

EFFICACY AND SAFETY OF ACETAMINOPHEN COMPARED TO TRAMADOL AFTER LAPAROSCOPIC CHOLECYSTECTOMY

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ABSTRACT

Objective: This study was aimed to investigate the efficacy and safety of intravenous acetaminophen as post-operative analgesic agent for patients underwent laparoscopic cholecystectomy.

Methods: A prospective randomized clinical trial was carried out on 27 adults undergoing elective laparoscopic cholecystectomy were randomly assigned to two groups in this study (13 patients) to receive intravenously 1000 mg acetaminophen and (14 patients) to receive intramuscularly tramadol 100 mg postoperatively; visual analog scale (VAS) was utilized to assess pain severity and efficacy of analgesic agents. Pain scores were assessed at 0, 2, 4, 6, 8, 10 and 12 hrs after surgery the incidence of adverse effects was also assessed.

Results: Over the period of 12 hrs, VAS scores were significantly lower in each group at each time interval compared to zero time; there is a nonsignificant difference in pain score between the different groups; the incidence of adverse effects like nausea and vomiting was significant in tramadol group compared to acetaminophen group.

Conclusion: Post-operative intravenous acetaminophen infusion of 1000 mg is useful for reducing pain scores after elective laparoscopic cholecystectomy and it is effective and safe analgesic with less adverse effects compared to tramadol.

Keywords: Laparoscopic cholecystectomy, Acetaminophen, Tramadol, Post-operative analgesia.

INTRODUCTION

Cholecystitis is a very common pathological condition encountered by population; acute cholecystitis is almost always associated with obstruction of the gallbladder neck or cystic duct by a gallstone. Occasionally, obstruction may be by mucus, parasitic worms or a tumor, or may follow endoscopic bile duct stenting. The pathogenesis is unclear but the initial inflammation is possibly chemically induced. The cardinal feature is pain in the right upper quadrant but also in the epigastrium and the right shoulder tip, and this pain is severe and prolonged with fever and leukocytosis. The management includes bed rest, pain relief, antibiotics and intravenous fluids, but the surgery (cholecystectomy) is usually needed when the complications develop [1,2].

In the view of cholecystectomy, Calot's triangle is an important surgical landmark and should be identified by surgeons performing a cholecystectomy to avoid damage to the extrahepatic biliary system. The anesthetized patient is positioned on the opening table and a pneumoperitoneum is created. Four ports are placed in the abdomen usually at the umbilicus and the epigastrium, with two 5 mm ports laterally. The cystic duct is carefully defined, as is the cystic artery, which is divided. Once the triangle of Calot is laid widely open, the cystic duct is clipped and divided. The gall bladder then removed from the gallbladder bed and once free removed via the umbilicus [3].

Since first reported in 1987, laparoscopic cholecystectomy has become a popular technique worldwide because of its several advantages over conventional cholecystectomy. These advantages include less pain, more rapid convalescence, earlier discharge, and more expeditious return to normal activities [4,5], but still experience moderate to severe pain in the abdomen or shoulder region, therefore, post-operative pain management is indicated especially by opioids. Tramadol is a centrally acting opioid which is effective for moderate to severe pain and is being used for various acute and chronic pain conditions [6]. Tramadol, an

analgesic with a mean potency one-tenth that of morphine. Tramadol relieve pain by the weak agonistic action on μ opioid receptor leading to the depression of central nervous system pain transmitters. In addition, tramadol inhibits the reuptake of norepinephrine and serotonin in the brain. It has half-life of about 6-8 hrs. Like other opioids, tramadol is associated with unpleasant side effects including nausea, vomiting, dizziness, sedation, pruritus, and urinary retention. Its respiratory depression is less than that of morphine [7].

Acetaminophen is a non-opioid analgesic with antipyretic and weak or absent anti-inflammatory properties.

Intravenous acetaminophen has both rapid and effective analgesic properties and is considered to be safe at therapeutic doses and well tolerated because, unlike other non-steroidal anti-inflammatory drug, it does not affect bleeding time and does not damage the gastrointestinal mucosa [8].

The exact mechanism by which acetaminophen produces analgesia has yet to be fully elucidated. Suggested mechanisms include inhibition of the synthesis of cyclooxygenases (COX) which are involved in prostaglandin production [9]. Biochemical tests showed, it to be only a weak COX inhibitor with some selectivity for brain COX. It remains contentious whether paracetamol relieves pain centrally by inhibiting COX-3 or by inhibiting COX-2 at low rates of enzyme activity [10]. It also may act on serotonin pathways that regulate spinal nociception. Following surgery, patients release inflammatory mediators such as histamine, leukotrienes, cytokines, and prostaglandins. Afferent neurons release glutamate, substance P, neurokinins, and other peptides. Intravenous acetaminophen may inhibit the formation of these inflammatory markers and block pain pathways to achieve an analgesic effect and reduce pain in patients postoperatively [11]. The aim of this study was to investigate the efficacy and safety of acetaminophen as analgesic drug after laparoscopic cholecystectomy compared to tramadol.

METHODS

After obtaining the formal approval from Scientific and Ethical Committee in Al-Kindy College of Medicine, this randomized prospective clinical trial was carried out on 27 patients of both sexes with ages range (39.6±11.6) who have undergone elective laparoscopic cholecystectomy at the general surgery wards in Al-Kindy College of Medicine, Baghdad, for the time period between February and April 2016. Written informed consent was taken from all the participants, the patients had been divided into two groups, the first group consists of 14 patients who administered intramuscular tramadol (100 mg/2 ml) (obtained from Doltap), and the second group consists of 13 patients are administered intravenous acetaminophen infusion (1000 mg/100 ml) (obtained from Kalpain) as post-operative analgesia.

Visual analog scale (VAS) is used to evaluate pain score after each 2 hrs intervals starting from zero time which is the time of drug injection, 2, 4, 6, 8, 10 and 12 hrs postoperatively to assess the efficacy of analgesic agent.

The incidence of adverse effects is assessed including post-operative nausea, vomiting, dizziness, urine retention, headache, hypotension, and hypertension.

RESULTS

All enrolled patients completed the study, and data from all 27 patients were included in the analysis. There were no significant differences between groups concerning gender, age, weight and height.

Pain score for patients receiving acetaminophen after 2 hrs postoperatively was reduced significantly ($p \leq 0.00$) by 25%, while for patients administered tramadol at the same time period, the VAS changed significantly ($p \leq 0.00$) by 22%.

Analgesic treatment with acetaminophen was continued changing the VAS as following: From 2 to 4 hrs (23%), 4 to 6 (14%), 6 to 8 (14%), 8 to 10 (23%), 10 to 12 (3%) resulting in significant pain reduction ($p \leq 0.00$) by 58% at 12 hrs, while treatment with tramadol during the same period changing the VAS as following: From 2 to 4 hrs (15%), 4 to 6 (22%), 6 to 8 (17%), 8 to 10 (21%), 10 to 12 (3%) resulting in significant pain reduction ($p \leq 0.00$) by 59% at 12 hrs (Table 1).

The incidence of post-operative adverse effects during the use of tramadol revealed that all patients administrated this drug experienced nausea except 2 patients, while 9 patients developed vomiting, despite that most patients in this group were administrated the antiemetic metoclopramide concomitantly. In comparison, only 3 patients in acetaminophen group developed nausea and only two developed vomiting. Table 2 showed the incidence frequency of nausea and vomiting according to corresponding time periods.

Besides that, most patients in both groups developed mild to moderate dizziness, also, 3 patients developed fever in tramadol group, while 2 patients develop fever in acetaminophen group.

We noted that there is no incidence of pruritus, urinary retention, and respiratory depression occurs in studied groups.

DISCUSSIONS

Although laparoscopic surgery produces substantially less severe discomfort than the corresponding open procedure, pain associated with laparoscopy can still be considerable. Pain in the early period after laparoscopic cholecystectomy arises from several mechanisms including abdominal wall trauma, intra-abdominal trauma, abdominal or peritoneal distension, and pneumoperitoneum using carbon dioxide. Opioids remain the agents of choice for severe pain; however, this class of analgesics is associated with dose-dependent adverse effects and negative post-operative outcomes [12].

Table 1: Visual analog scale (VAS) of the post-operative treatment with acetaminophen compared to tramadol

Time (hrs)	Acetaminophen, n=13		Tramadol, n=14		p value
	Mean±SD	p value	Mean±SD	p value	
0	6.46±0.77		7.14±1.02		0.032
2	4.84±0.69 ^a	0	5.57±1.22 ^a	0	0.483
4	3.69±0.75 ^b	0.001	4.71±0.91 ^b	0	0.413
6	3.15±0.37 ^c	0.012	3.64±0.93 ^c	0	0.280
8	2.69±0.63 ^d	0.027	3±0.87 ^d	0	0.878
10	2.07±0.27 ^e	0.005	2.35±0.63 ^e	0.002	0.561
12	2±0.00 ^e	0.337	2.28±0.61 ^e	0.0583	0.633

Results represented mean±SD; different subscripts represent significant changes among the same group for corresponding period; *Significant change between different groups. SD: Standard deviation

Table 2: Incidence of adverse effects in patients treated with post-operative tramadol or acetaminophen

Time	Acetaminophen, n=13		Tramadol, n=14	
	Nausea %	Vomiting %	Nausea %	Vomiting %
0	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
2	0 (0.0)	0 (0.0)	6 (42.84)	3 (21.42)
4	1 (7.7)	0 (0.0)	5 (35.7)	0 (0.0)
6	3 (23.1)	0 (0.0)	9 (64.26)	4 (28.56)
8	3 (23.1)	2 (15.4)	7 (49.98)	3 (21.42)
10	0 (0.0)	0 (0.0)	2 (14.28)	2 (14.28)
12	0 (0.0)	0 (0.0)	1 (7.14)	1 (7.14)

Results represent percentage of total

Acetaminophen has a well-established safety and analgesic profile. It has few contraindications and lacks significant drug interactions [13].

However, clinical trials and studies about acetaminophen as post-operative analgesic are rare and only few of them carried out in the last few years; in addition, acetaminophen is about 70% more expensive and less available in Iraqi hospitals than tramadol. These factors attenuate the tendency toward using acetaminophen as post-operative analgesic. Despite the limited number of patients in this study, results showed that patients administered 1 g acetaminophen infusion postoperatively developed only a few adverse effects specially nausea and vomiting which represents important issue in patient underwent laparoscopic cholecystectomy because such adverse effects might impact negatively on the post-operative condition, on the contrary, most patients in tramadol group developed nausea and vomiting. Concerning analgesic efficacy, both acetaminophen and tramadol have nearly the same impact in post-operative pain relief [14]. Many clinical trials conducted in patients with moderate to severe pain after different types of surgery confirmed the analgesic effect of acetaminophen [2]. Paul *et al.* performed a randomized, prospective study on 68 patients which compare the analgesic effect of intravenous 1 g of acetaminophen with that of 75 mg of c after laparoscopic cholecystectomy. These medications were given 30 minutes before the end of surgery as the first dose and subsequent doses at 8 hourly interval after shifting the patients to the ward. The result revealed that administration of intravenous acetaminophen in the intraoperative period 30 minutes before the surgery followed by administration of 1 g acetaminophen every 8 hourly in post-operative periods gives better quality of analgesia with low pain score, as well as no immediate side effect was observed in patient using acetaminophen [15].

Furthermore, Arslan *et al.*, supported the analgesic effect of acetaminophen. They suggested that preemptive intravenous acetaminophen provides effective and reliable pain control after cholecystectomy surgery and reduced post-operative pain scores, the need for and use of supplementary opioids and the time to first request of analgesic [16].

Alimian *et al.* performed a randomized clinical study which compares analgesic effect of intravenous acetaminophen and morphine infusion after elective laparotomy. They found that acetaminophen is efficient enough for pain management as morphine after 8 hrs following surgery [17].

Another clinical trial that found usefulness and safety of acetaminophen infusion of 1 g after laparoscopic sleeve gastrectomy that is performed by Sloo. It compares post-operative analgesic action and side effect profile of acetaminophen and tramadol. This study noted that both agents are nearly effective postoperatively, but acetaminophen has no incidence of adverse effect comparing with tramadol [18].

Similar clinical studies that used intravenous acetaminophen infusion as non-opioids analgesic after orthopedic [19] and gynecology [20], as well as study about analgesic efficacy of acetaminophen after breast surgery [21], all these clinical trials support the usefulness and safety of acetaminophen as postsurgical analgesic.

CONCLUSIONS

The results of this study clearly demonstrate the efficacy of acetaminophen as post-operative analgesic agent after laparoscopic cholecystectomy compared to tramadol, beside better safety profile which made it superior to the classical and standard narcotic agent tramadol.

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