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Effect on morphine requirement of early administration of oral acetaminophen versus acetaminophen/tramadol combination in acute pain

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INTRODUCTION

Pain is one of the most common causes of emergency department (ED) admission, yet it remains inadequately managed despite the availability of a great number of analgesics (1,2). Although it is widely recognized that severe pain is very common in EDs, studies have shown that up to 70% of patients do not receive analgesics during their stay in the ED (3,4).

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Moreover, it has been indicated that pain treatment is often delayed in the ED; in general it is started after clinical examination or at the end of the diagnostic investigation (4-7). The average waiting time is estimated to range from 70 to 90 minutes before the first administration of analgesia, with a dose often insufficient to relieve patients' discomfort (4, 7,8). For all these reasons, patients presenting in ED remain largely dissatisfied (9-11). Over the past two decades, medical societies have sought to initiate recommendations to improve the treatment of pain which is now regarded as the fifth "vital sign" (12,13). Efforts aiming at improving the quality of pain management resulted in the widespread use of opioid analgesics and their overall consumption increased by 400% and their use in EDs increased by more than 60% (14,15). However, available data suggest a strong correlation between frequency of opioids prescription and deaths from opiate use or abuse (16). Severe adverse events such as hypoxia, and hypotension are known to be associated with opioid use in particular when they are administered repeatedly to patients with acute pain. One possible key strategy to decrease the need to rescue opioid prescription in the EDs is an early use of opioid-sparing analgesics within the triage process (17,18). The aim of this study was to evaluate the impact of starting analgesic treatment with acetaminophen or tramadol/acetaminophen combination at the triage step on morphine requirement and on satisfaction in patients admitted to ED for acute pain.

METHODS

Patients and study design

This was a multicenter, randomized and controlled, single-blind trial carried out in EDs of 3 university hospitals over a nine-month period extending from January 2016 to September 2016. The study population consisted of patients over 18 years of age with a visual analog

scale (VAS) equal to or higher than 30/100 having given their informed consent to participation at the triage area. VAS pain scores varied from 0 for no pain to 100 for unbearable pain. Pain is described as mild when the VAS is less than 30, as moderate when the VAS is between 30 and 70, and as severe pain when the VAS is equal to or greater than 70. Excluded from this study were all patients aged under 18 or over 80 years, having a vital compromise (hemodynamic, respiratory or neurological distress), an inability to assess pain intensity according to the VAS, swallowing disorders, or a contraindication or an allergy to the treatments used. We also excluded from this study all patients whose data were incomplete or inaccurate. Patients included in the study were randomly assigned (1:1:1) to placebo, acetaminophen (1000mg) or tramadol/acetaminophen combination (75mg/650mg) which were given in the triage area. Patients were stratified according to centralized randomization. To ensure that almost equal numbers of patients receive each of the 3 treatment, a computer based randomization block was used. All drugs and placebo were given once. Acetaminophen (stopalgic 500mg) and tramadol/ acetaminophen combination (synalvic 37.5mg/325mg) were manufactured and donated by Medis Laboratories, Tunisia. Placebo was provided by FB university hospital pharmacy department. Each treatment consisted of two oral tablets given with a glass of water and prepared by an independent clinical research pharmacist. Total dose was 1000mg of acetaminophen, and 75/650mg for tramadol/acetaminophen. The nurses administering the treatment could have recognized the different treatments because of the different shape and size of the tablets. Patients and treating physicians were masked to protocol treatment. Included patients were followed and monitored until their discharge from the ED. Demographic data were recorded prospectively; they included age, sex, past medical history, the reason for consultation and the type of pain. Clinical data recorded at ED admission included VAS, temperature, systolic and diastolic blood pressure, heart rate and pulse oxygen saturation.

Outcome assessment

The primary outcome is the need for rescue morphine during ED stay. Secondary outcome included patient satisfaction regarding the overall management quality in the ED, ED length of stay, and percentage of patients discharged from the ED with VAS <30. During their ED stay, patients were monitored in order to evaluate the need for rescue analgesic treatment with morphine. Rescue intravenous morphine was given for all patients having a VAS >70 at 30 minute post-triage assessment. Morphine was administered in 2 mg boluses at 5-minute intervals until the maximum prescribed dose has been achieved (15 mg) or until 50% decrease of initial VAS is achieved. Patients having a VAS score at 30 minute post-triage between 30 and 70 were given a first step analgesic at the discretion of the treating physician (acetaminophen or a non-steroid anti-inflammatory drug).

VAS pain score assessment was repeated 30 minutes after the medications were given and at ED discharge. Patients 'satisfaction regarding the overall management quality in the ED was assessed by Likert's verbal scale at ED discharge: they mentioned whether they were very satisfied, satisfied, neutral, unsatisfied or very unsatisfied with the overall management quality. Length of ED stay was also recorded. All individual parameters were recorded on case report form at admission. The study was conducted in accordance with the guidelines of the declaration of Helsinki and the Ethic committee of F.B. university hospital of Monastir approved the protocol. Written informed consent was obtained from all patients before enrollment. This trial is registered at clinicaltrial.gov (number NCT03243006). Medis Laboratories had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Statistical analysis

Variables are expressed as mean and SD and median and 25% to 75% interquartile range (IQR) or 95% confidence interval (CI) as appropriate. Repeated ANOVA was used for VAS scores analysis. $\chi 2$ Or Fisher exact test was used for discrete variables. Comparison between the 3 groups was examined using Kruskal-Wallis test. A p value <0.05 was considered to be statistically significant. If we assume that almost 25% of patients with acute pain should receive morphine in the ED and using an alpha value of 0.05, a sample of 450 patients per study group will have 90% power to detect an absolute10% decrease in the use of these analgesic agents. The sample size was increased by 10% to cover randomized but lost-to-follow patients, i.e 500 patients per study group and a total sample of 1500 patients was needed. Analysis of the results was based on the intention to treat principle. The results obtained in this study were recorded and analyzed by SPSS computer software (English version 17).

RESULTS

A total of 1500 patients were randomized; 500 in each group. Fourteen patients were excluded after randomization for the following reasons: 1 patient presented an episode of vomiting in group tramadol, 14 patients refused treatment (7 in group tramadol/acetaminophen combination, 4 in group placebo and 3 in group acetaminophen) (figure1). A total of 1485 patients completed the study. The mean age of our study population was 37.9±14 years with extremes ranging from 18 years to 80 years. Our study population comprised 827 men (55.1%).The majority of patients (80%) were under 50 years of age with no previous medical history. For 804 participants (54.1%), the primary cause of pain was trauma. Treatment arms were well balanced in terms of age, sex, and baseline admission vital signs between the 3 groups (table 1).

VAS pain scores

The mean VAS at triage was 65±11 for placebo group, 64±13 for acetaminophen group, and 67±12 for tramadol/acetaminophen combination group (p = 0.93). VAS scores were not significantly different at triage between trauma pain and non-trauma pain groups (63±14vs 63±15; p=0.8). The VAS value 30 minute post-triage and at ED discharge in the 3 groups are shown in table 2. The mean VAS decrease was statistically significant between group tramadol/acetaminophen combination and group placebo (p <0.001) but not significant between group acetaminophen and group placebo. The difference between group tramadol/ acetaminophen combination and group acetaminophen was not significant (p=0.59) (figure 2). No additional analgesics after triage was more frequent in tramadol/acetaminophen combination and acetaminophen groups compared to placebo group (p=0.03) (table 3).

Rescue morphine

Rescue morphine was observed in 115 (23.2%) patients in placebo group patients, 94 (18.9%) in acetaminophen group, and 57 (11.5%) patients in tramadol/ acetaminophen combination group. The difference was significant only between tramadol/acetaminophen combination and placebo groups. ED length of stay was significantly shorter in tramadol/acetaminophen combination group (median 152 minutes, IQR 53-266) compared to acetaminophen group (median181 minutes, IQR 62-291) (p=0.02) and placebo group (median 195 minutes, IQR 65-287) (p=0.04). Nausea and dizziness were the most reported side effects in the 3 groups (29 in the overall population, 11 in placebo group, 10 in acetaminophen group and 8 in tramadol/ acetaminophen combination group (p=0.78) No severe adverse effects occurred in either group during the study. At ED discharge, the mean VAS measured in the three groups

was comparable [20±12 in group placebo, 22±11 in group acetaminophen, and 21±10 in group tramadol/ acetaminophen combination; (p=0.23)].

Patients' satisfaction

Patient satisfaction regarding the overall quality of care in the ED was higher in tramadol/ acetaminophen combination group (77%) compared to acetaminophen group (69%) and placebo group (68%) (figure3). Eighty four percent of patients in group placebo were discharged with a VAS lower than 30, compared with 83% in group acetaminophen and 87% in group tramadol/ acetaminophen combination. The difference in the percentage of patients discharged with VAS score <30 was only significant between acetaminophen group and tramadol/ acetaminophen combination group (p=0.01) (table 2).

DISCUSSION

The results of the present study showed statistically significant decrease in the use of rescue morphine treatment when tramadol/ acetaminophen combination was systematically prescribed in the triage area, a higher rate of patient satisfaction compared to acetaminophen or placebo and a higher pain relief.

Optimal pain management is imperative in ED. Indeed, the consequences of pain on the cardiovascular and the neurovegetative systems are susceptible to aggravate the already unstable patients. In addition, anxious, agitated or aggressive behaviors frequently observed in patients with acute pain can lead to diagnostic errors and treatment failure. It is clear that beyond all these considerations, a significant obstacle to optimal pain management in ED patients would be related to the high medical and nursing workload in this setting (5,19). A

study by Pines et al (20) concluded that there is a linear correlation between emergency department overcrowding and the failure to receive adequate pain treatment. As a result, clinical practice guidelines have been developed with the goal of promoting effective pain treatment in ED.

Opiates are the current mainstay of severe pain relief; however, side effects can impede their use and their clinical effectiveness. In addition, there are growing concerns about opioid abuse and misuse in the ED (14,15). Accordingly, opioid-sparing approaches that achieve adequate pain control in ED patients are needed. Several methods and guidelines have been proposed to decrease opioid use in ED patients (21-23). Our study demonstrates that a simple action based on the early prescription of tramadol/acetaminophen combinationwas associated with decrease in the amount of opioid prescriptions written by emergency physicians. We found that this practice could decrease almost the half in the need of opioid prescriptions. In the era of increasing opioid use, this benefit could have a significant clinical and public health relevance that should be highly considered. Our study showed that tramadol is superior to acetaminophen in decreasing pain intensity and the need of rescue morphine treatment suggesting the weak opioid-sparing effects of acetaminophen alone as concluded by a recent meta-analysis (24). Indeed in the last two decades, evidence-based multimodal opiate-sparing analgesia has become increasingly widespread in different clinical setting. The concept is to combine drugs from different classes to provide a better analgesia at reduced doses of individual agents with an opiate-sparing effect. As demonstrated in our study, affixed-dose combination of acetaminophen and tramadol provides such comprehensive multimodal approach for moderate-to-severe acute pain.

A second important finding in the present study is that patients who received tramadol/acetaminophen combination in the triage were more satisfied than those in the other groups. The fact that an independent investigator measured patients' satisfaction added an

important validation to our results. Of course, various factors could have positively influenced patients‘ satisfaction such as perceived quality of care and socio-cultural conditions. However, in ED patients having acute pain as the principal complaint, satisfaction is mainly influenced by the precocity and efficacy of analgesic treatment. Jao et al.(10) and Shill et al. (26) reported a significant association between the rate of pain relief and a higher level of patients' satisfaction. Although, we focused our objective on reduction of opioid prescriptions, we acknowledge that this strategy should provide adequate pain relieve and minimize time waiting for analgesia. Previous studies conducted in ED found that patients preferred that their pain be treated immediately upon admission (27). Unfortunately, in real practice, diagnostic challenges and overcrowding usually lead to increased time to analgesia or to no analgesia at all. In a large multicenter study involving patients with pain scores of 4 or more, Todd et al. (4) observed a 90-minute interval between ED admission and analgesia. In 2012, Vazirani et al (8) observed a delay of approximately 70 minutes in intravenous administration of analgesic treatment, which is comparable to that observed in other studies.

The results of this study should be interpreted in the light of some potential limitations. This is a single blind study, which could have led to a bias, though its multicenter design should minimize the influence on our final results. The question related to the choice of the best treatment that should be given at triage should also be discussed. Although tramadol is considered a synthetic centrally acting opioid, it produces less respiratory depression than traditional opioids and had no significant cardiac effects. Number of previous studies have demonstrated that it reduced morphine consumption when used at low doses as in the present study (28,29). Additionally, tramadol/acetaminophen combination could be a suitable choice because it was demonstrated that combining a lower dose of tramadol with acetaminophen provides greater and faster efficacy than either tramadol or acetaminophen alone with longer duration of action (30).We however acknowledge that other drug

combinations with significant degree of opioid sparing effect were described (31). Tramadol with non-steroid anti-inflammatory drugs could be one of such combinations. Although we demonstrated a significant reduction in opioid requirements, clinical benefit would be enhanced if there is also a reduction in opioid related adverse effects. Our study was not powered for this outcome which definition and thresholds vary across studies.

In summary, our findings suggest that early oral treatment of pain with tramadol/acetaminophen at the triage would have a significant effect on pain relief and would reduce the use of opioids in the ED without significant increase in side effects. This intervention may be considered in EDs with an aim of similar benefits.

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Table 1. Demographic data and clinical information

	Total n=1485	Placebo n=496	Acetaminophen n=497	Tramadol/ Acetaminophen n=492	P
Age, mean(DS) years	37.9 ±14	37.7 ±15	37.9 ±14	38.1 ±14	0.88
Sex ratio	1.22	1.16	1.09	1.46	0.56
Comorbidities, n (%)					
Diabetes	158 (10.6)	53 (10.6)	49 (9.8)	56 (11.4)	0.90
Smoking	352 (23.7)	114 (22.9)	120 (24.1)	118(30.0)	0.77
Trauma pain, n (%)	804 (54.1)	254 (51.2)	246 (49.5)	304 (61.8)	
Muscular		148 (29.8)	135 (27.2)	158 (32.2)	
Skeletal		91 (18.3)	75 (15.1)	94 (19.1)	
Thoracic		10 (2.0)	11 (2.1)	8 (1.6)	
Other		5 (1.1)	25 (5.1)	44 (8.9)	
Non trauma pain, n (%)	681 (45.9)	242 (48.8)	251 (50.5)	188 (38.2)	
Abdominal pain		92 (18.5)	101 (20.3)	92 (18.6)	
Headache		34 (6.9)	21 (4.2)	12 (2.4)	
Low back pain		83 (16.7)	90 (18.2)	75 (15.2)	
Other		33 (6.7)	39 (7.8)	9 (1.8)	
Clinical admission findings					
SBP, mean±DS mmHg	130±16	130±16	128±17	130±16	0.15
DBP, mean±DS mmHg	73±10	72±10	72±15	74±12	0.10
Heart rate, beats/min	79±14	79±14	78±15	80±14	0.13
Pulse oxygen saturation,%	98±1	97±1	98±1	97±2	0.83
Temperature, °C	37±0.3	36.7±0.5	37.2±0.3	36.9±0.4	0.36

Abbreviations: SBP systolic blood pressure, DBP diastolic blood pressure.

Table 2. Visual Analog Scale in the three protocol groups at triage, 30 minute post-triage, and at discharge.

	Placebo	Acetaminophen	Tramadol/ Acetaminophen	p
Mean VAS pain scores				
at triage	65±11	64±13	67±12	0.93
post-triage	54±10	49±12	45±10	<0.01¶*¥
at discharge	22±12	22±11	21±11	0.23

Abbreviation : VAS visual analog scale

¶ : Placebo vs Acetaminophen groups $p<0.05$

* : Placebo vs Acetaminophen/Tramadol groups $p<0.05$

¥ : Acetaminophen vs Acetaminophen/Tramadol groups $p<0.05$.

Table 3. Rescue Analgesic Consumption

	No additional analgesics	Rescue first step analgesics	Rescue morphine
Protocol Groups			
Placebo n (%)	28 (5.7)	353 (71.1)	115 (23.2)
Acetaminophen n (%)	120 (24.1)	292 (64.0)	94 (18.9)
Tramadol/Acetaminophen n (%)	137 (27.8)	298 (60.5)	57 (11.6)
p value	0.03 ¶*¥	0.50 ¶*	0.03*¥
Relative Risks [95% CI]			
Placebo vs Acetaminophen	0.24 [0.17-0.33]	1.11 [1.02-1.21]	1.24 [1.01-1.52]
p value	<0.001	0.02	0.06
Placebo vs Tramadol/Acetaminophen	0.20 [0.15-0.29]	1.18 [1.07-1.29]	2.02 [1.31-3.11]
p value	<0.001	0.001	<0.001
Acetaminophen vs Tramadol/ Acetaminophen	0.87 [0.70-1.07]	1.06 [0.96-1.17]	1.63 [1.21-2.2]
p value	0.18	0.27	0.001

¶ : Placebo vs Acetaminophen group $p<0.05$

* : Placebo vs Acetaminophen/Tramadol group $p<0.05$

¥ : Acetaminophen vs Acetaminophen/Tramadol $p<0.05$.

Figures Legend

Figure 1: Trial profile.

Figure 2: Mean decrease of pain score using visual analog scale (VAS) between first clinical assessment at triage and 30 minutes after. * p <0.05 Placebo vs Tramadol/ Acetaminophen combination.

Figure 3: Percentage of patients who were satisfied regarding quality of care. * p <0.05 Placebo vs Tramadol/ Acetaminophen combination ; Ψ p <0.05 Acetaminophen vs Tramadol/ Acetaminophen combination.

Figure 1.

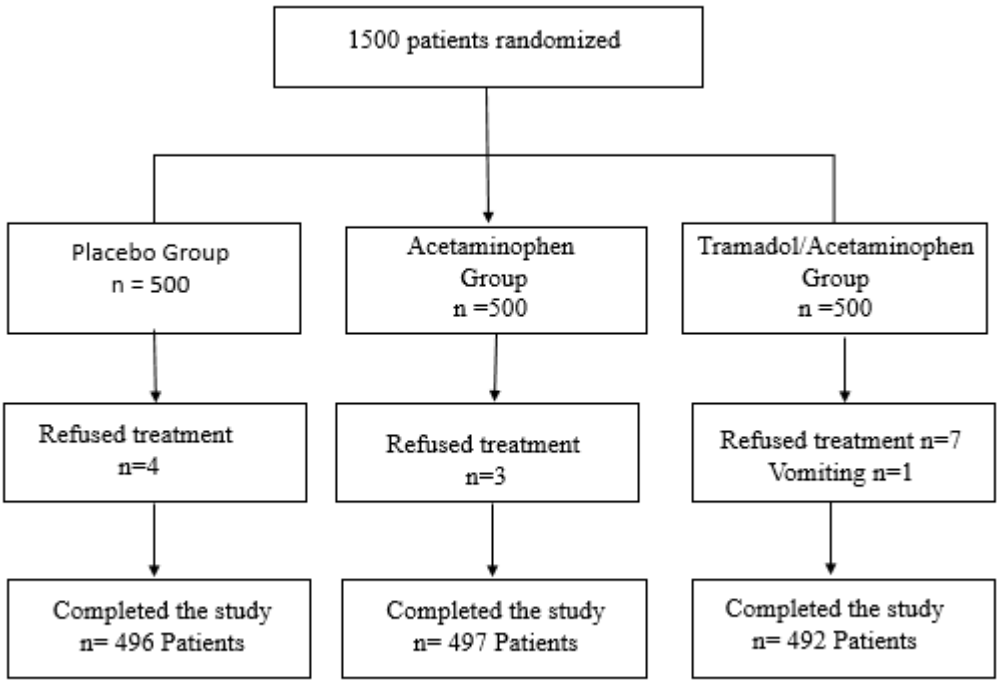

Figure 2.

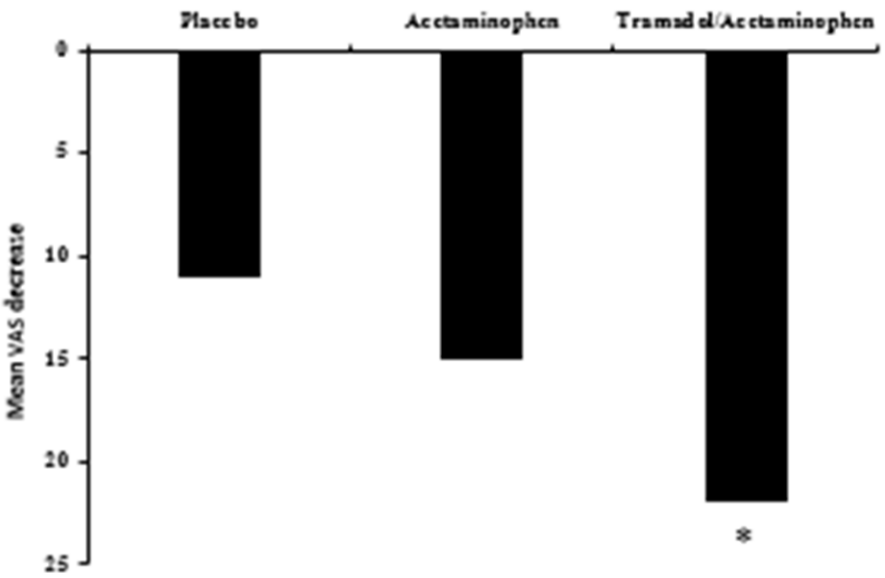

Figure 3.