VIA MEDICA

ORIGINAL ARTICLE

2019, Vol. 4, No. 3, 92–97
DOI: 10.5603/DEMJ.2019.0019

ISSN 2451–4691

RISK FACTORS FOR ADVERSE EVENTS IN PATIENTS ADMINISTERED INTRAVENOUS TRAMADOL HYDROCHLORIDE IN EMERGENCY DEPARTMENT

Eylem Kuday Kaykısız[1], Hatice Onturk[2], Lukasz Szarpak[3], Burak Katipoğlu[4], Semih Korkut[5]

[1]Department of Emergency Medicine, Denizli State Hospital, Denizli, Turkey
[2]Bitlis Eren University School of Nursery, Bitlis, Turkey
[3]Department of Emergency Medicine, Lazarski University, Warszawa, Poland
[4]Department of Emergency Medicine, Ufuk University Rıdvanege Research and Training Hospital, Ankara, Turkey
[5]Department of Emergency Medicine, Kartal Dr. Lutfi Kirdar Education and Research Hospital, University of Health Sciences, İstanbul, Turkey

ABSTRACT

INTRODUCTION: The aim of the present study was to assess the adverse events developing in patients treating with intravenous(iv) tramadol to provide moderate to severe pain control in emergency department (ED) and to investigate the association of these adverse events with age, sex and vital signs and to compose a set of rules for the identification of patients in the risk group.

MATERIAL AND METHODS: In this prospective cohort study, patients older than 18 years, admitted to ED during a 1-year period and administered iv tramadol were included in a secondary care public hospital. Information about age, sex, vital signs and adverse events were recorded. Patients defined as group 1 or group 2 with respect to adverse event development status and the groups were compared in terms of age, sex and vital signs.

RESULTS: A total of 408 patients were included in the study. Adverse events ratio after treatment was 21.1%. Adverse events were nausea, dizziness and vomiting. The age and the pulse rate per minute of the patients in group 1 were found to be higher and systolic blood pressure (SBP) was found to be lower than the patients in group 2.

CONCLUSİONS: The risk of adverse events development is higher in patients who are hypotensive, tachycardic and older than 56 years. Multicenter, prospective studies with larger patient groups are needed to support our results.

KEY WORDS: tramadol hydrochloride; opioids analgesics; emergency department; adverse event; side effect

Disaster Emerg Med J 2019; 4(3): 92–97

INTRODUCTION

Pain constitutes of approximately half of the admissions to the emergency department (ED) and is counted for the most frequent cause of admissions [1, 2]. A policy includes key points in pain management has been published by the American College of Emergency Physicians [3]. However optimal pain management is still controversial.

Opioids are the options of medication in patients with moderate to severe pain in ED [4].

ADDRESS FOR CORRESPONDENCE:
Eylem Kuday Kaykısız, Department of Emergency Medicine, Denizli State Hospital, Denizli, Turkey;
e-mail: eylemkuday@hotmail.com

Tramadol has been suggested as an option for treatment of severe pain of any cause; renal colic, dental problems, migraine, musculoskeletal disorders and such. According to the Institute for safe medication practice, opioids are considered as high-risk drugs and opioid-related medication errors can have serious consequences [5]. Safety is an important issue, especially during opioid therapy. Common side effects such as nausea and vomiting may prolong the duration of the patient's stay in the ED. Moreover, rare but serious side effects such as respiratory depression are the reasons for important morbidity and even death.The incidence of adverse effects depends on the dose and the mode of administration [6]. These drugs are most frequently given by oral and parenteral routes, it can be given rectally, epidurally and can be added to local anaesthetics for peripheral nerve blockade [7, 8]. Intravenous (iv) route is associated with more frequent adverse effect than subcutaneous (sc) and intramuscularly (im) route. Therefore, it is essential that emergency physicians have knowledge of appropriate patient selection and doses in EDs where these drugs are usually administered as iv route. Because there are also some clinical situations or patients' group where pain management is more problematic. While the aim of the acute pain management should be delivering effective pain relief, assessing its 'effectiveness' must be taken into account not only a patients pain scores but also adverse events that might impact on patient outcome [9].

The aim of the present study was to assess the adverse events developing in patients who are treating with iv tramadol to provide moderate to severe pain control in ED and to investigate the association of these adverse events with age, sex, comorbidities and vital signs and to compose a set of rules for the identification of patients in the risk group.

MATERIALS AND METHODS

In this prospective cohort study, after the approval of a local ethics committee of Bitlis Eren University, patients older than 18 years, admitted to ED between 01.01.2018–31.12.2018 and administered iv tramadol were included in a secondary care public hospital that has approximately 150.000 patients admission to ED, annually. Information about age, sex and medication status, vital signs (blood pressure, pulse, oxygen saturation) before the tramadol administration in triage field, time of administration, route of administration, whether adverse events were developed and if so, which adverse event was developed, were recorded. Patients under 18 years, whose data are missing in computerized system, pregnant patients and also patients treated with any other concomitant drug, to eliminate potential drug interactions or adverse events of any other drug, were excluded.

An adverse event is defined as nausea and dizziness, drowsiness, fatigue, headache, increased sweating, vomiting, dry mouth, diarrhoea and cardiovascular dysregulation (palpitations, tachycardia, postural hypotension) and serotonin syndrome, occurs during the ivtramadol treatment or within the next 2 hours despite the correct administration of the drug. Patients with adverse events were defined as group 1 and those without adverse events were defined as group 2 and the groups were compared in terms of age, sex and vital signs.

STATISTICAL ANALYSIS

Statistical analysis was performed with the SPSS 22.0 Statistical Package for Windows (SPSS Inc, Chicago, IL, USA). The median and standard deviation of the continuous variables were given, and the categorical variables were defined as percentages. Data were tested for normal distribution using the Shapiro-Wilk test. Categorical variables were compared with the Pearson's Chi-Squared Test. Mann-Whitney U-test was used to compare non-continuous variables. The Receiver Operating Characteristics (ROC) curve was used to demonstrate the cut-off values of age, systolic blood pressure (SBP) and pulse beat. A value of $p < 0.05$ was statistically significant.

RESULTS

During the study period, a total of 1134 patients were administered iv tramadol. 24 of these are under 18 years old; 410 patients were given any other medication before tramadol therapy and 292 patients whose data are missing in the system were excluded from the study. A total of 408 patients were included in the study. The mean age of the patients included in the study was 48.94 ± ± 19.56 (16–95) and 60.8% of these were female. Mean systolic blood pressure on triage field

was 115.83 ± 21 (80–190); mean pulse beat was 85.39 ± 14.54 (49–130). Adverse events ratio after treatment was 21.1% (n = 86). Adverse events were nausea in 74.4% (n = 64), dizziness in 32.6% (n = 28) and vomiting in 23.3% (n=20). The characteristics of patients are shown in Table 1. Head and neck pain (30.9%) and abdominal pain (27.5%) were the most common cause of tramadol-treated patients. These were followed by waist and back pain (14.7%), renal colic pain (11.7%), chest pain (9.3%) and extremity pain (5.9%).

When patient's characteristics are evaluated with respect to adverse event development status; the age and the pulse rate per minute of the patients in group 1 were found to be statistically significantly higher and SBP was found to be statistically significantly lower than the patients in group 2 ($p < 0.05$). Differences between groups in terms of age and vital signs are shown in Table 2.

There were no differences between male and female with respect to adverse events development ($p > 0.05$).

The cut-off value for SBP was determined to be 105 mmHg with respect to adverse event development. Patients with a SBP of 105 mm Hg or less had an increased incidence of adverse event (45.8% vs 7.6%). For this cut-off value, sensitivity is 76.74% and specificity is 75.78%. The area under the curve obtained in the Roc curve was 0.819 and this value was statistically significant (AUC: 0.819, 95% GA: 0.735–0.903, P: 0.001).

The cut-off value for age was determined to be 56 years in terms of adverse event development. Patients aged 56 years or older had an increased incidence of adverse event (31.6% vs 14.4%). For this cut-off value, sensitivity is 41.86% and specificity is 33.54%. The area under the curve obtained in the Roc curve was 0.666 and this value was statistically significant (AUC: 0.666, 95% GA: 0.562–0.769, P: 0.001).

The cut-off value for pulse rate was determined to be 90 beats/min in terms of adverse event development. Patients with a pulse 90 beats/min or higher had an increased incidence of adverse event (30.5% vs 12.8%). For this cut-off value, sensitivity is 32,56% and specificity is 40.99%. The area under the curve obtained in the Roc curve was 0.641 and this value was statistically significant (AUC: 0.641, 95% GA: 0.545–0.737, P: 0.005).

The comparison of groups in terms of age, SBP and pulse rate are shown in Table 3.

Table 1. The characteristics of participants (n = 408)

		Min-max	Average ± SD
Age (years)		16–95	48.94 ± 19.56 (48)
SBP (mm Hg)		80–190	115.83 ± 21.00 (110)
DBP (mm Hg)		50–110	72.84 ± 12.31 (70)
Pulse (/min)		49–130	85.39 ± 14.54 (87)
Saturation (%)		84–99	95.26 ± 2.86 (96)
		N	%
Sex	Female	248	60.8
	Male	160	39.2
Adverse events development	Group 1	86	21.1
	Group 2	322	78.9
Adverse events (n = 86)	Nause	64	74.4
	Vomiting	20	23.3
	Dizziness	28	32.6

SBP — systolic blood pressure; DBP — diastolic blood pressure

Table 2. The comparison of groups with respect to age and vital signs

	Adverse event		Z-value	P-value
	Group 2 (n = 322)	Group 1 (n = 86)		
	Average ± SD	Average ± SD		
Age (years)	46.32 ± 17.82 (45)	58.74 ± 22.7 (66)	**-3.336**	**0.001****
SBP (mm Hg)	120.19 ± 19.92 (120)	99.53 ± 16.61 (90)	**-6.500**	**0.001****
DBP (mm Hg)	75.34 ± 12.09 (70)	63.49 ± 7.83 (60)	**-6.282**	**0.001****
Pulse (/min)	84.17 ± 13.83 (86)	89.98 ± 16.34 (94)	**-2.843**	**0.004****
Oxygen saturation (%)	95.16 ± 2.86 (96)	95.65 ± 2.85 (97)	-1.231	0.218

SBP — systolic blood pressure; DBP — diastolic blood pressure, Z — Mann -Whitney U Test, **p < 0.01

Table 3. The comparison of groups with respect to age, systolic blood pressure and pulse rate.

		Adverse event		χ^2	p
		Group 2 (n = 322)	Group 1 (n = 86)		
		N(%)	N(%)		
Age (years)	< 56 years	214 (85.6%)	36 (14.4%)	7.649	0.006**
	≥ 56 years	108 (68.4%)	50 (31.6%)		
SBP (mm Hg)	≤ 105 mm Hg	78 (54.2%)	66 (45.8%)	38.722	0.001**
	> 105 mm Hg	244 (92.4%)	20 (7.6%)		
Pulse (/min)	< 90/min	190 (87.2%)	28 (12.8%)	8.507	0.004**
	≥ 90/min	132 (69.5%)	58 (30.5%)		

SBP — sistolic blood pressure; χ^2 — Continuity (Yates) correction; **p < 0.01

DISCUSSION

Opioid reliability-related debates are still common about patients in ED and it is required reliable data on opioid efficacy and safety in ED patients. Unfortunately, randomized controlled trials and studies have focused on classical opioids, especially morphine and its derivatives. In studies in the literature, the reported incidence of tramadol adverse events is highly variable. Niemi-Murola et al. reported a wide range of opioid-related short-term adverse events, ranging from 4%–46% due to small sample size, in a review of the adverse events of opioid agents that are given in ED setting in 2011 [10]. In a retrospective study that is involving 31.742 patients, Daoust et al. reported that all adverse event incidence is 5.9% and the most common adverse events are nausea-vomiting, hypotension, and desaturation [11]. Cepeda et al reported that the incidence of all adverse events was 8%; reported nausea and vomiting rate of 26% and a respiratory depression incidence of 1.5% [12].

In this study, the rate of patients who developed adverse event after treatment was 21.1%; the adverse events were 74.4% of nausea, 32.6% of dizziness and 23.3% of vomiting.Variable numbers were included in the literature, but the incidence of adverse events was higher than most studies. In these studies, However, if major adverse event rates such as respiratory depression and minor adverse events such as nausea and vomiting were evaluated separately, it is seen that the adverse event rates of minor adverse events were similar, even lower, to those of our study [12]. In this study, there were no patients with any major adverse event. One reason for this is that the drug had not already been administered to patients who were hypotensive, desaturate, allergic persons, after the pre-evaluation of the relevant physician, as the common opioid side effects were well-known. The frequency and rate of developing adverse events are in accordance with the short-term adverse events reported in the literature.

In addition, opioid-related adverse event development is affected by many factors. For example, female patients are more likely to have nausea and vomiting; elderly patients are less prone to vomiting and developing more respiratory depression [13–15]. A study conducted in 2015, it is reported that more adverse events in the female gender, patients older than 65 years, patients receiving medication via iv route and patients with chronic obstructive pulmonary disease (COPD) [11]. Similarly, there are studies reporting that the incidence of adverse events, especially nausea and vomiting are higher in females in the literature [18, 19]. Many studies have reported that females have more numerous and frequent pain and more chronic symptoms than men [16]. In our study, there was no statistically significant difference in adverse event development in terms of gender. This may be due to changes in socialization and social rules, the frequency of abuse and trauma, or the frequency of depressive and anxiety disorders.

Several studies have supported that the incidence of adverse events in elderly patients is higher than younger patients [10–13]. Cepeda et al. reported that the incidence of adverse events increased as the age increased, at the same time the risk of respiratory depression increased, and the risk of nausea and vomiting decreased in their studies in which 8855 patients were evaluated [12]. It is reported that more frequently hypotension is developed in patients older than 65 years in another study [11].

There was a single randomized controlled trial in which only patients older than 65 years were assessed, which is the result of a lower rate of adverse events than other studies in the literature [17]. This lower rate of adverse events is attributed to the administration of opioid analgesics in half dose. Similar to the literature, in our study, the incidence of adverse events increases as age increases. Increased adverse events can be explained with decreased clearance of opioids, prolongation of elimination half-life and low distribution volume, namely pharmacokinetic differences in the elderly [12]. However, unlike the literature, the cut-off value for age was found to be 56 in our study. This can be attributed to the low age-average of the participants of the study.

In the literature, in the ED setting, there were no studies investigating the relationship between vital signs and adverse events development in patients receiving iv tramadol. Only in a study conducted in 2015, that were evaluated adverse events of opioid agents, it is reported that tachycardic patients had more frequently hypotension. However, no cut-off pulse rate is mentioned in this study, and this adverse event is not especially worked on the tramadol [11]. In this study, patients with lower SBP than 105 mm Hg and higher pulse rate than 90 beats per minute were more likely to develop adverse events. The more frequently adverse event development in tachycardic patients is consistent with the literature.

STUDY LIMITATIONS

The first limitation of this study is that the authors do not have information on whether the drug is administered at the optimal dose since the patient's weight is not known. Another limitation is that adverse events following drug administration are recorded only according to patient's symptoms. Detecting changes in vital signs by re-recording vital findings may be a separate study topic.

CONCLUSION

In this study, it was aimed to identify a set of rules that could be used in predicting adverse event development in patients who are given iv tramadol treatment in emergency setting. The incidence of adverse events was found to be statistically significantly higher in patients older than 56 years of age, patients with a SBP of 105 mm Hg or less and patients with a pulse rate 90 beats/min or higher. Multi-centre, prospective studies with larger patient groups are needed to support these results.

Funding and support: None.

Conflict of interest: All authors declare that they have no conflict of interest.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

REFERENCES

1. Cordell WH, Keene KK, Giles BK, et al. The high prevalence of pain in emergency medical care. Am J Emerg Med. 2002; 20(3): 165–169, doi: 10.1053/ajem.2002.32643, indexed in Pubmed: 11992334.
2. Grenman D, Niemi-Murola L, Kalso E. Management of pain in a surgical emergency unit—Underlying factors affecting its delivery. Acute Pain. 2008; 10(3-4): 137–144, doi: 10.1016/j.acpain.2008.05.013.
3. Pain management in the emergency department. Annals of Emergency Medicine. 2004; 44(2): 198, doi: 10.1016/j.annemergmed.2004.04.003.
4. Smith MD, Wang Y, Cudnik M, et al. The effectiveness and adverse events of morphine versus fentanyl on a physician-staffed helicopter. J Emerg Med. 2012; 43(1): 69–75, doi: 10.1016/j.jemermed.2011.05.018, indexed in Pubmed: 21689900.
5. Institute for Safe Medication Practices. ISMP's list of high alert medications. https://ismp.org/Tools/highalertmedications.pdf (29.06.2010).
6. Barkin RL. Extended-release Tramadol (ULTRAM ER): a pharmacotherapeutic, pharmacokinetic, and pharmacodynamic focus on effectiveness and safety in patients with chronic/persistent pain. Am J Ther. 2008; 15(2): 157–166, doi: 10.1097/MJT.0b013e31815b035b, indexed in Pubmed: 18356636.
7. Wu CL, Naqibuddin M, Fleisher LA. Measurement of patient satisfaction as an outcome of regional anesthesia and analgesia: a systematic review. Reg Anesth Pain Med. 2001; 26(3): 196–208, doi: 10.1053/rapm.2001.22257, indexed in Pubmed: 11359218.
8. Schug SA. Patient satisfaction--politically correct fashion of the nineties or a valuable measure of outcome? Reg Anesth Pain Med. 2001; 26(3): 193–195, doi: 10.1053/rapm.2001.21433, indexed in Pubmed: 11359217.
9. Wu CL, Hurley RW, Anderson GF, et al. Effect of postoperative epidural analgesia on morbidity and mortality following surgery in medicare patients. Reg Anesth Pain Med. 2004; 29(6): 525–33; discussion 515, indexed in Pubmed: 15635510.

10. Niemi-Murola L, Unkuri J, Hamunen K. Parenteral opioids in emergency medicine — A systematic review of efficacy and safety. Scand J Pain. 2011; 2(4): 187–194, doi: 10.1016/j.sjpain.2011.05.008, indexed in Pubmed: 29913751.
11. Daoust R, Paquet J, Lavigne G, et al. Impact of age, sex and route of administration on adverse events after opioid treatment in the emergency department: a retrospective study. Pain Res Manag. 2015; 20(1): 23–28, doi: 10.1155/2015/316275, indexed in Pubmed: 25664538.
12. Cepeda MS, Farrar JT, Baumgarten M, et al. Side effects of opioids during short-term administration: effect of age, gender, and race. Clin Pharmacol Ther. 2003; 74(2): 102–112, doi: 10.1016/S0009-9236(03)00152-8, indexed in Pubmed: 12891220.
13. Bijur PE, Esses D, Birnbaum A, et al. Response to morphine in male and female patients: analgesia and adverse events. Clin J Pain. 2008; 24(3): 192–198, doi: 10.1097/AJP.0b013e31815d3619, indexed in Pubmed: 18287823.
14. Zun LS, Downey LaV, Gossman W, et al. Gender differences in narcotic-induced emesis in the ED. Am J Emerg Med. 2002; 20(3): 151–154, doi: 10.1053/ajem.2002.32631, indexed in Pubmed: 11992331.
15. Cepeda MS, Farrar JT, Baumgarten M, et al. Side effects of opioids during short-term administration: effect of age, gender, and race. Clin Pharmacol Ther. 2003; 74(2): 102–112, doi: 10.1016/S0009-9236(03)00152-8, indexed in Pubmed: 12891220.
16. Barsky AJ, Peekna HM, Borus JF. Somatic symptom reporting in women and men. J Gen Intern Med. 2001; 16(4): 266–275, indexed in Pubmed: 11318929.
17. Chang AK, Bijur PE, Gallagher EJ. Randomized clinical trial comparing the safety and efficacy of a hydromorphone titration protocol to usual care in the management of adult emergency department patients with acute severe pain. Ann Emerg Med. 2011; 58(4): 352–359, doi: 10.1016/j.annemergmed.2011.03.003, indexed in Pubmed: 21507527.