbA1c less than 6.5%. Taken together, it can be assumed that for diabetic patients, pain reduction may decrease with uncontrolled diabetes determined by high HbA1c values [27].

It is known that non-diabetic patients with open cholecystectomy show moderate to severe postoperative pain [28] [29]. In this sense, Polanco-García *et al.*, (2017) have shown that mean score pain after general surgery was about to 6 NRS (severe pain) and percentage of patients was about 40% [30]. Although, non-diabetic and diabetic patients reported moderate to severe postoperative pain, the incidence of severe postoperative pain was higher diabetic patients. The results of present study and other clinical studies [23] suggest that diabetes increases surgery-induced painful hypersensitivity, similarly, as described in several preclinical studies [1] [3]. Postoperative pain is associated with tissue injury due to the surgical procedure. Tissue damage typically produces persistent pain and hyperalgesia. Mounting evidence indicates that persistent pain and hyperalgesia result from peripheral and central sensitization. All these mechanisms contribute to the post-injury pain hypersensitivity state. Experimental models of tissue injury have shown that diabetic animals develop more hyperalgesia as compared with non-diabetic animals [1] [2] [4] [5]. The mechanisms that lead to this hypersensitivity in diabetic animals are not total clear. However, it has been proposed that peripheral and central mechanisms participate in this process. There is evidence for the participation of spinal cyclooxygenase 2 (COX-2), cholecystokinin (CCK) receptors and  $K^+$ - $Cl^-$  co-transporter 2 (KCC2), among others, in hypersensitivity-induced diabetes [1] [2] [31] [32]. There is consensus that a better understanding of acute pain after surgery is needed, and that there are risk factors that contribute to the severity of postoperative pain, including the patient's preexisting pain [33] such painful diabetic neuropathies. The results of the present study suggest that diabetic patients show a pain hypersensitivity, which can further increase surgical procedure-induced pain. Thus, diabetic patients should be considered as a special population regarding postoperative pain. Analgesic treatment in those patients should consider this point in order to provide a satisfactory postoperative analgesia.

Our study has the following limitations. First, included lack of randomized allocation of patients to the two groups. Second, pain assessment was limited to the evaluation of onset pain after arriving to recovery room only, so the time course of pain was not evaluated. Third, because of the observational nature of the study, no particular postoperative analgesic treatment was proposed, were administered analgesic drugs that are routinely used for this type of surgery

(diclofenac or ketorolac). Therefore, rescue analgesia was not evaluated.

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## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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