Abstract. – Introduction: The management of pain in polytrauma patients is mandatory. While non-steroidal anti-inflammatory drugs (NSAIDs) represent the most used drugs in polytrauma patients, their use may be associated with an increased risk of haemorrhage. Opioids may represent a valid alternative to NSAIDs either alone or in combination with acetaminophen. Whether their efficacy is comparable to that produced by NSAIDs in polytrauma patients has never been studied.

Patients and Methods: 60 polytrauma patients were enrolled for this study. 30 patients were treated with acetaminophen 1000 mg plus codeine 60 mg tid for 24 hours (Group A), while the remaining 30 with ketorolac 10 mg qid for 24 hours (Group B). Pain intensity has been evaluated using an analogical visual scale (VAS) ranging from 0 (no pain) to 10 (very severe pain). The level of pain was evaluated at enrolment (T0) as well as after 2 (T2), 12 (T12) and 24 (T24) hours from the starting of the analgesic therapy. Results obtained by the group A were compared with those reported by the group B.

Results: T0: Group A mean score was 6.4±1.5 compared with 6.6±1.5 of Group B (p=ns); T2: Group A mean score was 3.4±2.8, compared with 3.5±2.4 of group B (p=ns); T12: Group A mean score was 3.4±3.4, compared with 3.5±3 of Group B (p=ns); T24: Group A mean score was 2.9±1.5, compared to 3.0±1.6 of Group B (p=ns). All those drugs determined a significant reduction of pain intensity during the course of therapy.

Conclusions: Acetaminophen plus codeine is effective in pain control in polytrauma patients at least in our series. It may represent a valid alternative to NSAIDs, especially in patients with a documented haemorrhage or with a high hemorrhagic risk.

Key Words: Polytrauma, Acetaminophen, Codeine, Ketorolac.

Introduction

Polytrauma is a clinical condition defined by the following criteria: injuries of at least two long bone fractures, or one life-threatening injury and at least one additional injury, or severe head trauma and at least one additional. Treatment of acute pain in polytrauma patients is mandatory; ideally, we should administrate a drug with a very strong analgesic activity and a reduced risk of side effects. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used also in polytrauma patients; nevertheless, we should take into consideration that polytrauma represents a haemorrhagic risk and bleeding is a possible side effect of NSAIDs.

Ketorolac is one of the most used analgesic drugs, classified as NSAID. While it possesses a very strong activity in pain control, is also characterized by the occurrence of some potential dangerous side effects, including bleeding. In fact, digestive upper GI tract bleeding is not so rare in patients treated with ketorolac, due to a toxic effect on gastro-duodenal mucosa, which is increased in patients with a previous history of peptic ulcer or chronic gastritis and in post-surgery patients.

Opioids, such as tramadol, oxycodone, codeine and morphine, represent an alternative to NSAIDs. One of the main side effects of those drugs is mental status alteration, which can make difficult to clinically evaluate polytrauma patients, especially those with a head trauma. Interestingly, opioids may also be used in combination with acetaminophen; in this case the synergistic action of two different molecules increases the analgesic activity, reducing at the same time either the dosage or the occurrence of side effects. On this subject, a combination of acetam-
minophen plus codeine is available as painkiller medication⁹.

Acetaminophen is a very known antipyretic and analgesic drug⁹,¹⁰,¹¹. It has no effect on inflammation as well as in platelet aggregation like all NSAIDs. Codeine is a semisynthetic analgesic opioid derived from an opium alkaloid. Although its precise mechanism of action is still unknown, some studies have shown that Codeine is a mu-opioid receptor partial-agonist, which confers to this drug strong analgesic properties, as demonstrated by its efficacy in the treatment of different kind of pain, including postoperative, malignant and non-malignant¹². Acetaminophen plus codeine is indicated in patients with NSAIDs contraindications such history of peptic ulcers, allergic asthma or haemophilia. An another important characteristic of this combination is the possibility to treat patients with concomitant use of anti-platelet or anti-coagulant drugs, as it has no effect on platelet aggregation All those characteristics make this drug more suitable for pain management in polytrauma patients than NSAIDs¹³.

Up to now, there are no data on the efficacy of acetaminophen plus codeine compared to ketorolac in polytrauma patients in acute setting; therefore, we designed a pilot trial able to verify this issue.

Patients and Methods

Sixty polytrauma patients admitted to the Emergency Department were enrolled. All patients underwent full evaluation by the trauma team, which included FAST exam, “total body” CT scanning and blood tests. All those patients were considered to be stable by the trauma team, without expectation of immediate surgical intervention and Glasgow coma scale > 13; thirty patients were treated with acetaminophen plus codeine (Group A) while the remaining 30 with ketorolac (group B). For safety reasons, patients with active bleeding were automatically included in the Group A as ketorolac may increasing the haemorrhagic risk¹⁴.

Group A was composed by 22 males and 8 female with a mean age of 46±18 yrs. In this group all patients had head trauma; among these, 12 patients presents an intracranial haemorrhage (10 males, mean age 43±18 years) differently form the remaining 18 (13 males, mean age 47±20 yrs). All patients had chest and abdominal trauma, both without severe injuries. Six patients (5 males, mean age 44±18 yrs) showed fractures, (2 pelvic, 2 tibial and 2 clavicular fractures), while 18 subjects reported lumbo-sacral traumas (16 males, mean age 44±17 yrs).

Group B consisted of 23 males and 7 females with a mean age of 45±19 yrs. In this group none of the patients reported head trauma. On the other hand all patients showed chest and abdominal trauma, 7 patients (5 males, mean age 44±18 yrs) had bone fractures, (3 pelvic, 2 femoral, 1 clavicular and 1 calcaneal fractures). Eighteen patients had lumbo-sacral traumas (16 males, mean age of 44±17 yrs).

The main characteristics of the two group of patients enrolled for this study are summarized in the Table 1.

Results

Group A

Acetaminophen plus codeine determined a progressive and significant reduction of the pain score during the entire course of the treatment. In particular, the main pain score was 6.4±1.5 at enrolment and decreased to 3.4±2.8 after 2 hours (p<0.008), 3.4±3.4 after 12 hours (p<0.01) and 2.9±1.5 (p<0.001) after 24 hours from the starting of the analgesic treatment (Figure 1). No adverse effects were observed among treated subjects, except for light dizziness in only one pa-
Table 1. General characteristics of polytrauma patients enrolled for this study.

<table>
<thead>
<tr>
<th>Groups</th>
<th>Acetaminophen + Codeine</th>
<th>Ketorolac</th>
</tr>
</thead>
<tbody>
<tr>
<td>No patients</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td>Mean age</td>
<td>46 ± 18</td>
<td>45 ± 19</td>
</tr>
<tr>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>No patients</td>
<td>22</td>
<td>8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Region interested by trauma</th>
<th>Acetaminophen + Codeine</th>
<th>Ketorolac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head (with hemorrhage)</td>
<td>23 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Chest</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Abdomen</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>Lumbo-sacral</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Fractures</td>
<td>5</td>
<td>1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subsites of fracture</th>
<th>Acetaminophen + Codeine</th>
<th>Ketorolac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvis</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Femur</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Tibia</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Heel</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Clavicle</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

Patient with cerebral haemorrhage. However, in this case it was not possible to clearly discriminate whether the symptom was related to the drug or to the cerebral damage.

**Group B**

Ketorolac determined a significant decrease of the pain score during the entire course of the treatment. In particular, the main pain score was 6.6±1.5 at enrolment and decreased to 3.5±2.4 after 2 hours (p<0.009), 3.5±3 after 12 hours (p<0.02) and 3.0±1.6 (p<0.001) after 24 hours from the starting of the analgesic treatment (Figure 2). Two patients reported epigastric pain, which required the concomitant administration of proton pump inhibitors.

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**Figure 1.** Effect of the administration of acetaminophen plus codeine in polytrauma patients evaluated at enrolment (T0) and 2 (T2), 12 (T12) and 24 (T24) hours after the starting of the analgesic treatment. Acetaminophen plus codeine determined a significant decrease of the pain score during all the observational time.
Group A vs Group B

No significant differences were found between Group A and Group B concerning the mean pain score obtained at different time of observation. In particular, at enrolment Group A mean score was 6.4±1.5 compared with 6.6±1.5 of Group B (p=ns). Two hours after the starting of the therapy, the mean pain score was 3.4±2.8 in Group A and 3.5±2.4 in Group B (p=ns), while 12 hours later the main pain score 3.4±3.4 in Group A,
compared with 3.5±3 of Group B (p=ns). Finally, 24 hours after the starting of the analgesic treatment, the main pain score of Group A was 2.9±1.5, compared to 3.0±1.6 of Group B (p=ns) (Figure 3).

Discussion

This study shows that the analgesic effect provided by the combination of acetaminophen plus codeine is equivalent to those obtained by ketorolac in polytrauma patients, during an observational time of 24 hours. In fact, we observed a significant reduction of the pain score in patients treated with acetaminophen plus codeine during the entire course of the treatment and this effect did not differ with that obtained by ketorolac. Interestingly, we did not observed significant side effects in patients treated with acetaminophen plus codeine.

Besides the efficacy showed by the combination of acetaminophen plus codeine, there are three main points making this drug more suitable than ketorolac in the treatment of polytrauma: (1) it can be safely used also in patients with cerebral hemorrhage; (2) it requires 3 administration per day only compared to 4 of ketorolac, making this drug more versatile especially in the acute setting; 3) it does not cause GI side effects.

Haemorrhage, in particular represents a main issue in polytrauma patients16 and it is known that NSAIDs increase bleeding risk17. Using a drug able to strongly and quickly control the pain without increasing the haemorrhagic risk may then represent a significant goal in the treatment of polytrauma patients.

Another interesting aspect related to the use of acetaminophen plus codeine is that it has been able to reduce the pain score as low as 2.9 in our patients; since the World Health Organisation stated that a pain score higher than 3 is not acceptable for patients admitted to the hospital, even though this is intended for cancer pain18, we may acknowledge that this drug respected this recommendation.

In conclusion, the association of acetaminophen plus codeine represents a valid alternative to ketorolac in the treatment of the pain in polytrauma patients, up to 24 hours after the trauma occurred. Further studies are now needed in order to evaluate its effect in polytrauma patients during a more prolonged time of observation.

References

2) HOYT DB. A clinical review of bleeding dilemmas in trauma. Semin Hematol 2004; 41: 40-43.


