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Tramadol or paracetamol do not effect the diagnostic accuracy of acute abdominal pain with significant pain relief – a prospective, randomized, placebo controlled double blind study

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Abstract. – OBJECTIVES: To examine the effects of early administration of analgesics in patients with acute abdominal pain on pain severity, abdominal findings and diagnostic accuracy.

METHODS: 210 patients with non-traumatic acute abdominal pain lasting less than 72 hours were enrolled to this trial. Patients were administrated by placebo, tramadol (1 mg/kg), or paracetamol (15 mg/kg) randomly after the first evaluation of pain severity scores (standard 100 mm visual analog scale) and abdominal findings (rebound, rigidity, tenderness). After 20 and 40 minutes of administrations, pain severity scores and abdominal findings were re-examined. Complete blood count, electrocardiography, plain abdominal x-ray, urine analysis and abdominal ultrasound were used for the initial diagnosis. The final diagnoses were decided after re-examinations, biochemical blood analysis, abdominal computed tomography in all patients and consultations or other diagnostic methods when necessary.

RESULTS: There were 70 patients in each group. Baseline pain severity scores and abdominal findings were similar at all groups. After 20 minutes, pain severity scores were decreased in tramadol and paracetamol groups compared with the placebo group as 55% and 45% vs 1% respectively ($p < 0.001$). After 40 minutes, decreases on pain severity scores were more significant at treatment groups, 67% and 60% vs 0 ($p < 0.001$). When compared to placebo tramadol and paracetamol increased the new onset or worsening nausea or vomiting. There was no difference on abdominal findings among the groups after 20 and 40 minutes examinations. Diagnostic accuracy of tramadol, paracetamol and placebo groups were 96%, 94% and 94% respectively.

CONCLUSIONS: Early administration of tramadol and paracetamol provided effective pain relief in patients with non-traumatic acute abdominal pain and those administrations did not interfere with diagnosis.

Key Words:

Emergency Department, Abdominal pain, Tramadol, Paracetamol.

Introduction

Studies have shown that withholding analgesics from patients with acute abdominal pain were prevalent among the Emergency Department doctors[1]. The main reasons for this myth may be the fear of masking the true diagnosis. The diagnostic process of abdominal pain often takes time because of consecutive abdominal physical examinations, imaging investigations, consultations or laboratory tests. Meta-analyses have demonstrate that, while waiting for diagnostic process, the use of opioid analgesics in patients with acute abdominal pain is helpful in terms of patient comfort and don't result with diagnostic errors[2,3]. Those studies usually include morphine, one of the most preferred as analgesic in Emergency Departments[1]. Other analgesics such as meperidine, tramadol, nonsteroidal antiinflammatory drugs (NSAIDs) or paracetamol are used extensively for abdominal pain relief in Emergency Departments as well[1,4]. We aimed to examine the effects of intravenous administration of tramadol (an opioid analgesic) and paracetamol (a non-opioid analgesic) on pain severity, abdominal findings and final diagnosis over the placebo group in patients with non-traumatic acute abdominal pain.

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Patients and Methods

This prospective, randomized, double blind, placebo-controlled study was conducted in the Emergency Department of our University Hospital with a volume of 35,000 patients per year. From May 2010 until October 2010, we enrolled a convenience sample of patients with non-traumatic acute abdominal pain. They all gave written informed consent. The study protocol was reviewed by Ethical Committee, and their permission was granted. Statistic advisory recommended more than 200 patients for the study and we decided for 210 patients.

Inclusion and Exclusion Criteria

Patients were eligible if they were older than 17 years with abdominal pain less than 72 hours' duration without any traumatic origin. Patients who were admitted several times during the study were eligible to participate only once. Patients with pregnancy, allergy to opioids or paracetamol, hypotension (< 100 mmHg) and self-medication with analgesia were excluded.

First examinations of the patients were done by the Emergency physicians and they assessed the patients for study inclusion criteria. Patients eligible for study were informed and the accepted patients were enrolled. A Visual Analog Scale (VAS) including an unmarked 100 mm range was used to record the pain level that the patient perceived. Both the VAS score and the components of the abdominal findings (rigidity, rebound and tenderness) were evaluated and recorded to a prepared sheet by the physician. Physical examination findings were graded as absent or present. An intravenous access was created in all patients.

The block allocation schedule was performed by an online randomization plan generator (www.randomization.com). Enrolled patients were randomized to receive intravenous 1 mg/kg tramadol (Abdi Ibrahim, Istanbul), 15 mg/kg paracetamol (Bristol-Myers Squibb, Itxassou) or an equal volume of normal saline. All the medications were infused intravenously over three minutes by a nurse who was blinded to the medication. The treating physician and the patients were also blinded to the medication. After randomization and medications, laboratory and radiographic studies were done. Complete blood count, electrocardiography, plain abdominal x-ray, urine analysis and abdominal ultrasound were used for the initial diagnosis. All those diagnostic procedures were done within the first 40 minutes of admissions.

During the diagnostic process, patients were re-evaluated by the physicians for the pain severity scores and abdominal findings at 20 and 40 minutes. The final diagnoses were decided after re-examinations, biochemical blood analysis, abdominal computed tomography (CT) in all patients, consultations when necessary and other diagnostic methods such as surgical findings before discharge of the patients.

Data Analysis

Data were expressed as numbers and percentages or mean ± SD or median with minimum and maximum values. Using α value of 0.05 power of the 80% and formula provided to calculate difference among three groups. We calculated that the minimal needed number of patients should be 70 patients per group. Normality was confirmed using Kolmogorov Smirnov test for VAS and age. Independent sample *t*-test was used for quantitative data. Cochran Q test was used for the comparison of the categorical groups with repeated measures. Since VAS variable was not normally distributed, Friedman test was used for VAS. Multiple comparisons were carried out by Mann Whitney U test with Bonferroni correction. Also, Pearson Chi-Square test was carried out. Data were analyzed using SPSS software program, version 15.0, for Windows (SPSS Inc., Chicago, IL, USA). $p < 0.05$ was regarded as statistically significant.

Results

There were 93 (44.3.%) men and 117 (55.7%) women. The mean age was 33.8±12.2 and 32.1±12.0 for men and women, respectively. Age and sex distribution of three groups were similar (Table I). Each group were including 70 patients and baseline VAS pain score were similar in patients receiving tramadol, paracetamol and those receiving placebo.

After 20 minutes, pain severity scores were decreased in tramadol and paracetamol groups compared with the placebo group as 55% and 45% vs 1% respectively ($p < 0.001$). After 40 minutes, decreases on pain severity scores were more significant at both treatment groups, 67% and 60% vs 0 ($p < 0.001$). Pain relief of tramadol at 20 minutes was better than paracetamol, but they were similar at 40 minutes (Table II). There

Table I. Demographics and clinical characteristics of abdominal pain patients.

Variable	Tramadol	Paracetamol	Placebo	Total
Abdominal pain	N: 70	N: 70	N: 70	N: 210
Median age (year)	30.8 ± 10.8	33.6 ± 12.2	34.2 ± 13.0	32.8 ± 12.1
Male (%)	31 (44.3%)	24 (34.3%)	38 (54.3%)	93 (44.3%)
Female (%)	39 (55.7%)	46 (65.7%)	32 (45.7%)	117 (55.7%)
Nausea (%)	8 (11.4%)*	7 (10%)*	10 (14.3%)	25 (11.9%)
Vomiting (%)	6 (8.6%)*	6 (8.6%)*	7 (10%)	19 (9%)
Dizziness(%)	1 (1.4%)*	0 (0%)*	2 (2.9%)	3 (1.42%)
Diarrhea (%)	6 (8.6%)	7 (10%)	7 (10%)	21 (10%)
Constipation (%)	5 (7.1%)	6 (8.6%)	4 (5.7%)	15 (7.1%)
Dysuria (%)	6 (8.6%)	8 (11.4%)	8 (11.4%)	22 (10.5%)

*The findings that begin and/or become severe after given drugs.

was no difference on abdominal findings among the groups after 20 and 40 minutes examinations (Table III).

Nonspecific abdominal pain was the most detected diagnosis (26.7-24.8%) in either initial or the final diagnosis (Table IV). Final diagnosis was changed in 11 (5.2%) of 210 patients (Table V). Diagnostic accuracy of tramadol, paracetamol and placebo groups were 96%, 94% and 94% respectively.

Twenty-eight patients (13.3%) reported side effects, 27 of them had reported new onset or worsening nausea or vomiting 14 (20%) patients in tramadol group, 13 (18.6%) patients in paracetamol, and in one (1.4%) patient dizziness (tramadol group) were found. There was no significant relationship between the three groups and side effects (p = 0.80). Adverse effects were recorded in both study groups (Table I). No patient received an intervention due to a side effect.

Table II. Pain scores assessment before and after medications.

	Tramadol (n: 70)	Paracetamol (n: 70)	Control (n: 70)	*p* value
VAS 0	85 (71-97)	83 (73-97)	83.5 (73-97)	0.13
VAS 20	38 (26-62)*	45 (30-70)#	82.5 (70-90)	< 0.001
VAS 40	27.5 (18-30)*	33 (30-37)#	85 (74-93)	< 0.001

VAS scores are expressed as medians. Values in parentheses are the minimum and maximum values. *Significantly different from control and paracetamol groups. #Significantly different from control group.

Table III. Physical examination findings before and after medication.

	Tramadol (n: 70)	Paracetamol (n: 70)	Control (n: 70)	Total (n: 210)
Rebound 0	27 (38.5)*	35 (50.0)	36 (51.4)	98 (47)
Rebound 20	30 (42.5)	36 (51.4)	36 (51.4)	102 (48.6)
Rebound 40	30 (42.5)	36 (51.4)	36 (51.4)	102 (48.6)
Rigidity 0	12 (17.1)	9 (12.9)	10 (14.3)	31 (14.8)
Rigidity 20	12 (17.1)	10 (14.3)	11 (15.7)	33 (15.7)
Rigidity 40	12 (17.1)	10 (14.3)	11 (15.7)	33 (15.7)
Tenderness 0	68 (97.1)	68 (97.1)	70 (100)	206 (98.1)
Tenderness 20	68 (97.1)	68 (97.1)	70 (100)	206 (98.1)
Tenderness 40	68 (97.1)	68 (97.1)	70 (100)	206 (98.1)

*Percentage in the parenthesis.

Table IV. Early and final diagnosis of 210 patients in the study.

	Early n	Diagnosis %	Final n	Diagnosis %
Nonspecific abdominal pain	56	26.7	52	24.8
Acute appendicitis	28	13.3	26	12.4
Biliary tract disease	16	7.6	18	8.6
Peptic disease	20	9.5	20	9.5
Gastroenteritis	21	10.0	22	10.5
Bowell obstruction	14	6.7	16	7.6
Peritonitis	6	2.8	6	2.8
Renal colic	22	10.5	20	9.5
Urinary tract infection	11	5.2	9	4.3
Pancreatitis	6	2.9	7	3.4
Inflammatory bowel disease	3	1.4	3	1.4
Ovarian cyst rupture	2	1.0	3	1.4
Intraabdominal abcess	5	2.4	8	3.8
Total	210	100.0	210	100.0

*Percentage in the parenthesis.

In this study, none of the patients died. Also any serious drug adverse effect was not observed related to the study patients in our Emergency Department. No patient required naloxone or any other opioid antagonist during the study protocol.

Discussion

We preferred two analgesics (tramadol and paracetamol) to reduce for abdominal pain in Emergency Department. Tramadol is a synthetic, centrally active analgesic that selectively activates the μ-receptor. It is effective in the control of moderate and severe pain and we preferred it because it has been reported to be as efficacious as morphine in pain reduction with fewer side effects[5]. The other drug, paracetamol is used as an analgesic and antipyretic. Paracetamol products are suitable for most people including the elderly and young children. Interactions with other treatments usually do not cause any problem. Paracetamol is well tolerated by people with peptic ulcers and in general those who suffer from asthma. The main mechanism of paracetamol is considered to be the inhibition of cyclooxygenase (COX), and recent findings suggest that it is highly selective for COX-2. Available without a prescription, it has in recent years increasingly become a common household drug. Paracetamol,

Table V. Early and final diagnosis of 210 patients in the study.

Early diagnosis	Final diagnosis	Group
Nonspecific abdominal pain	Gastroenteritis	Tramadol
Nonspecific abdominal pain	Bowel obstruction	Tramadol
Nonspecific abdominal pain	Renal colic	Paracetamol
Nonspecific abdominal pain	Bowel obstruction	Control
Acute appendicitis	Intraabdominal abcess	Paracetamol
Acute appendicitis	Biliary tract disease	Tramadol
Urinary tract infection	Intraabdominal abcess	Control
Urinary tract infection	Ovarian cyst rupture	Control
Renal colic	Intraabdominal abcess	Paracetamol
Renal colic	Biliary tract disease	Control
Renal colic	Pancreatitis	Paracetamol

Group variable is not significantly related with the diagnosis (p=0.9).

unlike other common analgesics such as aspirin and ibuprofen, has relatively little anti-inflammatory activity[6,7]. In our study, both drugs were effective for pain relief after 20 and 40 minutes of administrations. Both tramadol and paracetamol provided a decrease of 20 mm at 20 and 40 minutes. This is in concordance with the results from the previous studies that a decrease of 12-16 mm on a 100 mm VAS scale is needed to produce the minimum clinically significant improvement in patients with acute pain[8-11].

Peritoneal signs, such as tenderness, rebound, rigidity, are the classic descriptors of an acute abdomen. Rigidity is though to be a reflex spasm of the abdominal wall and thus should not be affected by analgesia[3]. On of the hypothesized advantages of early analgesia is that it allows the patient to relax. Through relaxation, tenderness can be better appreciated. Studies have demonstrate that early intravenous opioids do not impair clinical evaluation of patients with acute abdominal pain[12-14]. In our study we evaluated whether the administration of intravenous analgesics would result in significant alteration of three abdominal signs (rigidity, rebound and tenderness) when compared with control group and found no difference.

Many studies dealing with analgesics use at acute abdominal pain have been done with diagnostic accuracy test. Attard et al[12] reported diagnostic accuracy rate of 96% in drug group (papaveratum) and 82% in control group. Two other studies including morphine demonstrated that accuracy of initial diagnosis in medication and control groups were 80-61% and 64-67%, respectively[11,13]. Another randomized controlled study found no difference in the accuracy rate of Emergency physicians' provisional diagnosis between groups of patients administered morphine and placebo. The endpoint was not changed in their physical examination, but diagnostic accuracy based on physical examination[15]. Also, Lo Vechio et al[16] documented that there was some changes of physical examination findings and differences in diagnosis between patients receiving analgesia and placebo. The use of opioids was associated with some change in physical examination finding (tenderness) and localization in half the patients but led to no delays in care. Early diagnosis differed from the final diagnosis in 4 of the 49 total patients. There was no delay in outcome on time to treatment in any patient. These recently collected data showed that administration of analgesia did not interfere with the diagnosis of acute abdominal pain. Experimental evidence suggests that, when compared with placebo, analgesia administration to patients with acute abdominal pain does not significantly increase the risk of diagnostic error or incorrect management decisions[12,16,17]. In addition, these studies demonstrate that providing this analgesia results in significant improvements in patient comfort[12,16]. Finally, the use of analgesics in acute abdominal pain does not appear to delay the diagnosis. Likewise, in our study, it was determined 96, 94, and 94% of accordance respectively between fist and final diagnosis in tramadol-paracetamol and control groups, our findings suggest that the early medication of analgesics is both safe and effective in patients with abdominal pain in Emergency Service. We found a considerable reduction in pain experienced after the medication (tramadol or paracetamol). Therefore, our patients comfort levels increased.

Ultrasound has become a major tool for investigating and diagnosing many abdominal pathologic entities. CT scanning and ultrasound imaging are now used frequently to help determine not only the underlying cause of a patient's abdominal pain, but also the urgency and type of surgical intervention that may be needed. Indeed, for the final diagnosis in all patients tomography and ultrasound significantly contributed to the reviews.

Last, there is concern that current studies have not enrolled enough patients to allow a statistical estimate of the adverse effect rate with analgesia. One prospective study followed patients with abdominal pain severe enough to require opioid analgesics. The assessors found no adverse effects associated with analgesic administration[17]. In the present study, no serious analgesics related adverse events occurred in the patients given tramadol and paracetamol. The side effects of the medications were not differed by the three groups. Despite some limitations, it seems that analgesia is safe and reasonable.

Conclusions

In modern medicine there is no place for undue suffering. Tramadol and paracetamol lead to decrease in the level of abdominal pain. The appropriate use of analgesics in patients with acute abdominal pain effectively decreased pain and did not interfere with diagnosis or treatment.

This investigation has several limitations. First, this study was from a single centre. Second, the reliability of each VAS score was not tested with the second independent ranking. Further studies are needed before this practice can be established without at least some concern and should address both the benefit and risk/harm in expediency and accuracy of the diagnosis.

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