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Original Research

The Effects of Intravenously Administered Tramadol, Dexketoprofen Trometamol, and Midazolam in the Management of Renal Colic Pain; A Prospective Randomized Study

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ABSTRACT
Objective: This study aims to assess the effects of analgesic treatment combinations on ultrasonography findings and pain scales in patients with renal colic pain who were admitted to the emergency department of Gaziantep University Medical Faculty.
Methods: This prospective randomized clinical study was conducted in 100 patients with renal colic pain who were admitted to the emergency department of Gaziantep University Medical Faculty between September 2013 and September 2014. The patients were divided into four groups: the first group received tramadol, the second received dexketoprofen trometamol, the third received a tramadol-midazolam combination, and the fourth group received a dexketoprofen trometamol-midazolam combination. Blood pressure, pulse, and bedside renal ultrasonography (USG) findings were evaluated. Pain severity levels were assessed using the visual analog scale (VAS) and the renal colic symptom score (RCSS), and were recorded as pre-treatment (0 min) and post-treatment (30 min) scores. These values were then statistically compared.
Results: There was no statistically significant difference among the four groups in terms of gender and age (p=0.951 and p=0.890, respectively). A significant decrease was detected in the pre-treatment (0 min) and post-treatment (30 min) VAS and RCSS scores of all groups. The largest decrease was observed in the tramadol-midazolam group in the between-group comparison. In the evaluation of the alterations of the bedside USG findings, the largest change in renal parenchymal diameter of painful kidney was also observed in the tramadol-midazolam group.
Conclusion: The efficacy and safety of a tramadol-midazolam combination as an analgesic in management of renal colic may be used as an alternative, or add-on, therapy to currently available options.
Keywords: Renal colic, bedside ultrasonography, analgesic

INTRODUCTION

Pain is the symptom for which people usually consult their physicians. Renal colic is an emergency that usually develops secondary to renal stone disease, presents as acute and severe pain, and is primarily diagnosed and treated in emergency departments (EDs). The incidence and prevalence of renal stone disease is reportedly increasing worldwide, and acute renal colic episodes, typically described by patients as "coming out of the blue", cause severe distress and warrant emergency medical attention. These patients are treated with opioids and non-steroidal anti-inflammatory drugs (NSAIDs) to relieve pain in the acute setting (1).

Tramadol is a centrally acting synthetic opioid analgesic that binds to specific opioid receptors. It is used to treat moderate to moderately severe pain. Onset of action is dose dependent, but it generally occurs within 5–10 min of intravenous (IV) dosing (2). Dexketoprofen trometamol is a newly developed NSAID that is used in treatment of moderate pain. Itproducesan analgesic effect within 30 min of administration (3). Midazolam is a short-acting central nervous system (CNS) depressant of the benzodiazepine class. Intravenous midazolam is indicated for procedural sedation (often in combination with an opioid), for preoperative sedation, for the induction of general anesthesia. Light intravenous sedation with midazolam is used to make anxious patients more comfortable before medical procedures (4).

Multimodal analgesic techniques provide potent and synergistic effects. Therefore, pain control can be achieved with balanced and effective analgesia. Concomitant use of anxiolytic and sedative drugs with analgesic agents may reduce anxiety and increase early mobilization and early discharge from the emergency services.

The primary objective of this study was to measure the severity of pain by using appropriate assessments in patients admitted to the ED with renal colic, and to determine renal parenchymal di-

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ameters by ultrasonography (USG). The secondary objective was to compare the efficacy of tramadol, dexketoprofen trometamol, tramadol-midazolam, and dexketoprofen trometamol-midazolam combinations in relieving pain associated with acute renal colic.

METHODS

This prospective, randomized, single-blind study was performed in the ED of the Gaziantep University Medical Faculty. The study protocol conformed to the principles of the Declaration of Helsinki, and was approved by the Gaziantep University Ethics Committee (Ethical committee resolution no: 06-2009/264, date 18.06.2009). The study was funded by the Commission of Scientific Research Projects, Gaziantep University (Project no: TF.12.31). All participants were given details of the study protocol, and written consents were obtained from them.

This study was conducted between September 2013 and September 2014 in 100 patients who were admitted to the ED and diagnosed with renal colic, met the study criteria, and gave approval voluntarily to participate in the study. Patients who were diagnosed with acute renal colic based on their chief complaint, history, and physical examination, and, hematuria in urine analysis and, or past medical history of renal stone, were enrolled in the study. In all participants, kidney or urinary tract stones were confirmed by ultrasound, plus kidney-ureter-bladder (KUB) X-ray or CT scan. The participants (all aged over 16 years) were randomly allocated, without gender discrimination, using computer-generated random numbers to four groups receiving differing medications: tramadol (Group 1, 100 mg), dexketoprofen trometamol (Group 2, 50 mg), tramadol-midazolam (Group 3, 100 mg to 0.01mg/kg), and dexketoprofen trometamol-midazolam (Group 4, 50 mg to 0.01 mg/kg). A detailed medical history was taken, and a thorough physical examination was performed for each participant. Vascular access was established in each participant, and complete blood count, urinalysis, urea, and creatinine level measurements were conducted. In addition, blood pressure and pulse were measured. Diagnosis, USG, and treatment efficacy were all evaluated by the same physician. The relevant physician had been certificated after 8 h of theoretical and practical training in a basic emergency USG course. Patients for whom ultrasonographic measurements could not be performed for technical and anatomical reasons, such as obesity and excessive abdominal gas, were excluded from the study. The participants who had received an analgesic medication during the previous 24 h, had an NSAID allergy, had a history of peptic ulcer or gastrointestinal bleeding, or were receiving anticoagulant treatment, as well as those in whom a solitary kidney or bilateral urinary obstruction was detected, were also excluded, as were those with a serum creatinine level above 2 mg/dL, visual and hearing defects, and female patients in menstruation. Pregnant and nursing females were also excluded.

All participants were taken into the intervention room, and were laid on stretchers and monitored. Then, 500 cc 0.9% NaCl was administered via the left antecubital vein to each individual. Medications were administered via the same intravenous route. Pain severity was evaluated in each participant, using the visual analog scale (VAS) and renal colic symptom score (RCSS), immediately before administering medications and after 30 min (Figure 1). Pre-treatment and post-treatment renal and parenchymal sizes were measured in the supine position using the Logiq P6 (GE Healthcare, 2008) device and a 3.5 MHz convex probe to obtain longitudinal and axial images. The participants were examined for nephrolithiasis, hydronephrosis, and pelvicalyceal dilatation. Pre-treatment and post-treatment anteroposterior diameters were measured in those with detected pelvicalyceal dilatation.

Statistical Analysis

Statistical Package for the Social Sciences for Windows version 18.0 (SPSS Inc.; Chicago, IL, USA) was used for statistical evaluation. The distribution of the permanent data that were obtained in this study was examined graphically and using a Kolmogorov–Smirnov test. An analysis of variance test was used in an intra-group comparison of independent and normally distributed data. As the data were independent and normally distributed, groups were compared using an independent-sample t test. As the data were normally distributed and dependent, groups were compared using a paired-sample t test. A Kruskal–Wallis test was used in intra-group comparison of independent and not normally distributed data, while a Mann–Whitney U test was used for paired comparison. The relationship between variables was analyzed using the Pearson correlation test. All data were expressed as mean±standard deviation. In all comparisons, $p<0.05$ was considered statistically significant**.**

RESULTS

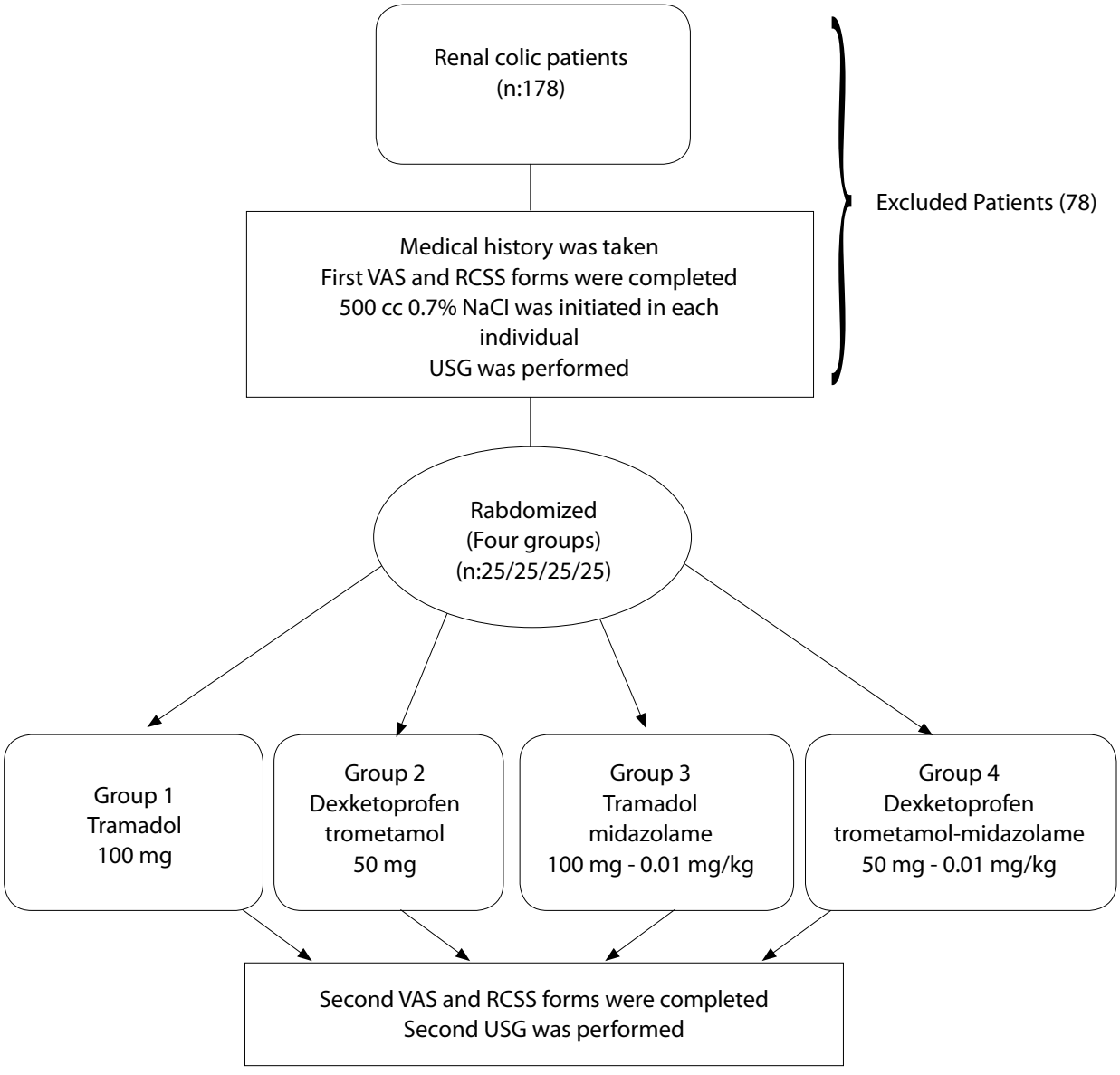
In a year, approximately 100,000 patients (over 16 years old) are referred to our ED for diagnosis and treatment. Of these patients, approximately 200 are admitted due to renal colic. This study involved 100 participants who had been admitted to the ED with renal colic, with the numbers of enrolled females and males being 36 (36%) and 64 (64%), respectively. The mean age of the participants was 34.6±13.3 years. Pre-treatment urea, creatinine, and WBC values were measured, recorded, and compared between the groups. Between the groups,there was no statistical difference in the mean ages, gender, and laboratory results (Table 1), and there was no statistically significant difference in terms of pre-treatment and post-treatment blood pressure and pulse values (Table 2).

A significant decrease was detected in post-treatment VAS and RCSS scores when compared to pre-treatment values (Table 3). In addition, there was a significant difference between the groups with regard to pre-treatment VAS and RCSS scores (p=0.000 and p=0.001, respectively), while no significant difference was observed for post-treatment values (p=0.286 and p=0.937) (Table 3).

The highest decrease between pre-treatment (0 min) and post-treatment (30 min) VAS scores was observed in Group 3, as 75.3%±26.7%. A statistically significant difference was found between the groups in decrease in pre-treatment (0 min) and post-treatment (30 min) VAS scores (p=0.025) (Table 4).

There was no statistically significant difference between the groups in pre-treatment and post-treatment renal long axis and short axis (Table 5).

Figure 1. Flow chart of the study design
VAS: visual analog scala; RCSS: renal colic symptom score; USG: ultrasonography



DISCUSSION

Renal colic is a common worldwide disease. It often leads to ED visits, and frequently requires imaging evaluation (1, 5). Acute renal colic is one of the most painful events that an individual can experience, and relief of this pain becomes an urgent and daunting task for the ED physicians. Different drug groups used for pain relief in acute renal colic have been studied and described (1, 6). Although morphine and pethidine were formerly used as first-line treatment agents for this disorder, NSAIDs have been used as medications with proven efficacy since the 1970s (6, 7). Current medical treatment of acute renal colic includes the use of calcium channel blockers, steroids, NSAIDs, and α blockers. The European Association of Urology guidelines suggest the use of NSAIDs, such as diclofenac, indomethacin, or ibuprofen, as first-choice treatment when renal colic is initially diagnosed. Opioids, such as hydromorphine and tramadol, are suggested as the second-choice options (7). Some previous studies have assessed the use of NSAIDs and opioid combinations; however, there are no available studies on the concomitant use of anxiolytic and sedative drugs with analgesic agents (1, 6, 8).

In previous studies, comparisons of vital signs obtained during renal colic have been performed in participants receiving different groups of drugs (9, 10), and these have revealed differing results. In our study, inter-group comparison of systole-diastole and pulse data demonstrated no differences (Table 2). In the pre-treatment and post-treatment in-group comparison, we found that systolic-diastolic pressure significantly decreased in

Table 1. Comparison of demographic data, laboratory, and urine analysis results

	Group 1	Group 2	Group 3	Group 4	p
Male (n)	15	16	17	16	0,951[α]
Female (n)	10	9	8	9	
Age (year)	34.8±16.1	33±13.9	34.8±11.7	35.9±11.9	0.89[β]
Urea (mg/dL)	28.7±7.1	33.6±18.8	29.9±7.5	28.8±9.1	0.403[β]
Creatinine (mg/dL)	0.8±0.2	0.9±0.3	0.9±0.1	1.03±0.3	0.261[β]
WBC (uL)	9579±2298	9268±3460	10171±4057	99.5±2516	0.780[β]
Urine leukocytes					
Positive	5	14	14	12	0.032[α]
Negative	20	11	11	13	
Urine erythrocytes					
Positive	12	17	22	19	0.020[α]
Negative	13	8	3	6	

[β]: analysis of variance; [α]: Chi–square test; WBC: white blood cell

Table 2. Comparison of measured parameters

	Group 1	Group 2	Group 3	Group 4	p[α]
Pre–treatment					
Systole	118±15	116±22	122±20	122±23	0.679
Diastole (mmHg)	67±12	71.8±14	77±11	72.2±17	0.105
Post–treatment					
Systole	110±13	114±13	114±14	111±18	0.625
Diastole (mmHg)	66±12	72.7±10	71±10	72.1±15	0.215
Pre–treatment					
Pulse (Pulse/min)	87±9	83±14	84±14	81.2±11	0.611
Post–treatment					
Pulse (Pulse/min)	78.56±8	79.52±8.8	80±11	78.1±12	0.734
Pre–Post P[β] (Systole)	0.003	0.491	0.043	0.010	
(Diastole)	0.681	0.720	0.034	0.965	
(Pulse)	<0.001	0.167	0.189	0.968	

[α]: analysis of variance; [β]: paired simple test

Group 3. We believe that the anxiolytic and cardio depressive effects of midazolam might have caused it.

As in other painful conditions, pain-scoring systems are used to grade pain severity in acute renal colic. In this study, we utilized VAS and RCSS, and we used four drug groups to relieve pain and decrease pain-related anxiety. We detected a significant decrease in post-treatment VAS and RCSS scores in all groups (Table 3, 4), with this being most prominent in Group 3, which shows that addition of midazolam to tramadol increases treatment efficacy. No information on the concomitant use of midazolam and tramadol is currently available, and few previous studies have investigated the use of tramadol as a single agent (11, 12). In our study, we found a statistically significant decrease in VAS and RCSS scores because of the concomitant use of tramadol and midazolam when compared to other combinations.

Table 3. Comparative analysis of changes in the VAS and RCSS levels

	Group 1	Group 2	Group 3	Group 4	p[α]
VAS					
Pre-treatment	7.28±1.4[a]	7.72±1.5[b]	8.7±1.2[c]	8.6±1.3[d]	0.000
Post-treatment	3.1±1.8	2.1±1.5	2.2±2.5	2.5±2.2	0.286
RCSS					
Pre-treatment	3.8±1.4[e]	4.7±2.2[f]	6.4±2.3[g]	5±2.6[h]	0.001
Post-treatment	1.5±1.3	1.4±1	1.3±0.8	1.3±0.1	0.937
Pre-Post P[β]					
VAS	<0.001	<0.001	<0.001	<0.001	<0.001
RCSS	<0.001	<0.001	<0.001	<0.001	<0.001

[α]: analysis of variance; [β]: paired simple test, Mann-Whitney U test (avs c, avsd, bvsc, bvsd, evsg, evsh, fvs g for p<0.05); VAS: visual analog scale; RCSS: renal colic symptom score

Table 4. Comparison of percentage reduction of VAS and RCSS levels

	Group 1	Group 2	Group 3	Group 4	p[α]
VAS Decrease (%)	57.6±25[a]	73.2±17.7[b]	75.3±26.7[c]	70.5±25.2[d]	0.025
RCSS Decrease (%)	63.4±25.4	70±19	77±15.6	72±22.8	0.095

[α]: Kruskal-Wallis test, Mann-Whitney U test (avsb, c, d for p<0.05); VAS: visual analog scale; RCSS: renal colic symptom score

Table 5. Comparison of renal sizes

Aching side	Group 1	Group 2	Group 3	Group 4	p[α]
Pre-treatment					
Long axis	10.7±1.1	10.6±1.2	11.3±1.2	10.84±0.9	0.161
Short axis	5±0.7	5.2±1	5±0.97	5.1±1	0.402
Parenchyma	1.35±0.2	1.4±0.3	1.3±0.27	1.33±0.1	0.304
Post-treatment					
Long axis	10.7±1.1	10.6±1.3	11.2±0.9	10.80±0.7	0.161
Short axis	5±0.8	5.3±0.9	5.3±0.9	5±0.9	0.402
Parenchyma	1.33±0.1[e]	1.3±0.3[f]	1.1±0.25[g]	1.31±0.2[h]	0.014
Pre-treatment					
Anteroposterior	1.322±0.21	1.1±0.6	1.3±0.54	1.104±0.9	0.831
Post-treatment					
Anteroposterior	1.327±0.23	1.2±0.5	1.4±0.52	1.1±0.8	0.553
P[β] for Long axis	0.804	0.832	0.793	0.702	
P[β] for Short axis	0.539	0.446	0.673	0.186	
P[β] for Parenchyma	0.595	0.367	0.066	0.374	
P[β] for Anteroposterior	0.604	0.410	0.152	0.863	

[α]: Analysis of variance; [β]: paired simple test, *Mann-Whitney U test (gvse, f, h for p<0.05)

This may be due to a possible additive effect obtained by the concomitant use of these agents. Another possible explanation is that decreasing anxiety in patients who are admitted to the ED may decrease anxiety-induced pain.

Although no previous studies have shown the relationship between renal diameters and analgesics, there have been several investigations of the correlation between hematuria and the presence of hydronephrosis (13, 14). A total of 70% of our study sample had hematuria, bedside USG revealed hydronephrosis in 21% of the cases, and there was no statistically significant difference between these patients in terms of measured pre-treatment (0 min) and post-treatment (30 min) anteroposterior diameter values (Table 5). In addition, we detected no in-group differences with regard to pre-treatment and post-treatment long axis, short axis, and parenchymal diameters (Table 1, 5). Inter-group comparison revealed a difference in post-treatment parenchymal diameters, which was related to the largest decrease being detected in Group 3. It remains unclear as to why the tramadol-midazolam combination led to a statistically significant decrease in renal parenchymal diameters.

The main limitation of the present study was its monocentric, single-blinded design, and relatively small sample size. A double-blinded design could have improved the investigation.

CONCLUSION

Renal colic treatment modalities have been generally evaluated for their efficacy within 60 min of analgesia application and using only VAS. This study evaluated the analgesic effects of four different renal colic treatment modalities for 30 min using both VAS and the RCSS, and also with renal diameters. This fact differentiates this study from others of the same genre. Tramadol-midazolame combination may represent an alternative or add-on analgesic to currently available options for renal colic.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziantep University.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – S.Z., G.K.; Design – S.Z.; Supervision – S.Z.; Materials – G.K.; Data Collection and/or Processing – G.K.; Analysis and/or Interpretation – S.Z.; Literature Search – B.A.; Writing Manuscript – S.Z., B.A.; Critical Review – C.Y.; Other – C.Y.

Conflict of Interest: The authors have no conflicts of interest to declare.

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