

The Randomized Clinical Trial of Safety and Efficacy of Oral Tramadol in Patients Undergoing Colonoscopy

Abstract

Background and Study Aims: Colonoscopy is a wide-spreading procedure with pain as a habitual challenge for the therapeutic team. The aim of this study is to evaluate safety and efficacy of oral tramadol in patients undergoing colonoscopy. **Patients and Methods:** This randomized controlled trial was performed in 124 consecutive patients who completed total colonoscopy, which is randomly divided into two groups, receiving either 100 mg single dose oral tramadol or placebo. Pain intensity during colonoscopy is evaluated by numerical rating scale (NRS) criteria in four levels: no pain, mild, moderate, and severe pain. This study was registered in www.IRCT.ir, number: IRCT2015010820610N1. **Results:** Two groups were matched in age, sex, and colonoscopy indication. The pain intensity in patients receiving tramadol was significantly lower than that in patients receiving placebo ($P < 0.05$). Nausea, sweating, moaning, and palpitation during colonoscopy were significantly lower, and desire to do a colonoscopy without sedation was significantly higher in the tramadol group. **Conclusion:** Oral tramadol in patients undergoing colonoscopy is effective in reducing pain and symptoms.

Keywords: Clinical, colonoscopy, pain, safety, tramadol

Introduction

Diagnostic and therapeutic colonoscopy is performed for the investigation, surveillance, and treatment of colon diseases in hospitalized and outpatient settings. During colonoscopy, pain is annoying for patients and cumbersome for physicians, thus sedative and analgesic drugs are often used for convenience of patients and physicians.^[1-3] Visceral pain is mainly caused by stretching of the mesenteric attachments and less likely is the result of air distension.^[4] Colonoscopy without sedation is usually well tolerated, and there is a trend toward using lower levels of sedation and analgesia for increasing safety.^[5]

The need for more analgesia is increased due to advanced age and cardiovascular and pulmonary diseases.^[6] Gastrointestinal endoscopy is usually performed in outpatient settings without deep anesthesia and intubation. Lack of anesthesiologists and necessary equipment during colonoscopy rise the risk of sedation for resuscitation and left side position. In addition, cardiopulmonary resuscitation will be difficult, with increasing mortality.^[7,8] Therefore, any methods for analgesia must be safe and effective. The

most common method for analgesia and sedation is to use benzodiazepine and opioids, such as midazolam and pethidine, in most digestive clinics without anesthesiologists.^[9,10] Midazolam sedation prolongs, and using of flumazenil is very costly for returning its effects. Also risks of nausea, vomiting, hypoventilation, and hypoxia increase with opioids. The use of fentanyl, due to short duration of action, compared with pethidine is a more favorable method.^[11,12] The combination of propofol and fentanyl is safer with less side effects and greater patient satisfaction.^[13] Tramadol is a synthetic analog of opioid, which, compared with other opioids, has fewer incidences of respiratory, cardiac depression, and abuse potential.^[14]

After oral administration, tramadol is rapidly and almost completely absorbed, and the simultaneous intake of food does not affect the extent of absorption. Analgesic effects reach its maximum after 2–3 h and continue up to 6 h. The metabolic pathway depends on hepatic cytochrome p450, and 60% of the drug is excreted in the urine after metabolism. Tramadol is a drug that is well tolerated in usual doses. The most common known side effects of tramadol are gastrointestinal and neurological complications.^[15,16] The analgesic effect of the tramadol arises from the effect

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of μ -opioid receptor agonist and reuptake inhibition of norepinephrine and serotonin.^[16]

In some studies, tramadol has similar analgesic effects compared to morphine, but despite its widespread use, uncertainty still exists regarding the use of this medication.^[14,15]

The aim of this randomized clinical study is to evaluate the safety and efficacy of oral analgesic approach with tramadol because it is easy to administer in patients undergoing outpatient colonoscopy; due to the use of analgesia and sedative, its dose in patients undergoing colonoscopy is still under study and research.

Patients and Methods

This prospective, controlled, and randomized study was conducted in an outpatient special clinic of Kermanshah University of Medical Sciences during July 2014 and September 2015. Inclusion criteria include all patients aged between 20 and 65 years who were scheduled for colonoscopy due to any causes by a gastroenterologist. Patients having a history of drug or alcohol abuse, drug allergies, seizure, taking an antidepressant or tranquilizers, and presence of underlying diseases such as pulmonary, cardiac, and liver disease were excluded from the study. This study was approved by the Local Ethics Committee under number 23311. After obtaining informed consent by technicians, patients were randomized to receive either single dose tramadol 100 mg or placebo, 4 h prior to colonoscopy. For randomization procedure, we used a random number table. Odd number was allocated to an intervention group and even number was allocated to the placebo group. The physician and patients were blind to the drug regimen. The enrolled patients were informed about the possible side effects associated with tramadol. We prospectively assessed 124 consecutive patients for whom total colonoscopy had been done. This sample size prepared more than 95% confidence level and 90% power of test for comparison of two groups in non-abdominal symptoms (20 vs. 50%). Then abdominal pain during colonoscopy was measured by a resident based on four levels of numerical rating scale (NRS); the pain score is based on 1–10 with no pain, mild, moderate, or severe pain. Also, change in breathing and other symptoms such as chest pain, nausea, and vomiting were evaluated. Measurable impact on the safety and efficacy like physician's convenience, sounds, sweating and movements of patients, and recovery time was monitored and recorded. Statistical analysis was performed with the Kolmogorov–Smirnov test for normality of quantitative variables, and then the Mann–Whitney *U*-test or the independent sample *t*-test was used for comparison of them. Also, the χ^2 test was used to compare qualitative variables. The collected data were analyzed by SPSS software version 18, and *P*-values ≤ 0.05 were considered statistically significant. This study was registered with www.IRCT.ir, number: IRCT2015010820610N1.

Results

In this study, 129 patients referred to the Kermanshah University of Medical Sciences special clinic for colonoscopy

were enrolled with inclusion criteria, and five cases dropped out because of drug intolerance (nausea, dizziness, and agitation) and their colonoscopy was postponed for 1–3 h later. Finally, 124 patients completed the procedure, which were randomly allocated into two equal groups. There were 62 cases of colonoscopy premeditated with oral tramadol and 62 controls with placebo. There was no significant difference among age, gender, body mass index (BMI), colonoscopy indications, findings, duration, and quality of preparation between the two groups ($P > 0.05$) [Table 1]. The differences between abdominal pains, other symptoms, and the desire to do colonoscopy without sedation have been significant ($P < 0.05$) [Table 2].

Discussion

The main result of this study is that the pain severity in patients undergoing colonoscopy receiving oral tramadol was significantly lower than that in patients receiving placebo. Also nausea, sweating, moaning, and palpitations during colonoscopy were significantly lower, and the tendency for repeating colonoscopy was significantly higher in the tramadol group. Thus, oral tramadol can reduce pain and symptoms in patients undergoing colonoscopy. Oral administration of analgesics for colonoscopy can be an attractive option for gastroenterologists and patients. Other oral agents have been used for pain relief, for example, peppermint oil has been shown to be safe as pain medication and increased satisfaction of patients and colonoscopy group in pediatric colonoscopy.^[17,18] Also, Colin *et al.*^[19] introduced a novel oral colonic analgesic drug named GIC-1001 as an alternative to intravascular sedation in patients undergoing colonoscopy. He showed that this drug was safe in healthy volunteers and patients in the Phase 2a trial.

In a few randomized studies of analgesia during colonoscopy, the effect of intravenous tramadol in various doses was lower relative to remifentanyl and fentanyl, but the sedative effect was comparable.^[20–22] Grossi *et al.*^[23] revealed that intravenous infusion of 100 mg tramadol as a monotherapy versus placebo does not show significant difference between the pain scores of the two groups during colonoscopy. But Hassan and Haggag,^[24] who randomized 212 women undergoing outpatient hysteroscopy, showed lower pain scores and well-tolerated oral tramadol 50 mg 1 h before the procedure. Tramadol is more effective than acetaminophen and other non-steroidal anti-inflammatory drugs (NSAIDs) for pain relief, but is considered less effective than opioids.^[25] Oral tramadol has been shown to be safe and effective in reducing postoperative pain after cesarean section.^[26,27] Common side effects with an overall incidence of 1.6–6.1% include dizziness, drowsiness, sweating, nausea, vomiting, dry mouth, and headache, but dangerous complications such as respiratory depression and seizure might occur at doses just above the therapeutic dose.^[28,29] The smallest dose of tramadol-induced seizure was reported to be 200–300 mg.^[29] Overall side effects in the tramadol group show no significant result; therefore, oral 100 mg single dose of tramadol was safe and well-tolerated. Further research is needed to detect the roles of

Table 1: Baseline characteristics (age, gender, BMI, results, duration, and quality of colonoscopy) in the two groups

Variables	Tramadol (n=62)	Placebo (n=62)	P-values
Age (year) (mean)	44.38±11.29	46.56±10.12	0.261
Gender (F/M)	33/29	32/30	0.875
Body mass index (kg/m ²)	26.89±4.01	27.67±5.15	0.339
Duration of colonoscopy (min)	15.69±2.49	16.5±2.62	0.08
Good quality of preparation	47 (75.8%)	42 (67.7%)	0.425
The indication for colonoscopy			
Bleeding	31 (50%)	30 (48.3)	
Abdominal pain	14 (22.6%)	21 (33.9%)	
Change in bowel habit	9 (14.5%)	8 (12.9%)	
Family history of colon cancer	8 (12.9%)	5 (8.1%)	0.586
Other (history of colon polyps, anal fistula, weight loss)	4 (6.4%)	2 (3.2%)	
The findings of the colonoscopy			
Normal	22 (35.5%)	23 (37.1%)	
Hemorrhoids	30 (48.4%)	32 (51.6%)	0.997
Other (colitis, hypertrophic internal papi, polyps, diverticulum, colon cancer, solitary rectal ulcer)	12 (19.4%)	13 (21.0%)	

P-values ≤ 0.05 were considered statistically significant and the Kolmogorov–Smirnov test was used for normality of quantitative variables, and then the Mann–Whitney U-test or independent sample t-test was used for comparison of them. Also, the χ^2 test was used to compare qualitative variables

Table 2: Comparisons between symptoms and desire to repeat colonoscopy in the tramadol vs. placebo groups

Variables	Tramadol (n=62)	Placebo (n=62)	P-values
Abdominal pain according to the NRS*	6 (9.7%)	1 (1.6%)	<0.001
Painless	18 (29%)	8 (12.9%)	
Mild	28 (45.2%)	15 (24.2%)	
Moderate	10 (16.1%)	38 (61.3%)	
Severe			
Non-abdominal symptoms (sweating, nausea, moaning, and palpitations)	10 (16.1%)	31 (50%)	0.001
Desire to repeat colonoscopy	41 (66.1%)	29 (46.8%)	0.046

* Numerical rating scale

P-values ≤ 0.05 were considered statistically significant and the Kolmogorov–Smirnov test was used for normality of quantitative variables, and then the Mann–Whitney U-test or independent sample t-test was used for comparison of them. Also, the χ^2 test was used to compare qualitative variables

oral opioids before outpatient colonoscopy. In conclusion, this study shows that oral tramadol is well-tolerated and effective in reducing pain and it is accepted by patients undergoing colonoscopy. The results of this study could be a new and useful guide for reducing pain and symptoms of painful procedure. The limitation of this study was the fixed dose of drug and lack of comparison with other analgesics.

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Conflicts of interest

There are no conflicts of interest.

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