

Pre emptive analgesia for reducing pain after cholecystectomy: Oral tramadol vs. acetaminophen codeine

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Abstract

Background: Considering that protocols of postoperative pain management would be planned regarding the facilities of each center or region and the importance of its proper management to reduce its related complication and improve patient's satisfaction, in this study we compared the effect of orally administrated tramadol and acetaminophen-codeine in this regard.

Materials and Methods: In this prospective randomized double-blind clinical trial, 136 (68 in tramadol and 68 in acetaminophen codeine groups) ASA I and II patients scheduled for open cholecystectomy under general anaesthesia were enrolled. They randomly allocated to receive oral tramadol (50 mg capsule) or acetaminophen-codeine (325/10 mg) 1 hour before surgery. After surgery they evaluated for postoperative pain using VAS score, analgesic consumption and vomiting.

Results: Mean of postoperative pain score during 24 hours after surgery was 2.1 ± 1.0 and 3.8 ± 2.0 in tramadol and acetaminophen-codeine groups, respectively ($P < 0.05$). Mean of analgesic consumption (morphine) during 24 hours after surgery was 6.2 ± 4.4 mg and 12.9 ± 5.7 mg in tramadol and acetaminophen-codeine groups, respectively ($P < 0.05$). Mean of vomiting during 24 hours after surgery was 1.2 ± 0.9 and 0.4 ± 0.5 in tramadol and acetaminophen-codeine groups, respectively ($P < 0.05$).

Conclusion: The findings of current study indicated that in lower dose of tramadol (50 mg) and acetaminophen/codeine (325 mg/10 mg) the analgesic effect of tramadol is better and its side effects are higher than acetaminophen/codeine, which limit its use for mentioned purpose. It seems that administration of each of studied agents it depends on patients' tolerance and decision of the physician.

Key Words: Acetaminophen codeine, postoperative pain, tramadol

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Received: 21-06-2012, Accepted: 26-07-2012

INTRODUCTION

Postoperative pain management considered as one of the challenging issues in anaesthesiology and an important part of a health professional's commitment. Proper management of it result in early mobilization, increased patients satisfaction, reduced hospitalization period and costs.^[1-3] Different pharmacological approaches have been introduced for proper management of postoperative pain by considering many factors such as clinical factors, patient-related factors and

Access this article online	
Quick Response Code:	Website: www.advbiores.net
	DOI: 10.4103/2277-9175.107964

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How to cite this article: Zavareh SH, Kashefi P, Saghaei M, Emami H. Pre emptive analgesia for reducing pain after cholecystectomy: Oral tramadol vs. acetaminophen codeine. Adv Biomed Res 2013;2:12.

organising factors. The goal of postoperative pain management is to reduce pain in order to minimize the dose of analgesics with minimum side effects; cost and adequate effect.^[4] Evidences indicated that this goal would be properly achieved by using multimodal and/or preemptive analgesia.^[5] Preemptive analgesia is the administration of analgesics prior to onset of noxious stimuli.^[3]

Of those Pharmacological agents, acetaminophen is the most common used agents for relieving mild to moderate pain. The efficacy and safety of acetaminophen have established in many studies. Moreover in cases which needed stronger pain relief the combination of acetaminophen-codeine is widely recommended. Codeine is a weak opioid and likewise morphine it is derived from opium alkaloids but is less active than morphine. The additive or synergistic effect of these two agents not only avoids the large doses of a single agent but also decrease their related side effects. Several studies confirmed the efficacy of these preparations for controlling post-operative pain. Oral formulation of this combination therapy considered as parts of balanced analgesic regimens for postoperative pain management.^[6-8]

Opioids are another group of agents used widely for mentioned purposes but some side effects of them have limited their use. On the other hand synthetic opioids such as tramadol with less side effects especially respiratory depression, tolerance and dependence are another preferable candidate for this purpose. It is a synthetic opioid of aminocyclohexanol group with dual mechanism of action including inhibition of re-uptake of serotonin (5-HT) and/or noradrenaline and activating the μ opioid receptors. It has higher oral bioavailability and is highly metabolised. The efficacy of tramadol for the relief of post-operative pain is reported previous reports.^[9-11]

Recent evidences suggest that administration of oral analgesics is more favourable for postoperative pain relief. This mode of administration not only could provide appropriate pain relief but also they have some advantages such as easy administration and low cost. In addition some serious side effects of IV form of tramadol have been reported and FDA was not approved the use of tramadol in IV form.^[12-14]

Considering that protocols of postoperative pain management would be planned regarding the facilities of each centre or region and the importance of its proper management to reduce its related complication and improve patients satisfaction. Acetaminophen and tramadol are two well-known analgesics and their staff familiarity encouraged us to do this

study. In this study we compared the effect of orally administrated tramadol and acetaminophen-codeine in the management of postoperative pain in patient's undergone general anaesthesia in Isfahan.

MATERIALS AND METHODS

In this prospective randomized double-blind clinical trial, 131 ASA I and II patients aged 18-60 years, scheduled for open cholecystectomy under general anaesthesia in hospitals affiliated to Isfahan University of Medical Sciences, were enrolled.

Patients with a history of convulsions and drug history of using antidepressants, carbamazepine and sedatives were excluded from the study. In addition patients who were hemodynamically unstable or had severe bleeding during surgery were excluded.

The Medical Ethics Committee of the Isfahan University of Medical Sciences approved the study protocol, and all subjects gave their written consent.

The patients were randomly allocated in two groups to receive oral tramadol (50 mg capsule) and acetaminophen-codeine (325/10 mg) with 50 cc water 1 hour before surgery. A physician who was administrated drugs was blinded to kinds of drugs.

The anaesthetic management of the patients was performed according to the standard protocol similarly in two studied groups. The anaesthesia was induced with IV fentanyl 2 μ g/kg, atracurium 0.5 mg/kg and sodium thiopental 5 mg/kg. After orotracheal intubation, anaesthesia was maintained with nitrous oxide 60% in oxygen and isoflurane 1-1.5%. Morphine was also administered in a dose of 0.1 mg/kg IV to all patients of both groups.

Vital signs, oxygen saturation, electrocardiography (ECG), non-invasive blood pressure (NIBP), pulse oximetry (SpO_2), and end tidal carbon dioxide ($EtCO_2$) were recorded before and during surgery. $EtCO_2$ during surgery was maintained at 30-35 mmHg. Systolic and diastolic blood pressure and pulse rate measured every 5 minutes during first 15 minutes after induction of anaesthesia and every 10 minutes till the end of operation.

Residual neuromuscular blockade was antagonized using neostigmine 0.04 mg/kg and atropine 0.02 mg/kg at the end of surgery. The time between inductions of anaesthesia till orotracheal was extubated defined as operation time.

After completion of surgery, when the patient had adequate respiratory efforts and responded to verbal commands properly the trachea was extubated.

Demographic characteristics and operative details such as age, weight, and height and operation time recorded.

After surgery all patients were evaluated for postoperative pain. Severity of pain assessed using Visual Analogue Scale (VAS) at 2, 4, 8, 16 and 24 hr after surgery by another physician who was not aware about drugs. All patients trained for recording their pain severity by this scale.

Side effects of the studied drug including, vomiting, constipation, light headedness, dizziness, drowsiness, headache, seizure, fever, diarrhea, rash and itching were recorded.

Complications, notably nausea and vomiting, were recorded by interviewing the patients and by inspecting the nursing report. The use of analgesics (IV morphine) was recorded also.

Statistical analysis

Obtained data analysed using SPSS version 15 for windows software and *t*-test and Chi-square test are used for qualitative data and all quantitative data respectively. *P* value < 0.05 was considered as significant.

RESULTS

In this study 136 patients (ASAI-II) was studied and randomized in two groups (68 in tramadol and 68 in acetaminophen codeine groups). And until end of research all patients followed without any exclusion from study.

Demographic characteristics and operative details of

studied population in two studied groups are presented in Table 1.

Mean ± SD of postoperative pain according to the VAS, vomiting and analgesic consumption in two studied groups during surgery at 2, 4, 8, 16 and 24 hours, are presented in Table 2.

Mean ± SD of postoperative pain score during 24 hours after surgery was 2.1 ± 1.0 and 3.8 ± 2.0 in tramadol and acetaminophen-codeine groups, respectively (*P* < 0.05).

Mean ± SD of analgesic consumption (morphine) during 24 hours after surgery was 6.2 ± 4.4 mg and 12.9 ± 5.7 min tramadol and acetaminophen-codeine groups, respectively (*P* < 0.05).

Mean ± SD of vomiting during 24 hours after

Table 2: Mean+/-SD of VAS, analgesic use and vomiting in tramadol and acetaminophen-codeine groups

	Hours	Tramadol group	Acetaminophen-codeine group	<i>P</i> value
VAS	2	3.0±2.4	6.4±2.5	<0.05
	4	2.5±1.9	4.8±3.3	<0.05
	8	2.5±2.3	3.5±2.9	<0.05
	16	1.2±1.1	2.4±2.2	<0.05
	24	1.1±1.0	2.2±2.3	<0.05
Analgesic use(mg)	2	2.5±2.5	4.2±1.8	<0.05
	4	1.6±2.3	3.5±2.3	<0.05
	8	1.5±2.3	2.6±2.5	<0.05
	16	1.2±1.0	2.4±2.2	<0.05
	24	0.2±1.0	0.9±1.9	<0.05
Vomiting	2	0.44±0.5	0.25±0.43	<0.05
	4	0.29±0.46	0.04±0.2	<0.05
	8	0.2±0.41	0.02±0.17	<0.05
	16	0.15±0.35	0.01±0.12	<0.05
	24	0.1±0.3	0.02±0.17	<0.05

Table 1: Demographic characteristics and operative details of studied population in tramadol and acetaminophen-codeine groups

Mean±SD	Tramadol group	Acetaminophen-codeine group	<i>P</i> value
Age (yr)	37.2±9.4	39.1±8.9	>0.05
Weight (kg)	66.4±12.8	67.9±13.2	>0.05
Mean Systolic blood pressure (mm/Hg)			
-before induction	123.1±10.2	121.2±11.2	>0.05
-During surgery	111.1±10.1	110.4±10.3	>0.05
-24 hours after surgery	110.3±11.3	110.5±10.4	>0.05
Mean Diastolic blood pressure (mm/Hg)			
-During surgery	70.4±8.0	70.3±7.0	>0.05
-24 hours after surgery	70.3±8.0	70.2±9.0	>0.05
Mean Pulse rate (beats/min)			
-During surgery	69.9±9	71±13	>0.05
-24 hours after surgery	76±11	79±12	>0.05
Operation time (hours)	2.25+/-0.9	2.16±0.7	>0.05

surgery was 1.2 ± 0.9 and 0.4 ± 0.5 in tramadol and acetaminophen-codeine groups, respectively ($P < 0.05$).

DISCUSSION

In this study the effect of orally administrated acetaminophen-codeine and tramadol for relieving postoperative pain was compared in a group of patient's undergone general anaesthesia. Our findings indicated that the analgesic effect of tramadol was significantly higher than acetaminophen-codeine, but side effects of tramadol i.e. vomiting events were higher in tramadol group.

The role of both mentioned agents in the management of postoperative pain was reported in many studies.

Toms and colleagues indicated that acetaminophen-codeine combination is a useful agent for relieving moderate to severe postoperative pain in about 50% of patients compared with <20% with placebo.^[15]

According to published evidences, tramadol has an important role in acute post-operative pain management and multi-modal analgesia setting due to its non-opioid analgesic effects particularly in patients that conventional opioid and other non-opioid analgesics is contraindicated or inappropriate.^[16,17] Whereas there are reports indicated that though tramadol is effective for postoperative pain but its associated side effects specially nausea and vomiting may result in delay in the patient's home-readiness.^[18]

In current study we compare these two agents. The findings indicated that though post-operative pain and consumption of morphine was significantly lower in tramadol group than acetaminophen-codeine group but the rate of emetic complications was higher in tramadol group, which could be a limiting factor for administration of tramadol as preemptive therapy.

Pluim and colleagues in the Netherlands compared the suitability of tramadol (100 mg qds) and acetaminophen/codeine (1000/20 mg qds) suppositories for the treatment of mild to moderate post-operative pain and concluded that pain score was not different in two groups but higher incidence rate of nausea and vomiting made tramadol as less suitable agent for investigated purpose than acetaminophen/codeine.^[19]

The difference between the findings of their study with ours is due to different dosage of administrated drugs and sample size. In our study we used 50 mg tramadol and 325/10 mg acetaminophen codeine. Dose

of tramadol in their study was double whereas the dose of acetaminophen was higher than double dose and our sample size was higher.

Stubhaug *et al.* have investigated the effect of single dose of 50 mg and 100 mg oral tramadol, acetaminophen/codeine (1000 mg/60 mg) and placebo for postoperative pain management in patients with orthopaedic surgery. They showed that acetaminophen/codeine had superior effect in this regard than tramadol and adverse effects especially nausea were more common with tramadol. The difference between the findings of their study with ours is due to higher dose of acetaminophen/codeine.

We used low dose of tramadol (50 mg) in current study, so it seems that in higher doses of tramadol the side effects would be more frequent, which considered the most important barrier for using tramadol for preemptive therapy.^[20]

The findings of current study indicated that in lower dose of tramadol (50 mg) and acetaminophen/codeine (325 mg/10 mg) the analgesic effect of tramadol is better and its side effects are higher than acetaminophen/codeine, which limit its use for mentioned purpose. It seems that administration of each of studied agents it depends on patient's tolerance and decision of the physician.

It is recommended to investigate different doses of tramadol (i.e., 100 mg) and acetaminophen/codeine (i.e., 500 mg/30 mg or 1000 mg/60 mg) and the combination effect of tramadol and acetaminophen/codeine for preemptive therapy, an issue which was investigated widely in recent studies.^[21,22]

However the combination will provide higher effect with lower side effects. In addition the quality of life of the patients should be investigated for evaluating their satisfaction.

In our study we didn't evaluate sedation score and recovery time after surgery. We suggest in future study these parameters will estimate.

ACKNOWLEDGMENT

Authors would like to thanks the vice chancellor for research, all patients who accept to participate in this research and also all physician and personnel of recovery and operative room of al-Zahra and kashani hospital.

REFERENCES

1. de Beer Jde V, Winemaker MJ, Donnelly GA, Miceli PC, Reiz JL, Harsanyi Z, et al. Efficacy and safety of controlled-release

- oxycodone and standard therapies for postoperative pain after knee or hip replacement. *Can J Surg* 2005;48:277-83.
2. Recart A, Duchene D, White PF, Thomas T, Johnson DB, Cadeddu JA. Efficacy and safety of fast-track recovery strategy for patients undergoing laparoscopic nephrectomy. *J Endourol* 2005;19:1165-9.
 3. Watcha MF, Issioui T, Klein KW, White PF. Costs and effectiveness of rofecoxib, celecoxib, and acetaminophen for preventing pain after ambulatory otolaryngologic surgery. *Anesth Analg* 2003;96:987-94.
 4. Ramsay MA. Acute postoperative pain management. *Proc (Bayl Univ Med Cent)* 2000;13:244-7.
 5. Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. *Curr Opin Anaesthesiol* 2009;2:588-93.
 6. Toms L, McQuay HJ, Derry S, Moore RA. Single dose oral paracetamol (acetaminophen) for postoperative pain in adults. *Cochrane Database Syst Rev* 2008;CD004602.
 7. Toms L, Derry S, Moore RA, McQuay HJ. Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. *Cochrane Database Syst Rev* 2009;CD001547.
 8. Barden J, Edwards J, Moore A, McQuay H. Single dose oral paracetamol (acetaminophen) for postoperative pain. *Cochrane Database Syst Rev.* 2004;CD004602.
 9. Grond S, Sablotzki A. Clinical pharmacology of tramadol. *Clin Pharmacokinet* 2004;43:879-923.
 10. le Roux PJ, Coetzee JF. Tramadol today. *Curr Opin Anaesthesiol* 2000;13:457-61.
 11. But AK, Erdil F, Yucel A, Gedik E, Durmus M, Ersoy MO. The effects of single-dose tramadol on post-operative pain and morphine requirements after coronary artery bypass surgery. *Acta Anaesthesiol Scand* 2007;51:601-6.
 12. Kaye K, Theaker N. TRAMADOL; A Position Statement of the NSW Therapeutic Assessment Group Inc. Sydney: NSW TAG, September 2001:1-15.
 13. Moore RA, Derry S, McQuay HJ, Wiffen PJ. Single dose oral analgesics for acute postoperative pain in adults. *Cochrane Database Syst Rev.* 2011;CD008659.
 14. DRUGS@FDA page. U.S. Food and Drug Administration Web site. Available from: <http://www.fda.gov/Drugs/default.htm> Accessed May 1, 2011.
 15. Toms L, Derry S, Moore RA, McQuay HJ. Single dose oral paracetamol (acetaminophen) with codeine for postoperative pain in adults. *Cochrane Database Syst Rev.* 2009;CD001547.
 16. Budd K, Langford R. Tramadol revisited (Editorial). *Brit J Anaesth* 1999; 82:493-95.
 17. Nossaman VE, Ramadhyani U, Kadowitz PJ, Nossaman BD. Advances in perioperative pain management: use of medications with dual analgesic mechanisms, tramadol and tapentadol. *Anesthesiol Clin.* 2010;28:647-66.
 18. Liukkonen K, Santanen U, Pere P, Erkola O, Rautoma P, Perora; Tramadol premedication increases postoperative nausea and delays home-readiness in day-case knee arthroscopy patients. *Scandinavian Journal of Surgery* 2002; 91: 365-8.
 19. Pluim MA, Wegener JT, Ruprecht J, Vulto AG. Tramadol suppositories are less suitable for post-operative pain relief than rectal acetaminophen/codeine. *Eur J Anaesthesiol* 1999;16:473-8.
 20. Rawal N, Allvin R, Amilon A, Ohlsson T, Hallén J. Postoperative analgesia at home after ambulatory hand surgery: A controlled comparison of tramadol, metamizol, and paracetamol. *Anesth Analg* 2001;92:347-51.
 21. Jung YS, Kim DK, Kim MK, Kim HJ, Cha IH, Lee EW. Onset of analgesia and analgesic efficacy of tramadol/acetaminophen and codeine/acetaminophen/ibuprofen in acute postoperative pain: A single-center, single-dose, randomized, active-controlled, parallel-group study in a dental surgery pain model. *Clin Ther* 2004;26:1037-45.
 22. Rawal N, Macquaire V, Catalá E, Berti M, Costa R, Wietlisbach M. Tramadol/paracetamol combination tablet for postoperative pain following ambulatory hand surgery: A double-blind, double-dummy, randomized, parallel-group trial. *J Pain Res* 2011;4: 103-10.

Source of Support: Nil, **Conflict of Interest:** None declared.