Emergency Department Administration of Oxycodone by Nurses Treating Musculoskeletal Pain: An Observational Prospective

Mansour Khoury MD[1], Sigalit Caspi RN[2], Ruth Stalnikowics MD[2], Elad Peless RN[2], Ela Raiizman RN MA[3] and Shaden Salameh MD MHA[2]

[1]Hebrew University Hadassah Medical School, Jerusalem, Israel
[2]Department of Emergency Medicine, Hadassah University Hospital Mount Scopus, Jerusalem, Israel
[3]Szold School of Nursing, Hadassah–Hebrew University, Jerusalem, Israel

ABSTRACT: **Background:** Acute musculoskeletal pain is one of the most commonly reported symptoms among patients visiting the emergency department (ED). Treatment with over-the-counter pain medications, given by nurses, results in improved pain management and reduces the waiting time to drug administration without significant side effects. Opioid analgesics are extensively used for acute pain in the ED. Compared to morphine, oxycodone has a much more specific pharmacological activity, higher analgesic potential, and more tolerable side effects.

Objectives: To assess the degree of pain reduction using different protocols, including dypirone and oxycodone given by nurses, in treating acute musculoskeletal pain in the emergency department (primary outcome) and to evaluate the need for rescue medications (secondary outcome).

Methods: This observational prospective clinical trial compared two groups of 50 patients, each one visiting the ED due to musculoskeletal pain. One group was treated with dipyrone syrup and the other was treated with oxycodone syrup. The primary outcome was pain reduction measured by the Numeric Rating Scale (NRS). The secondary outcome was the difference in need for rescue medications.

Results: The reduction in the NRS was greater in the patients treated with oxycodone. This finding was statistically and clinically significant ($P < 0.001$). The need for rescue medications was also significantly reduced in this group of patients ($P = 0.007$).

Conclusions: This study showed that the administration of over-the-counter oxycodone syrup by nurses decreases the post-treatment pain reported by patients, reduces the need for rescue medications, and increases the satisfaction of the medical staff.

IMAJ 2018; 20: 281–285

KEY WORDS: musculoskeletal pain, oxycodone, dypirone, emergency department (ED), over-the-counter medication

Oligoanalgesia is defined as the under-treatment of pain. This phenomenon is quite common among referrals to the emergency department (ED). Despite the efforts being made, pain relief medications (PRMs) are not used enough, and delays in pain treatment are still common [1,2]. Todd and colleagues [3] conducted a multicenter prospective study on pain management in the ED at 20 different medical centers in the United States and Canada. Pain intensity was evaluated using the Numeric Rating Scale (NRS). In their study, only 60% of patients received PRMs, and treatment was delayed for most patients. Of the participants who came to the ED, 74% still endured moderate to severe pain at discharge, indicating that oligoanalgesia remains a common problem in treatment at the ED.

Acute musculoskeletal pain (AMSP) is one of the most common symptoms among patients visiting the ED [4,5]. Treatment and evaluation of AMSP among patients admitted to the ED is an integral part of a nurse's assessment. Pain evaluation is the fifth vital sign and is checked routinely at admission. PRMs are given regularly following a physician's prescription. Stalnikowicz and colleagues [6] found that treatment with over-the-counter (OTC) pain relief medications, such as dypirone syrup (1 gram) and paracetamol (0.5 gram), resulted in improved pain management including a reduction in pain intensity and shortening of the waiting time to drug administration. Yet, despite OTC protocols for pain management in patients visiting the ED, the response was still unsatisfactory and a high percentage of patients required rescue medications.

Many hospitals have protocols for administration of opiate analgesics by nurses. This protocol contributes to a reduction in the waiting time for PRMs and results in more effective pain relief [7,8]. Kelly and colleagues [7] found that the administration of opiate analgesics for pain relief, most often morphine, by a nurse reduced the waiting time to drug administration, and had no significant side effects. Oxycodone, another effective opiate for the treatment of acute pain, has a much more specific pharmacological activity, higher analgesic potential, and more tolerable side effects profile [9]. It is administrated faster than

morphine, and 30 minutes after administration, it has the same analgesic effect [10].

The evidence supported the need to empower nurses to provide stronger analgesics without the need of physicians' orders. The aim of our study was to investigate the influence of the administration of oxycodone compared to dypirone on pain severity (primary outcome) and on the need for rescue pain relief medications for better analgesia (secondary outcome).

PATIENTS AND METHODS

STUDY SETTING AND POPULATION

We designed an observational prospective clinical trial to compare the efficacy of oxycodone and dypirone in ED patients with AMSP. The study was approved by the institutional review board. The local ethics committee of the medical center exempted the study from informed consent as it was an observational study.

Patients were eligible for enrollment if they were older than 16 years of age, were admitted to the ED, presented from AMSP (< 24 hours), and had an initial pain score of at least 5 on the NRS. AMSP was defined as pain caused by injury (e.g., fractures, dislocations, injuries from traffic accidents) not involving the head, abdomen, or chest.

Patients were excluded for the following reasons: head, abdomen, or chest trauma; known allergy to any of the study medications; hepatic or renal disease; and history of opioid abuse. Patients were also excluded if they were suspected to present with paralytic ileus or an increased intracranial pressure.

STUDY PROTOCOL

The study was conducted in two phases, each designed to collect data on a convenience sample of 50 patients over two 6 month periods: January to June 2012 (group A) and January to June 2013 (group B). This gap was designed to introduce the new protocol of opioid treatment to the medical staff and implement it into the daily work protocol. ED staff members completed a course presented by physicians who were experts in pain management.

Patients enrolled in group A were treated with dypirone syrup 1 gram/5 ml while patients in group B were treated with oxycodone syrup 0.1 mg/kg.

At admission, nurses evaluated the patient's medical status, which included vital signs including pain levels according to NRS score, cause of referral, age, medical treatment, and allergies to medications.

The nurses recorded the pain severity and study medication (dose, date, and hour of administration) on the medical chart. After 30–60 minutes, pain severity was reevaluated. All patients were offered rescue medications as needed. The choice of rescue medications was not standardized and was at the discretion of the treating physician. Any side effects were recorded and treated as needed. After rescue medication was offered or administered, each patient was asked to evaluate his/her satisfaction with the medical staff in general on a scale from 0 (not satisfied at all) to 10 (fully satisfied).

SAMPLE SIZE

A difference of pain severity of 2 on the averaged NRS score between the two groups, with 5% two-tailed significance, had 80% power and is considered to be significant in a sample size of 20 patients in each group [9]. In our opinion, this is a small sample, and thus, we decided to include 50 patients within each group, which has 99% power with 5% two-tailed significance.

DATA COLLECTION

The following data were collected from each patient: age, gender, diagnosis according to ICD-9 code, date and time of admission and discharge; date and time of medical treatment; pain NRS score before and 30–60 minutes after administration of the study drug, and whether there was a need for rescue medications.

The patients were divided into four groups based on diagnosis [Table 1]. Each group included patients with a similar diagnosis category as follows:

- Category 1: Extremity fractures and dislocations
- Category 2: Cuts and scratches, damage to the skin and subcutaneous tissue
- Category 3: Trauma
- Category 4: Other

Table 1. ICD-9 codes and diagnosis of the enrolled patients

ICD-9 Code	Diagnoses
Category 1: Extremity fractures and dislocations	
805–809	Fracture of neck and trunk
810–829	Fracture of upper and lower limb
830–839	Dislocation
840–848	Sprains and strains of joints and adjacent muscles
Category 2: Cuts and scratches, damage to the skin and subcutaneous tissue	
880–897	Open wound of upper and lower limb
900–904	Injury to blood vessels
910–919	Superficial injury
996–999	Complications of surgical and medical care, NOS
Category 3: Trauma	
E810–E819	Motor vehicle traffic accidents
E820–E825	Motor vehicle non-traffic accidents
E826–E829	Other road vehicle accidents
E880–E888	Accidental falls
E960–E969	Homicide and injury purposely inflicted by other persons
Category 4: Other	
710 – 719	Arthropathies and related disorders
720 – 724	Dorsopathies
725 – 729	Rheumatism, excluding the back
730 – 739	Acquired musculoskeletal deformities

NOS = not otherwise specified

These codes were determined by the treating physician. The categories were designed to correlate with the ICD-9 identifications; however, these categories are not the actual diagnosis. We encountered approximately 100 different diagnoses and decided to classify each under a relevant category.

DATA ANALYSIS

Statistical analyses were performed using IBM Statistical Package for the Social Sciences statistics software for Windows, version 22 (SPSS, IBM Corp, Armonk, NY, USA). Quantitative variables are presented as means and standard deviation (SD). Categorical variables are presented as numbers and percents. Quantitative variables between the two groups were compared using Student's *t*-test. Quantitative comparison of changes between four groups was made using analysis of variance (ANOVA). Categorical variables between the study groups were compared using a chi-square test. A relationship between two quantitative variables was assessed by calculating the Pearson correlation coefficient. Variables that were associated statistically significant to the dependent dichotomous variable (outcomes) were inserted into a multivariate logistic regression model using stepwise regression. Through this model, the adjusted odds ratio (adjusted OR) and the 95% confidence interval (95%CI) were calculated. All statistical tests were two-tailed and $P < 0.05$ was considered to be statistically significant.

RESULTS

The study was comprised of 100 patients who were divided into two groups of 50 patients each. Patient characteristics were similar in both study groups [Table 2]. Mean age was 38 ± 15.8, length of hospital stay was 199 ± 180.4 minutes, and time to treatment was 29.4 ± 85.7 minutes. Of the patients, 34 were female. The most common diagnosis was category 3 (32 patients). Minor side effects developed in three patients, all of whom were in group B.

Table 3 shows the results of pain NRS scores before and after treatment for the two study groups. A statistically significant reduction in pain 30–60 minutes after drug administration was reported in both groups (group A: OR 3.18, 95%CI 3.86–2.5; group B: OR 5.26, 95%CI 5.96–4.56, P < 0.001). Table 3 shows a statistically significant difference in the reduction of the NRS score after drug administration ($P < 0.001$) as well as a decrease in the need for rescue medications ($P = 0.007$) between both groups.

To assure that the type of PRM was the only factor that affected the NRS score reduction and the need for rescue medication, we examined the effect of other factors including age, gender, diagnosis, length of stay in the ED, type of PRM provided, and time from drug administration for this change.

The only factor that influenced the change in NRS significantly was the type of PRM provided ($P < 0.001$). The other factors were found to not affect it significantly.

However, the type of PRM was not the only variable significantly influencing the need of rescue medication ($P = 0.007$). NRS was also affected by patient's age ($P = 0.007$) and diagnosis ($P = 0.027$). To further investigate these results, we inserted the affecting variables into a multivariate logistic regression model using a stepwise regression, in which we checked whether the effect of the type of PRM on the need for rescue medications

Table 2. Characteristics of the study groups

Characteristics	Group A	Group B	Significance
Gender			
Male, n (%)	34 (68)	32 (65)	$P = 0.673$
Female, n (%)	16 (32)	18 (36)	
Age, years			
Mean	37.04	39.4	$P = 0.459$
Median ± SD	34.5 ± 16.53	40 ± 15.2	
Diagnosis in categories			
Category 1, n (%)	13 (26)	13 (26)	
Category 2, n (%)	13 (26)	12 (24)	$P = 0.992$
Category 3, n (%)	16 (32)	16 (32)	
Category 4, n (%)	8 (16)	9 (18)	
Length of stay in ED, minutes			
Mean	176.5	230	$P = 0.81$
Median ± SD	146 ± 103.51	167 ± 230.2	
Time to medicine administration, minutes			$P = 0.307$
Mean	20.62	38.24	
Median ± SD	12 ± 34.89	17 ± 116.12	
Reported side effects			
Yes, n (%)	0 (0)	3 (6)	$P = 0.157$
No, n (%)	50 (100)	47 (94)	

ED = emergency department, SD = standard deviation

Table 3. NRS score results and study outcomes

	Group A	Group B	Significance
NRS score before administration of PRM			
Mean	7.78	9.2	$P < 0.001$
Median ± SD	8 ± 1.83	10 ± 1.3	
NRS score after administration of PRM			
Mean	4.6	3.94	$P = 0.199$
Median ± SD	5 ± 2.78	4 ± 2.31	
NRS score reduction			
Mean ± SD (95%CI)	3.18 ± 2.405 (2.497–3.863)	5.26 ± 2.456 (4.562–5.958)	$P < 0.001$
Need for rescue medications			
Yes, n (%)	11 (22)	2 (5)	$P = 0.007$

NRS = Numeric Rating Scale, PRM = pain relief medications, SD = standard deviation, 95%CI = 95% confidence interval

Table 4. Satisfaction of patients in the study groups

	Group A	Group B	Significance
Satisfaction scale			
Mean	3.968	6.407	$P = 0.0256$
Median ± SD	3 ± 3.09	8 ± 2.89	

SD = standard deviation

was still statistically significant when it was standardized for the impact of age and diagnosis sub-categories.

Within this model, while examining the diagnosis categories variable, we merged category 1 and category 2 because no patients in category 2 needed rescue medications, which created too many cells with too little information in this specific model. It should be noted that after the merge, we still had a statistically significant result of the category's impact on the need for rescue medications ($P = 0.038$).

The effect of the type of PRM on the need for rescue medications remained statistically significant after the standardization ($P = 0.007$); however, the effect of age and diagnosis on the need for rescue medications remained statistically significant ($P = 0.006$ and $P = 0.034$, respectively).

SATISFACTION FROM MEDICAL STAFF:

Table 4 shows that patients in group B were much more satisfied with their medical treatment compared to group A. This result is also statistically significant ($P = 0.0256$).

DISCUSSION

Pain is a common reason of referral to the ED [4,5]. The role of the nursing staff is crucial in identifying and treating pain; however, there are many barriers that can hinder the administration of efficient analgesia by nurses (e.g., workload or the presence of other patients with life-threatening conditions). These barriers can limit the ability to evaluate, address, and follow pain severity. Another reason is that nurses often cannot treat pain complains independently without a doctor's prescription.

Pretorius and colleagues [12] noted that one of the most important elements to improved pain treatment is OTC protocols. However, despite efforts to raise awareness of the importance of pain treatment, under-treatment of pain continues to be a widespread problem [3,13-15].

Due to inefficient pain management of OTC (paracetamol and dypirone) administration, we felt a need for a new protocol to provide better pain control. This new protocol was based on the OTC administration of oxycodone syrup by nurses for patients referred to the ED with acute musculoskeletal pain.

Our study examined the benefits of the administration of dypirone OTC by comparing the pain NRS score reduction and the need for rescue medications.

The average reduction in pain severity on the NRS scores before and after administration of PRM in both groups was statistically and clinically significant, yet oxycodone syrup reduced the NRS more compared dypirone, which was given to group A. Analysis of the impact of confounding factors showed that none had a significant impact on the results; thus, we can conclude that the only factor determining the NRS score reduction was the type of medication administered.

The need for rescue medications was lower in group B than in group A. This finding was statistically significant, meaning that the administration of oxycodone syrup decreased the odds of asking for rescue medications. However, this outcome was influenced also by the age and diagnosis of the patient. Each additional year of a patient's age increased the odds for the need for rescue medications by 1.062, which can be attributed to the fact that older patients have a different metabolism, and most probably are being treated with multiple medications, which can affect the drug's metabolism. The effect of the diagnosis was statistically significant only in the sub-category 4. In this group, the odds for rescue medication requisition increased by approximately 12. The effect of category 4 on the need for rescue medication can be explained by its composition. This category had a great varied number of diagnoses, each with a small number of patients included, which made it difficult to analyze it statistically. It is not unreasonable to assume that the patients in this category may endure more chronic pain, which makes it even more difficult to treat.

Table 2 shows that, despite the use of oxycodone in the study group (group A), the length of stay and the number of side effects were not significantly different.

Satisfaction from medical treatment was greater ($P = 0.0256$) in the control group (group B), which shows the benefits of this protocol.

Our study has several limitations. This study is prospective observational but not randomized; with patients not recruited in parallel. One of the consequences of the study design was that the averaged basic pain score was different between both groups, and higher scores were documented in group B. Did this difference affected the degree of the pain control? Did it make it easier to relieve the pain? To the best of our knowledge, no studies have been conducted to investigate this issue.

Pain thresholds and the ability to report pain are different among different people, as well as the metabolism of medications, which is affected not only by liver or kidney function, but also by the volume and distribution of the drug and by the pain's site and blood supply. Still, this limitation is not specific to our study but is true in all studies dealing with pain management.

Finally, a selection bias might have been introduced to the study because the study groups were a convenience sample as data collectors were not always available in the ED.

CONCLUSIONS

This study showed that the administration of oxycodone syrup as an OTC decreases the pain NRS score reported by the patient and lowers the need for rescue medications, making patients much more satisfied with the medical treatment without causing serious side effects. Further studies are needed to investigate whether this protocol can decrease the number of repeat visits to the ED due to a more efficient approach to pain management. In addition, it can contribute to more satisfied patients in

addition to a more effective working environment and a much more satisfied staff.

Correspondence
Dr. S. Salameh
Dept. of Emergency Medicine, Hadassah University Hospital Mount Scopus, Jerusalem 12000, Israel
Phone: (972-2) 584-4111
Fax: (972-2) 584-4176
e-mail: shaden@hadassah.org.il

References

1. Jacob R, Shavit I. Emergency department pain management of acute abdominal pain and acute appendicitis in children. *IMAJ* 2016; 18 (11): 689-91.
2. Zimmerman O, Halpern P. Opinion survey of analgesia for abdominal pain in Israeli emergency departments. *IMAJ* 2004; 6 (11): 681-5.
3. Todd KH, Ducharme J, Choiniere M, et al. Pain in the emergency department: results of the pain and emergency medicine initiative (PEMI) multicenter study. *J Pain* 2007; 8 (6):460-6.
4. Downey LA, Zun LS. Pain management in the emergency department and its relationship to patient satisfaction. *J Emerg Trauma Shock* 2010; 3: 326-30.
5. Cordell WH, Keene KK, Giles BK, et al. The high prevalence of pain in emergency medical care. *Am J Emerg Med* 2002; 20: 165-9.
6. Stalnikowicz R, Mahamid R, Kaspi S, et al. Undertreatment of acute pain in the emergency department: a challenge. *Int J Qual Health Care* 2005; 17 (2): 173-6.
7. Kelly A, Brumby C, Barnes C. Nurse-initiated, titrated intravenous opioid analgesia reduces time to analgesia for selected painful conditions. *Can J Emerg Med* 2005; 7 (3): 149-54.
8. Fonsnocht DE, Swanson ER. Use of a triage pain protocol in the ED. *Am J Emerg Med* 2007; 25: 791-3.
9. Riley J, Eisenberg E, Müller-Schwefe G, et al. Oxycodone: a review of its use in the management of pain. *Curr Med Res Opin* 2008; 24 (1): 175-92.
10. Miner JR1, Moore J, Gray RO, et al. Oral versus intravenous opioid dosing for the initial treatment of acute musculoskeletal pain in the emergency department. *Acad Emerg Med* 2008; 15: 1234-40.
11. Hawker GA, Mian S, Kendzerska T, et al. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res (Hoboken)* 2011; 63 (Suppl 11): S240-2.
12. Pretorius A, Searle J, Marshall B. Barriers and enablers to emergency department nurses' management of patients' pain. *Pain Manag Nurs* 2015; 16 (3): 372-9.
13. Brennan F, Carr DB, Cousins M. Pain management: a fundamental human right. *Anesth Analg* 2007; 105: 205-21.
14. Sinatra R. Causes and consequences of inadequate management of acute pain. *Pain Med* 2010; 11: 1859-71.
15. Ducharme J. Clinical guidelines and policies: can they improve emergency department pain management? *J Law Med Ethics* 2005; 33: 783-90.

Capsule

Fueling T cell proliferation

Previous studies on BRCA1-associated protein-1 (BAP1) have documented its importance in suppressing the development of myeloid leukemia. BAP1 is a deubiquitinase (DUB) that acts on histone H2A monoubiquitinated at Lys119 (H2AK119ub), a chromatin modification associated with gene repression. **Arenzana** and colleagues reported that BAP1 is essential for the development of T cells in the thymus and for promoting peripheral T cell proliferation. Deletion of BAP1 impaired expression of genes associated with cell cycle progression in thymocytes and peripheral T cells. In both cases, the effect of BAP1 deletion was dependent on the DUB activity of BAP1, calling for a closer examination of the role of H2AK119ub in T cell development and differentiation.

Sci Immunol 2018; 3: eaal1953
Eitan Israeli

Capsule

Zika virus selectively kills aggressive human embryonal CNS tumor cells in vitro and in vivo

Zika virus (ZIKV) is largely known for causing brain abnormalities due to its ability to infect neural progenitor stem cells (NPC) during early development. **Kaid** et al. showed that ZIKV is also capable of infecting and destroying stem-like cancer cells from aggressive human embryonal tumors of the central nervous system (CNS). When evaluating the oncolytic properties of Brazilian Zika virus strain (ZIKVBR) against human breast, prostate, colorectal, and embryonal CNS tumor cell lines, the authors verified a selective infection of CNS tumor cells followed by massive tumor cell death. ZIKVBR was more efficient in destroying embryonal CNS tumorspheres than normal stem cell neurospheres. A single intracerebroventricular injection of ZIKVBR in BALB/c nude mice bearing orthotopic human embryonal CNS tumor xenografts resulted in a significantly longer survival, decreased tumor burden, fewer metastasis, and complete remission in some animals. Tumor cells closely resembling neural stem cells at the molecular level with activated Wnt signaling were more susceptible to the oncolytic effects of ZIKVBR. Furthermore, modulation of Wnt signaling pathway significantly affected ZIKVBR-induced tumor cell death and viral shedding. Altogether, these preclinical findings indicate that ZIKVBR could be an efficient agent to treat aggressive forms of embryonal CNS tumors and provide mechanistic insights regarding its oncolytic effect

Cancer res 2018; DOI: 10.1158/0008-5472.CAN-17-3201
Eitan Israeli