

# Efficacy and tolerability of fixed association of oxycodone and naloxone in elderly patients with ribs fracture: An 18-month retrospective study

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## Abstract

Blunt chest trauma with isolated or multiple rib fractures constitutes a common presentation in Emergency Department (ED), particularly in elderly people. Rib fractures in the elderly create short- and long-term disabilities with a dramatic impact. Pain management in the elderly could be problematic due to non-steroidal anti-inflammatory drugs (NSAIDs) contraindication or interaction with other drugs. We performed this retrospective study collecting and retrieving all patients aged 65 or older, with a diagnosis of rib(s) fracture(s) during an 18-month period. We analyzed the different treatments chosen, and divided them into subgroups: oxycodone-naloxone, and other treatments (also divided in: codeine-acetaminophen; NSAID or Acetaminophen; Tramadol or Tapentadol). A total of 475 elderly patients (aged 65 and older) with single or multiple rib fractures were evaluated in our ED in 18 months: of these 410 patients were considered eligible, with a

mean age of 79.28 years (standard deviation 7.83). 185 were male and 225 were female. Our study confirms the efficacy and tolerability of fixed association of oxycodone and naloxone. This association determined the highest and fastest reduction on Numeric Pain Scale reported by patients and is significantly better than other drugs in oral administration.

## Introduction

Blunt chest trauma with isolated or multiple rib fractures constitutes a common presentation in Emergency Department (ED), particularly in elderly people.<sup>1</sup> Rib fractures in the elderly create short- and long-term disabilities with a dramatic impact on the patient's quality of life.<sup>2</sup> Rib fractures are considered among the most painful injuries in thoracic blunt trauma,<sup>2</sup> but pain management in the elderly could be problematic due to non-steroidal anti-inflammatory drugs (NSAIDs) contraindication or interaction with other drugs:<sup>3</sup> further, comorbidities, frailty, cognitive dysfunction, and chronic illness require additional attention in the choice of drugs and doses.<sup>4,5</sup> Finally, acetaminophen could be ineffective in most severe pain, and opioids are considered the elective pharmacological treatment in these cases<sup>6,7</sup> although recent reports have highlighted the promising results given by regional anesthesia.<sup>8,9</sup> Oxycodone is a semisynthetic, strong opioid analgesic with high oral bioavailability and proven efficacy in treatment of severe pain.<sup>10-16</sup> The side effects of opioid use are well known, and constipation is the most frequently reported especially in the elderly:<sup>15-17</sup> constipation naturally increases with age,<sup>14,18-20</sup> and opioid treatments could potentially increase this aspect: in many cases, it may induce patients to reduce or discontinue their opioid therapy, determining oligoanalgesia.<sup>21,22</sup> Naloxone is an opioid antagonist with an oral bioavailability of 2% due to a strong first-pass hepatic metabolism:<sup>23</sup> when given by mouth, the naloxone systemic side effects are negligible, and it exerts its action on gut opioid receptors with a higher affinity than oxycodone preventing oxycodone from binding to these receptors.<sup>24,25</sup> So, the association between oxycodone and naloxone in a fixed ratio of 2:1 can reduce the prevalence of constipation or improve bowel function in patients with preexistent constipation without affecting analgesic effects.<sup>18,23,25,26</sup> We decided to evaluate the analgesic efficacy of the association of oxycodone-naloxone in pain management of elderly patients with isolated or multiple rib fractures and to investigate the prevalence of opioids side effects.

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## Materials and Methods

### Study setting and design

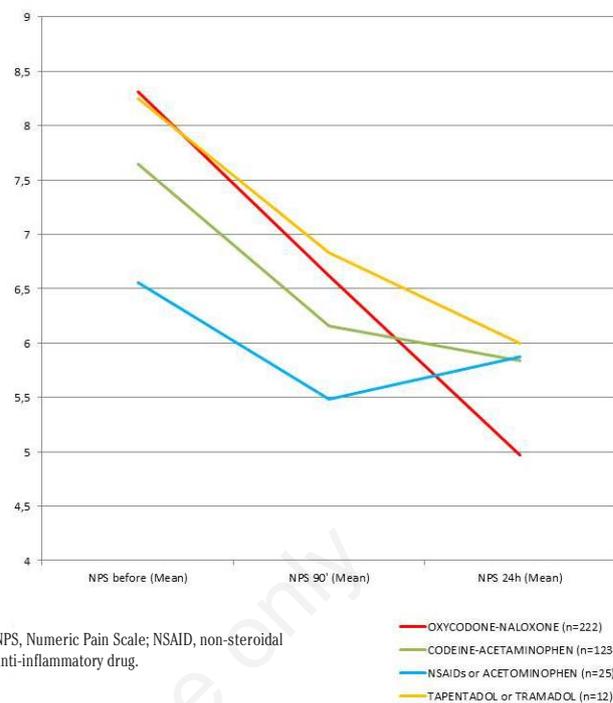
We performed this retrospective study in our ED (city hospital, approx. 55,000 access/year, San Paolo Hospital, Savona, Italy), collecting and retrieving all patients aged 65 or older, with a diagnosis of rib(s) fracture(s) (using specific query), during an 18-month period (June 1st, 2017-December 31st, 2018). Baseline data included demographics (age, gender) as well number of rib fractures were collected. We reviewed clinical records by physicians and nurses, and recorded data about pain evaluation and re-evaluation, and constipation. We excluded such patients with incomplete or incorrect clinical records.

Each patient received a first pain measurement using a verbal Numeric Pain Scale (NPS): subjects were asked to define their pain score using a verbal numeric rating scale, in which 0 is defined as *no pain* and 10 is defined as *worst pain imaginable*. Pain scores were measured at baseline. The physician decided on analgesia by oral route based on personal opinion, and re-evaluated NPS at 90 minutes. We analyzed the different treatments chosen, and divided them into subgroups: oxycodone-naloxone, and other treatments (also divided in: codeine-acetaminophen; NSAID or Acetaminophen; Tramadol or Tapentadol). Table 1 summarizes dosing information.

According to clinical conditions (*i.e.*, number of rib fractures, co-morbidities) physicians decided on discharge, or admission to hospital (mostly in our Emergency Medicine Ward): in these patients, we evaluated also NPS at 24 hours after admission (in the admitted patients the NPS was furtherly evaluated at 24 hours according to our internal protocol adopted in all patients with moderate or severe pain). In case of insufficient analgesia, the initial daily dose was increased. Changes in cognitive state, constipation, and other adverse events were assessed, like nausea.

### Data analysis

In the descriptive analysis, main trends and dispersion measurements (mean and standard deviations) were used for NPS. The significance of difference between different groups of pain treatment was evaluated by the Student's t-test. The correlation between parameters was calculated with Pearson Coefficient and Linear Regression. Data were analyzed using Microsoft Excel 2010. This study was authorized by the medical direction of our hospital and patients were informed and signed their consent to their data collection.



**Figure 1. Analgesic effect on Numeric Pain Scale reduction for different treatments used.**

**Table 1. Different analgesic treatments used and their dosing.**

Drug	Starting dose
Oxycodone – Naloxone group	
Oxycodone-Naloxone	5 mg-2.5 mg p.o.
Codeine-Acetaminophen group	
Codeine-Acetaminophen	30 mg-500 mg p.o.
NSAIDs or Acetaminophen group	
Acetaminophen	1000 mg p.o.
Ketoprofen	80 mg p.o.
Ibuprofen	600 mg p.o.
Tramadol or Tapentadol group	
Tramadol	50 mg p.o.
Tapentadol	50 mg p.o.

NSAIDs, non-steroidal anti-inflammatory drugs; p.o., per os.

**Table 2. Demographic characteristics of patients and response to different treatment options.**

	Oxycodone-Naloxone (n=222)	Other treatment (n=189)	Codeine-Acetaminophen (n=123)	NSAIDs or Acetaminophen (n=25)	Tapentadol or Tramadol (n=12)
NPS before (Mean)	8.315315315	7.542553191	7.650406504	6.56	8.25
NPS 90' (Mean)	6.617117117	6.207446809	6.154471545	5.48	6.833333333
NPS 24h (Mean)	4.972972973	5.972972973	5.837837838	5.875	6
Mean age	80.61 (65-101) SD 7.237	77.7 (65-95) SD 8.222	78.11 (65-95) SD 8.071	74.56 (65-91) SD 8.879	79.17 (65-90) SD 9.134
Number of ribs fractures (Mean)	2.02 (1-10) SD 1.223	2.07 (1-14) SD 1.554	1.94 (1-14) SD 1.252	1.76 (1-4) SD 0.95	2.72 (1-5) SD 1.42

NSAIDs, non-steroidal anti-inflammatory drugs; NPS, Numeric Pain Scale; SD, standard deviation.

## Results and Discussion

A total of 475 elderly patients (aged 65 and older) with single or multiple rib fractures were evaluated in our ED in 18 months: of these, 65 patients were excluded for incomplete clinical information. 410 patients were considered eligible, with a mean age of 79.28 years (standard deviation 7.83). 185 were male and 225 were female.

222 patients were treated with oxycodone and naloxone in a fixed ratio of 2:1, at initial dose of 5 mg-2.5 mg p.o. bid, and 63 patients (28%) needed an increased dose of 10 mg-5 mg at the 24-hour evaluation. 76 patients were admitted to hospital (34.23%).

189 patients were treated with other drugs, and 81 patients (42.85%) required an implementation of analgesia. In these group, 76 patients (40.21%) were admitted. In the *Other treatment group*, 123 were treated with codeine-acetaminophen association, and 37 were admitted (30.01%), 25 patients were treated with NSAIDs or acetaminophen, 10 were admitted (40%), and 12 patients were treated with tapentadol or tramadol, and all of them were admitted (Table 2).

We did not find any significant correlation between the intensity of pain and the number of rib fractures, both in the group of patients treated with oxycodone-naloxone (mean rib fractures 2.02, mean NPS at arrival 8.32, Pearson coefficient -0.12, R2 0.0085) and in the group of patients treated with other drugs (mean rib fractures 2.07, mean NPS at arrival 7.54, Pearson coefficient 0.54, R2 0.2917).

The treatment chosen seemed appropriate, according to the mean NPS at arrival, highest in the group of patients treated with opiates (8.31 in the oxycodone-naloxone group, 8.25 in the tapentadol or tramadol group), and lower in patients treated with acetaminophen or NSAIDs (6.56), but in this latter group we observed a slight reduction in NPS after administration (5.48), followed by an increased NPS at 24h (5.87). In the other groups, the NPS decreased after administration and at 24 hours, with the highest reduction in the oxycodone-naloxone group ( $P < 0.01$ ; Figure 1 and Table 3).

The association oxycodone-naloxone was well tolerated: we found drowsiness in 10 patients (4.5%), and constipation in 18 patients (8.1%), mostly pre-existent: we observed these symptoms in the 76 patients admitted in hospital (mean admission period of 4 days, range 2-12 days). The constipation did not worsen in anyone and improved in 4 patients. Nausea was very rare, observed in only 2 patients (0.9%), but we did not observe any vomiting; 1 of these patients decided to switch to other treatment for persistent nausea (0.45%).

## Conclusions

Our study confirms the efficacy and tolerability of fixed association of oxycodone and naloxone. This association determined the highest and fastest reduction on NPS reported by patients and is significantly better than other drugs in oral administration. When physicians decided to administer NSAIDs or Acetaminophen, due to a lower NPS value reported by patients, we demonstrated a slight increase in NPS at 24 hours, after an initial reduction, and these data confirm that such analgesic could be inappropriate for treatment of a painful condition like rib fractures.<sup>2,3</sup> The consequences of oligoanalgesia in the elderly are well-known and documented,<sup>21,22</sup> and opiophobia (especially in older patients) lead to over-prescription of NSAIDs,<sup>6</sup> even when they are contraindicated or ineffective,<sup>3-5</sup> with increased renal and gastrointestinal toxicity.<sup>27</sup> Acetaminophen has been recommended by most societies and by the World Health Organization as the first-line agent in the treatment of mild-to-moderate pain, given its tolerability, nevertheless its poor analgesic efficacy in severe pain limits its utilization.<sup>28</sup> The efficacy of oxycodone-naloxone are well documented, even in elderly people.<sup>23,24</sup>

Our study confirms also the good tolerability of the association of oxycodone-naloxone, as seen in literature:<sup>16,23,26</sup> the constipation is very common in elderly people, irrespective of opioid treatment,<sup>4,14,19,20</sup> but the treatment with oxycodone-naloxone not only does not deteriorate these symptoms, however sometimes it seems to improve them:<sup>18,23-26</sup> pain due to rib fractures could be particularly intense and the defecation could be very painful in these patients. So, pain itself could worsen the constipation,<sup>29</sup> and the better analgesia obtained with oxycodone alone could explain the improvement in constipation. We documented nausea with a lower prevalence as previously documented,<sup>10</sup> probably due to the lower dose prescribed. Drowsiness is quite common, but did not invalidate the adherence to treatment. We observed only one discontinuation of these treatments, due to severe and refractory nausea.

Our study also seems to confirm the absence of correlation between the intensity of a disease (in our case the numbers of rib fractures) and pain intensity, so pain analgesia could not be decided on a pure clinical basis and it would be driven by patients' pain scale.

The short period of observation limits the evaluation of the prevalence of side effects of the association of naloxone and oxycodone, but we could observe an improvement of constipation in some patients with preexistent condition. The rapid and the more intense analgesia, with its short-term tolerability makes the fixed association between oxycodone-naloxone a good choice in elderly patients with rib fractures.

**Table 3. Statistical analysis in pain response according to different treatment options.**

	Oxycodone-Naloxone <i>vs</i> other	Oxycodone-Naloxone <i>vs</i> Codeine-Acetaminophene	Oxycodone-Naloxone <i>vs</i> NSAIDs or Acetaminophene	Oxycodone-Naloxone <i>vs</i> Tapentadol or Tramadol
NPS before	P<0.01	P<0.01	P<0.01	P=0.831
NPS 90'	P<0.01	P<0.01	P<0.01	P=0.567
NPS 24h	P<0.01	P<0.01	P<0.01	P<0.01

NSAIDs, non-steroidal anti-inflammatory drugs; NPS, Numeric Pain Scale.

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