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Paracetamol-codeine compared to ketorolac for pain control in the Emergency Department

F. BUCCELLETTI, D. MARSILIANI, G. ZUCCALÀ, P. IACOMINI, L. PROIETTI, E. POLA, G. ZIRIO, M. GENITIEMPO, R. MARROCCO, C. CONTI, C. BRUNETTI, L. ROCCHI, G. MERENDI, G. D'AURIZIO, E. GILARDI, F. FRANCESCHI

Emergency Department, Catholic University of the Sacred Heart, School of Medicine, Rome, Italy

Abstract. – OBJECTIVE: Paracetamol /codeine has shown a strong analgesic activity in several studies conducted among different kind of subjects, including those with trauma. Nevertheless, its efficacy in patients accessing the Emergency Department (ED) for different kind of pain has never been tested.

PATIENTS AND METHODS: This is a cross-sectional, observational, prospective, cohort study. Inclusion criteria were patients > 18 year old presenting to the ED for localized traumatic or inflammatory pain involving only extremities. Numeric scale (NRS) was recorded thirty minutes and two hours after the administration of the analgesic therapy, consisting of 15 mg of ketorolac or 1000 mg/60 mg of paracetamol/ codeine, both orally.

RESULTS: Two-hundred patients were consecutively enrolled; 87 were treated with paracetamol/codeine and 113 with ketorolac. The combination paracetamol/codeine resulted to be not inferior to ketorolac in non-traumatic pain group and trauma group (p = 0.635 and p = 0.482, respectively). Compared to ketorolac, the combination paracetamol/codeine exerted a significantly higher analgesic activity in patients with fractures and muscular pain (p = 0.044) and was more effective in acute pain (p = 0.002), with a significant effect two hours after the administration (p = 0.029).

CONCLUSIONS: Paracetamol/codeine is equivalent to ketorolac in non-traumatic pain and post-traumatic pain, but is superior in acute pain and in patients with fractures and muscular pain. Those results play in favor of the use of the combination paracetamol/codeine in patients accessing the ED for non-traumatic or traumatic pain of the extremities.

Key Words:
Paracetamol, Codeine, NSAIDs, Pain, Trauma.

Introduction

Pain is the most common reason to seek medical attention. The ability to deliver analgesics in a very short time is one of the most important tasks for any Emergency Department (ED), since sometimes patients need to wait hours before seeing a doctor due to overcrowding[1,2]. Non steroideal antinflammatory drugs (NSAIDs), opioids and paracetamol are the most common drugs prescribed[3].

Somatic pain is commonly caused by trauma or inflammation such arthritis. The treatment usually consists in a prescription of NSAIDs. This kind of drugs are the most used drugs class as pain killer[4]. Unfortunately, NSAIDs have several class-regarded side effects which became more serious in elderly patients[5]. The most known side effect is bleeding, mostly by the GI tract, especially in patient who have previous history of peptic ulcer or gastritis and in post-surgery patients[6]. Moreover, their use may increase mortality for cardiovascular causes especially in patient who are in treatment whit aspirin for secondary prevention of transient ischaemic attack (TIA)/stroke or underwent coronary revascularization with stenting[7]. Many NSAIDs, in fact, may reduce glomerular filtration rate (GFR), possibly precipitating acute heart failure[8] and interfere with aspirin for platelet receptors, resulting in an incomplete platelet inhibition[9]. Finally, many evidences showed a role of the majority of NSAIDs, including ketorolac, in the precipitation of acute coronary syndromes[10,11]. Nevertheless, ketorolac still represents one of the most used analgesic in the EDs[12].

Opioids, such as tramadol, oxycodone, codeine and morphine, represent another option for pain treatment. Those drugs are safer in hemorrhagic patients and are not contraindicated in patients under primary or secondary antiplatelet treatment[13]. Unfortunately, they may alter the mental status, which in turn may reduce the possibility to assess and to monitor the neurological condition, especially in patients with traumatic brain injury[14]. In order to reduce those negative effects and the risk of an unintentional overtreatment, new formulation

Corresponding Author: Franceschi Francesco, MD; e-mail: francesco.franceschi@rm.unicatt.it

of opiates combined with other analgesic drugs, including paracetamol are now available[15]. This approach allows to reduce the dosage of both drugs as well as side effects and this is why the combination paracetamol/ codeine is one of the most used in the clinical practice[16].

Paracetamol is commonly used as antipyretic and analgesic drug all over the world. It has no effect on inflammation or on platelet aggregation, differently from NSAIDs, at least when administered at moderate doses[17]. Codeine is a semi-synthetic opiate analgesic derived from an opium alkaloid. Although its precise mechanism of action is still partially unknown, some studies have evidenced that it may act as a μ-opioid receptor partial-agonist. This ability to recognize the μ-opioid receptor is responsible for its strong analgesic activity in patients with post-operative, malignant and non malignant pain[13,18].

While the combination paracetamol/codeine has shown a good analgesic action in several studies conducted among different kind of subjects, including trauma patients[19], its efficacy in patients accessing the ED for different kind of pain has never been tested.

In this study, we have consecutively measured pain level at the ED visit time, thirty minutes and two hours after ketorolac or paracetamol/codeine administration to compare their effects in consecutive patients presenting to the ED for localized traumatic or inflammatory pain involving extremities.

Patients and Methods

Study Design

This is a cross-sectional, observational, prospective, cohort study (pseudo-randomized). The study was conducted according to the Declaration of Helsinki and was approved by local Ethics Committees. Inclusion criteria were patients > 18 year old presenting to the ED for localized traumatic or inflammatory pain involving only extremities. Exclusion criteria were history of renal failure on hemodialysis, pregnancy, hemodynamic unstable patients, unconscious patients (Glascow Coma Scale < 15), high energy trauma (i.e. falling from more than 3 feet or equivalent) migraine, headache or visceral pain.

Numeric scale (NRS)[20,21] was recorded by a research assistant at the time of enrolment, and thirty minutes and two hours after the administration of the analgesic therapy. Study was designed to include totally 200 patients treated with ketorolac or with paracetamol/codeine to achieve 80% of the power.

Patients enrollment lasted 5 months in a single tertiary care, university ED. As per institutional protocol, ketorolac was administered at the dosage of 15 mg while paracetamol/codeine at the dosage of 1000 mg/60 mg, both orally. Drugs were administered by the attending physician after a full medical evaluation. ED physicians were instructed to administer alternatively the two drugs in a consecutive 1:1 ratio, except when patient reported allergy to one of the drug. Therefore, this was a pseudo-randomized trial.

Research assistants' task was just to systematically record pain level and patients clinical information in a prospective way, and there were no other interventions for research purpose other than routine care.

Statistical Analysis

STATA 11.0 (Stata Corp, LP, College Station, TX, USA) was used for statistical analysis. For each patient demographics, medical and surgical history, home treatment, mechanism of trauma, pain quality, duration and localization were recorded along with pain treatment received and pain level measures in a dedicated and anonymous database. Also final diagnosis and ED disposition were included.

Cohort consisted, therefore, in two groups (ketorolac versus paracetamol/codein). First, the two groups were compared for baseline differences using non parametric Mann-Withney U test or chi squared test depending upon the type of variable considered. p values less than 0.05 were considered to be significant. Subsequently, pain levels measures with both scales were normalized for baseline clinical characteristics differences using multivariate linear regression model. In this way, a direct comparison between ketorolac and paracetamol/codeine efficacy was a possible limiting confounding factor due to a non strong-randomized design.

Finally, none of the patients reported significant side effects; however, we have to take into account that this may be due to the very short time of observation (2 hours).

Results

Two-hundred patients were consecutively enrolled; 87 were treated with paracetamol/codeine

Table I. Demographics and baseline clinical characteristics.

	Ketorolac group (N = 113)	Paracetamol/codeine group (N = 87)	*p* value
Age	30.0-67.2	28.0-69.2	0.98
Male	60 (53.1%)	42 (48.3%)	0.50
Pain duration < 24h	86 (79.6%)	59 (77.6%)	0.75
Traumatic pain	76 (67.3%)	58 (66.7%)	0.93
Inflammatory pain	37 (32.7%)	29 (33.3%)	0.93
Joint pain	28 (25.0%)	23 (26.4%)	0.90
Bone pain	44 (39.3%)	37 (42.5%)	0.90
Muscular pain	40 (35.7%)	27 (31.0%)	0.90
Numeric scale pain baseline	9-6	8-6	

and 113 with ketorolac. Table I shows demographics and baseline clinical characteristics for the two groups. Patients in the treatment groups did not globally differ in terms of comorbidity prevalence. Patients in the trauma group were younger and with less comorbidities than patients presenting with non-traumatic pain ($p < 0.05$), as expected.

To compare drug response (i.e. reduction in pain level) between the two groups, multivariate linear regression was used with age, duration and kind of pain (as described by patients) as covariates (Figure 1). The two drugs showed a similar analgesic efficacy.

Subgroups analysis was then carried out and we compared the analgesic effect in non-traumatic pain and post-traumatic pain. The combination paracetamol/codeine resulted to be not inferior to ketorolac in non-traumatic pain group and trauma group (non traumatic pain: T0 $p = 0.835$, T1 $p = 0.908$, T2 $p = 0.635$; trauma group: T0 $p = 0.482$, T1 $p = 0.770$, T2 $p = 0.482$).

The analgesic efficacy based on the anatomic source of pain (bone, muscular and articular) has also been evaluated. While the baseline pain level was similar in all groups, the combination paracetamol/codeine exerted a significantly higher analgesic activity in patients with fractures and muscular pain (T2 $p = 0.030$ and T2 $p = 0.044$ respectively) compared to ketorolac.

The effect on acute and chronic pain was also evaluated. While there was no statistical significant difference in chronic pain relief between the two drugs (T0 p: 0.664; T1 p: 0.347; T2 p: 0.319), acetaminophen/codeine was significantly more effective than ketorolac in acute pain (p: 0.002), with a significant effect two hours after the administration (T0 p: 0.248; T1 p: 0.029) and irrespectively of the anatomic site of pain except for that localized in the arms ($p = 0.03$).

Discussion

Pain management in the hospital is becoming a relevant problem in the last years especially when confined to the ED[1,22,23]. In this setting, pain is indeed the first cause of access and doctors need to know exactly how to treat it, without underestimating timing and safety[1].

The aim of this study was to compare the use of paracetamol/codeine versus ketorolac in the ED in minor traumatic and non-traumatic pain. In literature, there are different reports comparing the effect of those drugs in adults among different settings (post-operatory day surgery,

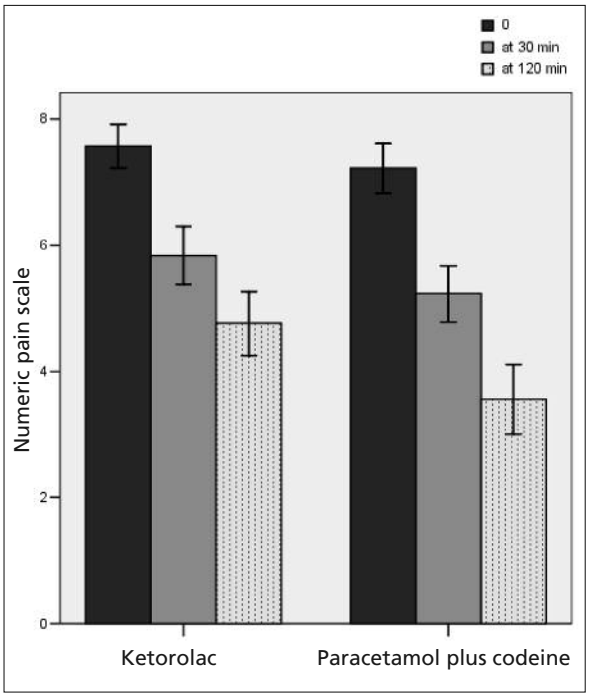

Figure 1. Total patients comparison between ketorolac and paracetamol/codeine.

dental pain, and others)[24-26] but there are only a few studies performed in the ED, mostly involving polytrauma patients or subjects with low back pain[19].

In a population with an increasing prevalence of chronic diseases, an effective and safe strategy for pain management is mandatory. Ideally, analgesic drugs should not interfere or exacerbate chronic syndromes such renal failure, coronary artery disease and heart failure and should not interfere with concomitant treatment, including antiplatelet drugs. On this topic, recent researches clearly showed that there is a strong association between using of NSAIDs and increased mortality[10-27].

In our work, the association paracetamol/codeine is not inferior to ketorolac in most cases, except when pain is primarily caused by inflammation, providing a good pain relief. Paracetamol/codeine resulted to be not inferior to ketorolac both in non-traumatic pain group and trauma group. Moreover, the higher efficacy of paracetamol/codeine was observed in patients with fractures and muscular pain. While the effect of both drugs was similar in chronic pain, acetaminophen/codeine was significantly more effective than ketorolac in acute pain, within two hours after the administration irrespective of the anatomic site of pain except for that localized in the arms.

Conclusions

Those results clearly show that the combination paracetamol/codeine is a good alternative to ketorolac in most of the settings analyzed by this study. Those findings are of crucial importance especially for patients with cardiovascular risk factors, high risk of GI bleeding or with all comorbidities contraindicating the use of NSAIDs.

Nevertheless, this study was not a randomized trial since physicians were free to decide which drug administer although they were instructed to do so in a 1 to 1 ratio (pseudo-randomization). Moreover, focusing our attention at the first two hours after the administration of the analgesic drug, we did not perform a long-term follow up, which in turn did not allow us to assess the occurrence of potential side effects. Further studies are thus needed in order to confirm our findings.

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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