Research Article

Can intravenous acetaminophen reduce the needs to more opioids to control pain in intubated patients?

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Abstract

Aims: To evaluate the effect of intravenous (IV) acetaminophen on reducing the need for morphine sulfate in intubated patients admitted to the Intensive Care Unit (ICU). **Settings and Design:** Current study was done as a clinical trial on the patients supported by mechanical ventilator. **Subjects and Methods:** Behavioral pain scale (BPS) scoring system was used to measure pain in the patients. All of the patients received 1 g, IV acetaminophen, every 6 h during the 1st and 3rd days of admission and placebo during the 2nd and 4th days. Total dose of morphine sulfate needed, its complications, and the BPS scores at the end of every 6 h interval were compared. **Results:** Totally forty patients were enrolled. The mean pain scores were significantly lower in the 2nd and 4th days (4.33 and 3.66, respectively; mean: 4.0) in which the patients had received just morphine sulfate compared to the 1st and 3rd days (7.36 and 3.93, respectively; mean: 5.65) in which the patients had received acetaminophen in addition to morphine sulfate too ($P < 0.001$). Cumulative dose of morphine sulfate used, was significantly higher in the 1st and 3rd days (8.92 and 3.15 mg, respectively; 12.07 mg in total) compared to the 2nd and 4th days (6.47 mg and 3.22 mg, respectively; 9.7 mg in total) ($P = 0.035$). **Conclusion:** In our study, IV acetaminophen had no effect on decreasing the BPSs and need of morphine sulfate in intubated patients admitted to ICU.

Keywords: Acetaminophen, analgesia, Intensive Care Unit, intubated patient, morphine sulfate, pain

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Introduction

Presence of endotracheal tube (ETT) can induce a significant pain, even in a patient not completely conscious. There are many ways to estimate the amount of pain in such patients who cannot communicate verbally with their caregivers. Most of these tools are simple and offer a rapid way to measure and monitor the amount of pain in these patients during hospitalization.[1-4] There are enormous pharmacological and nonpharmacological ways to manage pain. Morphine sulfate is the most popular medication of pain management in patients hospitalized to the Intensive Care Units (ICUs).[5] Unfortunately, its use is accompanied with some complications such as central nervous system and respiratory suppression, nausea/vomiting, histamine release, and consequent fall in blood pressure (BP) level.[6] Its use can induce hyperalgesia too[7] and as all of the other opiates, it can decrease the protective reflexes of the airway in addition to the level of consciousness and respiratory drive and so it can induce dependency to mechanical ventilation and

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decrease the success rate of weaning from mechanical ventilator and extubation.[8]

Acetaminophen is an antipyretic and analgesic agent, and it is more commonly used to relieve mild to moderate pain caused by different etiologies.[8,9] Considering the fact that in patients in need of critical care, intravenous (IV) acetaminophen has less complications while being injected and afterward compared to IV morphine sulfate, current study tries to evaluate the effect of acetaminophen on reducing the need for morphine sulfate in intubated patients admitted to ICU. Although there are many studies which have showed its effectiveness on decreasing the need to IV narcotics in pain management; to the best of our knowledge, none of them have been targeted intubated patients in ICU setting; our study is aimed to achieve it.

Subjects and Methods

Research design and ethics

Current study was done as a clinical trial in the ICU of Emergency Department (emergency ICU), on the patients supported by mechanical ventilator. The study was approved by the Ethics Committee of Iran University of Medical Sciences; referral code number is 884. Written consent was obtained from every patient's first degree relative to enter the study.

Sample and setting

We enrolled forty patients who were intubated and being mechanically ventilated in the ICU of Hazrat Rasoul Emergency Department, Tehran, Iran. All of the patients were eligible to take analgesia according to the behavioral pain scale (BPS) scoring system.

Inclusion criteria

All the intubated patients in need of mechanical ventilation at least for 96 h in ICU according to the preliminary clinical estimation of their responsible physicians were included in the study. The patients should have 18 or above years old. They entered the study if showed 5 or more score pain in the scale of BPS system, and responsive to painful or verbal stimuli.

Exclusion criteria

Patients with any previous history of hypersensitivity to morphine sulfate or acetaminophen, history of narcotic or alcohol abuse, quadriplegia, those being treated with neuromuscular blocking agent or considered noneligible to be treated with IV morphine sulfate or acetaminophen by the responsible physician, were excluded from the study.

Instrument

BPS scoring system has been used to measure pain in the patients with decreased level of consciousness and those under mechanical ventilation (Payen *et al*., 2001). It consists of three behavioral components, changes in facial expressions in favor of the fact that the patient suffers from pain, upper extremity movements, and tolerance of ETT and mechanical ventilator. Each component takes a score of 1 (no response) through 4 (strong response); so, BPS is measured 3 for no pain, through 12 for the most intense pain. In our study, BPS was measured in the maximally 6 h intervals and analgesic medication was prescribed for any patient having a score of 5 or more.

Procedure

Five milligrams of morphine sulfate was prescribed IV for any patient having a BPS score of 5 or more while monitoring his/her BP and heart rate. Morphine sulfate dose was decreased to 3 mg if the patient's serum creatinine (Cr) level was higher than normal (1.5 mg/dl). All of the patients received 1 g IV acetaminophen, dissolved in 100 mL normal saline (NS) over 15 min, q6 h during the 1st and 3rd days of admission. The patients received placebo (pure NS) in the same manner as acetaminophen, during the 2nd and 4th days. Total dose of morphine sulfate needed, its complications, and the BPS score at the end of every 6 h interval were recorded and compared between the 4 days.

Data analysis

Data recorded in datasheets were collected and analyzed using Statistical Package for the Social Sciences, Version 18 (SPSS Inc., Chicago, IL, USA). Continuous variables are expressed as mean (confidence interval [CI]), and categorical variables are expressed as frequency (percentile). Paired *t*-test was used for comparing the mean of pain scores and drug doses analysis. $P < 0.05$ was considered statistically significant.

Results

Totally forty intubated patients undergoing critical care were included in the study. The mean age of patients was 63.43 (95% CI, 56.60–69.52) ranging from 18 through 90. Sixteen of them (40%; 95% CI, 25–55) were female and 24 of them (60%; 95% CI, 45–75) were male. Each patient's level of consciousness was determined in the scale of AVPU (A: Awake, V: Responds to verbal stimuli, P: Responds to pain, U: Unresponsive). Twelve patients (30%; 95% CI, 17.5–45) were responsive to verbal stimuli (V) and 28 of them (70%; 95% CI, 55–82.5) were responsive to painful stimuli (P). Normal blood urea nitrogen/Cr levels were detected in 33 patients

(82.5%), whereas 7 of them (17.5%) had abnormal values. The patients' chief complaints and the main cause of admission to ICU have been listed in Table 1.

The mean pain score was determined in BPS scale, q6 h [Table 2]. It was 7.36 (95% CI, 6.83–7.91) in the 1st day and 4.33 (95% CI, 4.0–4.74), 3.93 (95% CI, 3.63–4.32), and 3.66 (95% CI, 3.37–4.08) in the days 2–4, respectively. The mean pain score was significantly lower in the 2nd and 4th days in which the patients had received morphine sulfate (4.0; 95% CI, 3.7–4.36) compared to the 1st and 3rd days in which the patients had received acetaminophen in addition to morphine sulfate too (5.65; 95% CI, 5.31–6.05) ($P < 0.001$).

Cumulative dose of morphine sulfate used in the 1st day was 8.92 mg (95% CI, 7.15–10.72), while it was 6.47 mg (95% CI, 5.17–7.92), 3.15 mg (95% CI, 2.2–4.2), and 3.22 mg (95% CI, 1.97–4.55) in the days 2–4, respectively. Altogether, in the 1st and 3rd days, the patients received 12.07 mg (95% CI, 9.75–14.37) compared to 9.7 mg (95% CI, 7.52–11.87) in the 2nd and 4th days. Statistical analysis showed significantly higher morphine sulfate in the days that patients had received acetaminophen compared to the days they had received placebo ($P = 0.035$; Table 3).

Table 1: Causes of ICU admission in the patients

	Frequency	Percent	Cumulative Percent
Decreased Level of Consciences	4	10.0	10.0
Chronic Obstructive Pulmonary Disease (COPD)	3	7.5	17.5
Asthma	1	2.5	20.0
Sepsis	8	20.0	40.0
Head Trauma	7	17.5	57.5
Stroke	8	20.0	77.5
Intra-cranial Hemorrhage (ICH)	3	7.5	85.0
Pulmonary Edema	2	5.0	90.0
Seizure	1	2.5	92.5
Chest Trauma	1	2.5	95.0
Others	2	5.0	100.0

Table 2: The pain scores of patients

	Mean	95% Confidence Interval
The Days Acetaminophen Prescribed		
First Day	7.36	6.83-7.91
Third Day	3.93	3.63-4.32
The Days Acetaminophen Withdrawn		
Second Day	4.33	4-4.74
Fourth Day	3.66	3.37-4.08
The Days Acetaminophen Prescribed		
First and Third Days	5.65	5.31-6.05
The Days Acetaminophen Withdrawn		
Second and Fourth Days	4	3.7-4.36

Table 3: The cumulative daily dose of morphine sulfate prescribed

	Mean	95% Confidence Interval
The Days Acetaminophen Prescribed		
First Day	8.92	7.15-10.72
Third Day	3.15	2.2-4.2
The Days Acetaminophen Withdrawn		
Second Day	6.47	5.17-7.92
Fourth Day	3.22	1.97-4.55
The Days Acetaminophen Prescribed		
First and Third Days	12.07	9.75-14.37
The Days Acetaminophen Withdrawn		
Second and Fourth Days	9.70	7.52-11.87

Discussion

Our study showed that IV acetaminophen had no role in decreasing the need of intubated patients to IV morphine in order to managing pain in ICU. To the best of our knowledge, all of the studies already done, evaluated the positive effect of IV acetaminophen on the decrease of opiates use and its complications in a selected group of patients needing surgical interventions and acetaminophen was prescribed prior to or during the intervention; none of them was designed for intubated patients in intensive care setting. Hence, it seems that it is the first prospective double-blind controlled trial done. Kelly *et al*. studied 100 patients in need of knee surgery, retrospectively. They found that the case group (consisting of 25 patients who received IV acetaminophen perioperatively) had no statistically significant difference with the control group (75 patients who did not receive IV acetaminophen) in the rate of opiates used after surgery ($P = 0.987$).[10] Considering the controlled and prospective nature of our trial, it can be more capable of proving this fact.

In a placebo-controlled double-blinded randomized trial, Cattabriga *et al*. prescribed IV acetaminophen for 72 h to 56 patients after cardiac surgery, whereas 57 counterparts received no acetaminophen; there was no statistically significant difference between the two groups from the point of cumulative morphine used ($P = 0.273$).[11]

In another double-blinded prospective clinical trial done by Grundmann *et al*., cumulative opioid consumption was evaluated during the 1st and 2nd h after lumbar microdiscectomy. The patients were divided into four groups of twenty cases; one of the four drugs, metamizol, acetaminophen, parecoxib, and placebo, were prescribed IV, prospectively, 45 min before the end of surgery. There was not any statistically significant difference among the groups from the point of cumulative opiate dosages needed.[12]

Both of the abovementioned studies were done in perioperative settings and their results are not applicable to intubated patients in intensive care setting.[11,12]

There are lots of studies which have shown that using IV acetaminophen as a multimodal analgesia has had a narcotic saving effect; it has reduced cumulative doses of morphine sulfate or other opioids needed to control pain on different clinical settings.[9,13-16]

Limitations

Small sample size and single center nature of study are the main limitations of our trial which decrease its applicability to the patients of other centers. Nonrandomized patient selection is another limitation of current study that may suggest a more comprehensive study in a randomized multi-center setting with a large sample size to increase its power and applicability.

Conclusion

Despite of certain limitations, the current study failed to show that as a multimodal analgesia, IV acetaminophen could decrease the cumulative dose of opiates and its complications in intubated patients in ICU. We could say that IV acetaminophen did not effect on pain reduction in intubated patients admitted to ICU.

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Conflicts of interest

There are no conflicts of interest.

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