


ORIGINAL CONTRIBUTION

Intravenous acetaminophen does not reduce morphine use for pain relief in emergency department patients: A multicenter, randomized, double-blind, placebo-controlled trial

Bruno Minotti MD¹  | Gregory Mansella MD² | Robert Sieber MD¹ | Alexander Ott MD³ | Christian H. Nickel MD² | Roland Bingisser MD²

¹Emergency Department, Cantonal Hospital of St. Gallen, St. Gallen, Switzerland

²Emergency Department, University Hospital Basel, University of Basel, Basel, Switzerland

³Interdisciplinary Pain Center, Cantonal Hospital of St. Gallen, St. Gallen, Switzerland

Correspondence

Bruno Minotti, Emergency Department, Cantonal Hospital of St. Gallen, Rorschacherstrasse 95, 9007 St. Gallen, Switzerland.

Email: bruno.minotti@kssg.ch

Funding information

BM received 74,160 CHF from the research committee of the cantonal hospital of St. Gallen, Switzerland, to support this study. No personal funding was included. All other authors have received no funding for this work.

Abstract

Background: Pain is one of the main reasons to present to emergency departments (EDs). Opioids are indispensable for acute pain management but are associated with side effects, misuse, and dependence. The aim of this study was to test whether a single dose of intravenous (IV) acetaminophen (paracetamol) can reduce the use of morphine for pain relief and/or morphine-related adverse events (AEs).

Methods: ED patients >18 years with acute pain (i.e., Numeric Rating Scale [NRS] > 4) were screened for eligibility. Patients with analgesia in the past 6 h, chronic pain, or clinical instability were excluded. Patients were randomized in a 1:1 ratio to receive either morphine 0.1 mg/kg and 1 g acetaminophen IV or morphine 0.1 mg/kg and placebo IV. The intervention was double-blinded. Additional morphine 0.05 mg/kg IV was administered every 15 minutes until pain relief (defined as NRS < 4) and whether the pain recurred. The primary outcome was the mean morphine dose for pain relief. Secondary outcomes were the total amount of morphine given, time to achieve pain relief, and AEs.

Results: A total of 220 patients were randomized and 202 evaluated for the primary outcome. The mean morphine dose for pain relief was similar in both groups (acetaminophen 0.15 mg ± 0.07 mg/kg, placebo 0.16 ± 0.07 mg/kg). There were no differences in the total amount of morphine given (acetaminophen 0.19 ± 0.09 mg/kg, placebo 0.19 ± 0.1 mg/kg), the time to achieve pain relief (acetaminophen 30 min [95% CI 17–31 min], placebo 30 min [95% CI 30–35 min]), and the frequency of AEs (overall 27.4%). Time to pain recurrence did not differ significantly between the groups (hazard ratio 1.23 [0.76–1.98], $p = 0.40$).

Conclusions: In ED patients, acetaminophen had no additional effect on pain control or morphine-sparing effect at the time of first morphine administration. Titrated morphine with the algorithm used was highly effective, with 80% of all patients reporting pain relief within 60 min of starting therapy.

Supervising Editor: Dr. James Miner.

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2022 The Authors. *Academic Emergency Medicine* published by Wiley Periodicals LLC on behalf of Society for Academic Emergency Medicine.

INTRODUCTION

Pain is one of the main reasons to present to the emergency departments (EDs),¹ and more than half of all patients present because of acute pain.² The efficacy of different pain medications in emergency situations remains highly controversial. A recent systematic review showed that the addition of opioids was no more effective than non-steroidal anti-inflammatory drugs (NSAIDs) or acetaminophen alone, but was associated with more adverse events (AEs) in musculoskeletal injuries.³ However, opioids are indispensable for acute severe pain,^{4,5} and early pain relief is of utmost importance to emergency patients.⁶ Titration of opioids has been shown to be highly effective for pain relief,⁵ but adherence to published protocols is often poor and needs to be monitored to optimize pain management.⁷ Opioids have significant disadvantages, such as frequent and expected adverse effects (nausea and vomiting), a narrow therapeutic margin limiting their use due to respiratory depression, and finally a significant potential for misuse and overdose. These problems are well known to caregivers and may contribute to opiophobia and subsequent oligoanalgesia.⁸ Therefore, opioid-sparing drugs or combinations of opioid and nonopioid analgesics may offer an advantage in acute pain control.^{9,10} Unfortunately, research on the combination of opioids with other pain medications in the emergency setting is still controversial and there is a paucity of data.¹⁰⁻¹³ Widely accepted concepts of pain management in the ED typically favor individual and titrated dosing of opioids,^{14,15} but particularly within these pain management concepts there is a lack of randomized trials of combining titrated opioids with other drugs such as acetaminophen (paracetamol), to reduce the total amount of opioids required for acute pain relief.

We therefore conducted this prospective multicenter trial with titrated and individualized opioid dosing in patients presenting to the EDs with moderate to severe pain of any origin, type, or location. Our hypothesis was that a double-blind addition of intravenous (IV) acetaminophen or placebo might favor acetaminophen in terms of faster pain relief or a lower opioid dose to achieve pain relief.

METHODS

Study design and setting

This is a multicenter, randomized (1:1), double-blind, placebo-controlled, parallel-group design trial, conducted in two tertiary EDs in Switzerland. The study was approved by the local ethics committee (EKOS/EKNZ ID 2018-02226) and registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT03843281), and Consolidated Standards of Reporting Trials (CONSORT) guidelines were followed.¹⁶

The study took place from May 2019 to October 2020 in the ED of the Cantonal Hospital of St. Gallen, Switzerland, with an annual census of 40,000 patients, and from October 2019 to October 2020 in the ED of the University Hospital of Basel, Switzerland, with an annual census of over 50,000 patients. Both EDs serve respectively

as tertiary referral care centers for the northeast and northwest of Switzerland.

Selection of participants

Patients were screened during daytime (from 07:30 to 23:00 at the ED of the Cantonal Hospital of St. Gallen and from 08:00 to 17:00 at the ED of the University Hospital of Basel) at triage by the triage team (nurse or physician). Eligible participants were all adults aged 18 or over presenting to the ED with a pain score on the Numeric Rating Scale (NRS; 0 to 10) of four or more who provided informed consent. Initial oral consent was permitted to rapidly treat patients with severe pain in accordance with the institutional review boards. In these cases, oral consent was registered on the case report form (CRF) of the study. Written consent was subsequently obtained after the patient's response to analgesia. Exclusion criteria were analgesia (including acetaminophen and/or NSAIDs) in the last 6 h prior to the ED visit, current analgesia with extended-release drugs and/or opioids, chronic pain (defined as pain lasting longer than 7 days), contraindications and/or refusal to either acetaminophen and/or morphine application, pregnancy and/or breastfeeding, Glasgow Coma Scale (GCS) < 13, systolic blood pressure (sBP) < 90 mmHg, peripheral oxygen saturation (SpO₂) < 90% under a maximum of 4 L/min O₂, "fast-track" patients (patients with minor injuries, see-and-treat patients), or a planned local anesthesia or nerve block at the time of triage.

Randomization and intervention

Patients were asked at triage to rate their pain using a NRS from 0 ("no pain") to 10 ("worst possible pain"). If a patient was eligible for the study, the study team was notified, ensuring that the study criteria were met, and obtained written (or initially oral) consent. The patients were randomly selected and initially received an IV infusion of 1 g acetaminophen for 10 min or the respective matching placebo (sodium chloride 0.9%). At the same time morphine 0.1 mg/kg body weight was administered intravenously. Participants were randomly assigned to one of the two treatment groups using simple randomization procedures. We used randomly permuted blocks with block sizes ranging from two to eight for up to 200 patients per study center to create an allocation sequence table. After enrollment in the study, an independent study assistant prepared the investigational compound (acetaminophen 1 g/100 ml or sodium chloride 0.9% 100 ml) and transferred the solution into a dark plastic bag to blind both patient and investigator. The blinded infusion and the patient were assigned a corresponding sequential number. The infusion was administered to the patient at the same time as the first dose of morphine. The patients, nurses, and physicians (including investigators) were blinded for the assigned intervention. After the initial treatment, pain was measured again every 15 min using the NRS (0-10) and blood pressure (BP), heart rate, and respiratory rate (RR), SpO₂,

and GCS were recorded. If pain was still ≥ 4 on the NRS, and all safety criteria absent (GCS < 13 , SpO₂ $< 90\%$ with a maximum of 4 L/min O₂, sBP < 90 mmHg), an additional dose of morphine 0.05 mg/kg IV was given. Morphine administration was repeated every 15 minutes until the pain reached < 4 (NRS) or the patient reached safety criteria. We used locally defined safety criteria for exclusion and subsequent dosing, as there are no internationally defined safety criteria.¹⁷ Pain < 4 (NRS) was defined as "pain relief." The patient was instructed to inform the study team if pain increased to ≥ 4 (NRS). In this case, the time was recorded and additional analgesia with morphine 0.05 mg/kg IV was administered every 15 min until the pain reached < 4 (NRS) again or the patient developed safety concerns. No other emergency medication was planned. Patients receiving sedation or other analgesics (according to the treating physician and after consultation with the principal investigator) were excluded from the analysis. The effect of the intervention was observed for a total of 4 h after the first infusion of the study medication (acetaminophen and morphine or placebo and morphine; Figure S1). All study-relevant data (pain scores, vitals, etc.) were recorded on a CRF by the treating team (nurse and physician) immediately after assessment. Demographic data were recorded at randomization by the study team using the same CRF. All data were transferred to the electronic CRF (SecuTrial, interActive Systems) by the study team.

Outcomes

The primary outcome was the total amount of morphine used until the first pain relief, comparing acetaminophen and placebo groups. Secondary outcomes were

- The total amount of morphine needed to achieve and maintain pain relief in the first 4 h;
- The time to pain relief (defined as the time to reach an NRS < 4 for the first time after administration of medication);
- The time to recurrence of pain after pain relief;
- And the frequency of AEs.

AEs were entered into the CRF by caregivers as previously described. Caregivers could choose a predefined AE (injection pain, dizziness, numbness, nausea, vomiting, hypotension, respiratory depression, GCS < 13) or free text. The severity of AE was classified as follows: mild (mild symptoms, clinical or diagnostic observation only, no intervention indicated), moderate (minimal, local or noninvasive intervention indicated), or severe (severe or medically significant but not immediately life-threatening, hospitalization indicated for AE only, disabling, life-threatening consequences, urgent intervention indicated, death related to AE).¹⁸ The causality of AE related to the intervention was classified as follows: definite (temporal relationship, improvement after dechallenge, recurrence after rechallenge, or other evidence of drug-related cause), probable (temporal relationship, improvement after dechallenge, no other cause evident), possible (temporal relationship, other cause possible), unlikely (any

assessable reaction that does not meet the other conditions), or unrelated (causal relationship can be excluded).

For the mean morphine dose required to reach pain relief, a subgroup analysis for the body region and type of pain was performed. The classification of the patients according to body region and pain time was carried out in a blinded manner by the principal investigator. Only subgroups including at least 20 patients were to be analyzed.

Statistical analysis

Sample size was calculated using simulations, which provide a flexible way to calculate sample size when simple formulae are not applicable.¹⁹ The required sample size was obtained by simulating cumulative doses of morphine for different numbers of patients with realistic assumptions about the initial distribution of pain scores based on clinical observations, the mean effect per injection of morphine and the individual variation of this effect based on standard deviations (2.0–2.5) reported by Masoumi et al.²⁰ The added effect of acetaminophen was chosen to reduce the mean morphine dose by 20% according to previous meta-analyses.^{11,21} Based on 1000 simulations per patient number, 100 patients per treatment group were calculated to achieve 90% power to reject the null hypothesis in a permutation test.

The morphine dose required for pain relief (primary endpoint) was calculated as the total morphine dose required to reduce pain to a NRS score < 4 . As each individual morphine bolus was determined by patient weight, the primary analysis was performed for morphine dose per kg body weight. Additionally, an analysis of the absolute morphine dose in mg was performed. The difference in mean dose between the two treatment groups was tested against a null distribution generated by random permutation of the treatment groups (10,000 permutations). The two-sided p-value was defined as the proportion of permutations resulting in a difference equal to or greater than that observed in absolute value. A nonparametric 95% confidence interval (CI) for the difference in mean dose was obtained by simple bootstrapping, using the 2.5% and 97.5% quantiles of 10,000 bootstrapped values. This method was chosen to avoid making assumptions about the underlying distribution. The same test principle was applied for total morphine dose needed until the end of the study.

The time required for pain relief was analyzed with Kaplan–Meier curves and compared between the two treatment groups with a log-rank test. Patients who received rescue medication were censored until the time of rescue medication. The pain-free interval was also analyzed with Kaplan–Meier curves and compared between the two treatment groups with a log-rank test. The median time to pain recurrence was compared using the Mann–Whitney U-test. As a subgroup analysis for the primary endpoint, total morphine dose was stratified by demographic criteria, pain type, and morphine-related AEs. The frequency of AEs was analyzed in two ways. First, the proportion of AEs observed in each

treatment group was compared with the proportion expected based on the number of patients in each group (50%) using an exact binomial test. This procedure was chosen because some patients experienced more than one AE. The frequency of each type of event was similarly analyzed. Second, the proportion of patients per group experiencing at least one AE was compared using a chi-square test. Significant permutation tests were adjusted for multiple testing using the Bonferroni–Holm method.

Each analysis was performed for the available data, except for the per-protocol analysis of the primary endpoint. Missing data were not imputed. We defined a p-value of less than 0.05 to be statistically significant in all analyses. All evaluations were performed with the R software language and environment for statistical computing, R Foundation for Statistical Computing (R version 4.0.2).

RESULTS

Characteristics of study subjects

A total of 4580 patients were screened for eligibility between May 2019 and October 2020. After the exclusion criteria were applied, 202 patients were included for the primary intention-to-treat (ITT) analysis (102 patients in the acetaminophen group, 100 in the placebo group). For the per-protocol (PP) analysis, three patients were excluded (two patients in the acetaminophen group, one in the placebo group), leaving 100 patients in the acetaminophen group and 99 patients in the placebo group (Figure 1).

Of the 202 patients included, 177 (87 in the acetaminophen group, 90 in the placebo group) were monitored for the planned 4h after the first treatment (acetaminophen and morphine or placebo and morphine). Secondary outcomes were analyzed for 212 (AEs) to 177 patients (total dose of morphine). Each subgroup is shown in Table S1 and Figure S2, respectively.

Baseline demographic and clinical characteristics were similar in the acetaminophen and placebo groups. The median age was 46 years (range 18–89 years), and 62% were male. The median initial pain score was 8 (range 4–10). Abdominal pain was the most common pain location (75 patients, 34.1%) and “dull” the most common pain quality (85 patients, 38.6%) (Table 1). The mean \pm SD time from randomization to the first dose of medication was 17.7 ± 11.8 min in the acetaminophen group, and 16.2 ± 11.1 min in the placebo group.

Outcomes

Primary outcome

The mean \pm SD morphine dose required to achieve initial pain relief in the ITT analysis was 0.15 ± 0.07 mg/kg or 12.0 ± 5.8 mg in the acetaminophen group and 0.15 ± 0.07 mg/kg or 13.0 ± 6.2 mg in the placebo group ($p = 0.2$). The results of the PP analysis were almost identical to those of the ITT analysis (Table 2).

Secondary outcomes

Total morphine dose during 4 h intervention

In the 177 patients with 4-h follow-up, the total morphine dose required to achieve and maintain pain relief was 0.19 ± 0.09 mg/kg or 15.1 ± 7.5 mg in the acetaminophen group, which was not significantly different from the placebo group (0.19 ± 0.10 mg/kg or 15.5 ± 8.6 mg; $p = 0.68$ or $p = 0.78$).

Time to pain relief

In the ITT analysis the median time to pain relief was 30 min (95% CI 17–31 min) in the acetaminophen group and 30 min (95% CI 30–35 min) in the placebo group (hazard ratio [HR] 1.21 [0.92–1.60], $p = 0.18$). In the PP analysis, the median time to pain relief was 26 min (95% CI 16–31 min) in the acetaminophen group and 30 min (95% CI 30–35 min) in the placebo group (HR 1.23 [95% CI 0.93–1.63], $p = 0.14$).

Time to pain recurrence

Forty patients (39.6%) in the acetaminophen group and 38 (38.4%) in the placebo group experienced pain again during the intervention time. The median pain-free period was not determined, as >50% of the patients in both treatment groups were still pain-free at the end of the observation period. The time to pain recurrence was not significantly different between treatment groups (HR 1.23 [95% CI 0.76–1.98], $p = 0.40$). At 180 minutes after pain relief, the estimated proportion of patients who remained pain-free was 63.1% (95% CI 54.2%–73.5%) in the acetaminophen group and 69.9% (95% CI 61.3%–79.8%) in the placebo group (Table 2).

AEs

Twenty-four patients (22.9%) in the acetaminophen group and 34 patients (32.4%) in the placebo group experienced at least one AE. The proportion of patients with at least one AE did not differ significantly between the two groups (chi-squared test, $p = 0.16$). A total of 73 AEs were registered (31 in the acetaminophen group, 42 in the placebo group). The proportion of AEs in the acetaminophen group (42.5%, 95% CI 31.0%–54.6%) was not significantly lower than that expected from the proportion of patients (50%) included in this group (exact binomial test, $p = 0.24$). The most frequent type of AE was nausea, followed by dizziness and vomiting. The proportion of each type of event that occurred in the acetaminophen group ranged from 29% to 75%, but never differed significantly from the expected 50% (Table 3). Of the 31 AEs recorded in the acetaminophen group, 15 (48.4%) were classified as related to the intervention (nine definitely, six probably) and 16 as possibly related or unrelated. Of the 42 AEs recorded in the placebo group, 31 (73.8%) were classified as related to the intervention (seven definitely, 24 probably) and 11 as possibly related. The proportion of related AEs appeared to be lower in the acetaminophen group but this difference was not statistically significant (chi-square test, $p = 0.079$). Of the 31 AEs recorded in the acetaminophen group, 15 (48.4%) were rated as moderate and one (3.2%) as severe. This severe case was a young patient with a

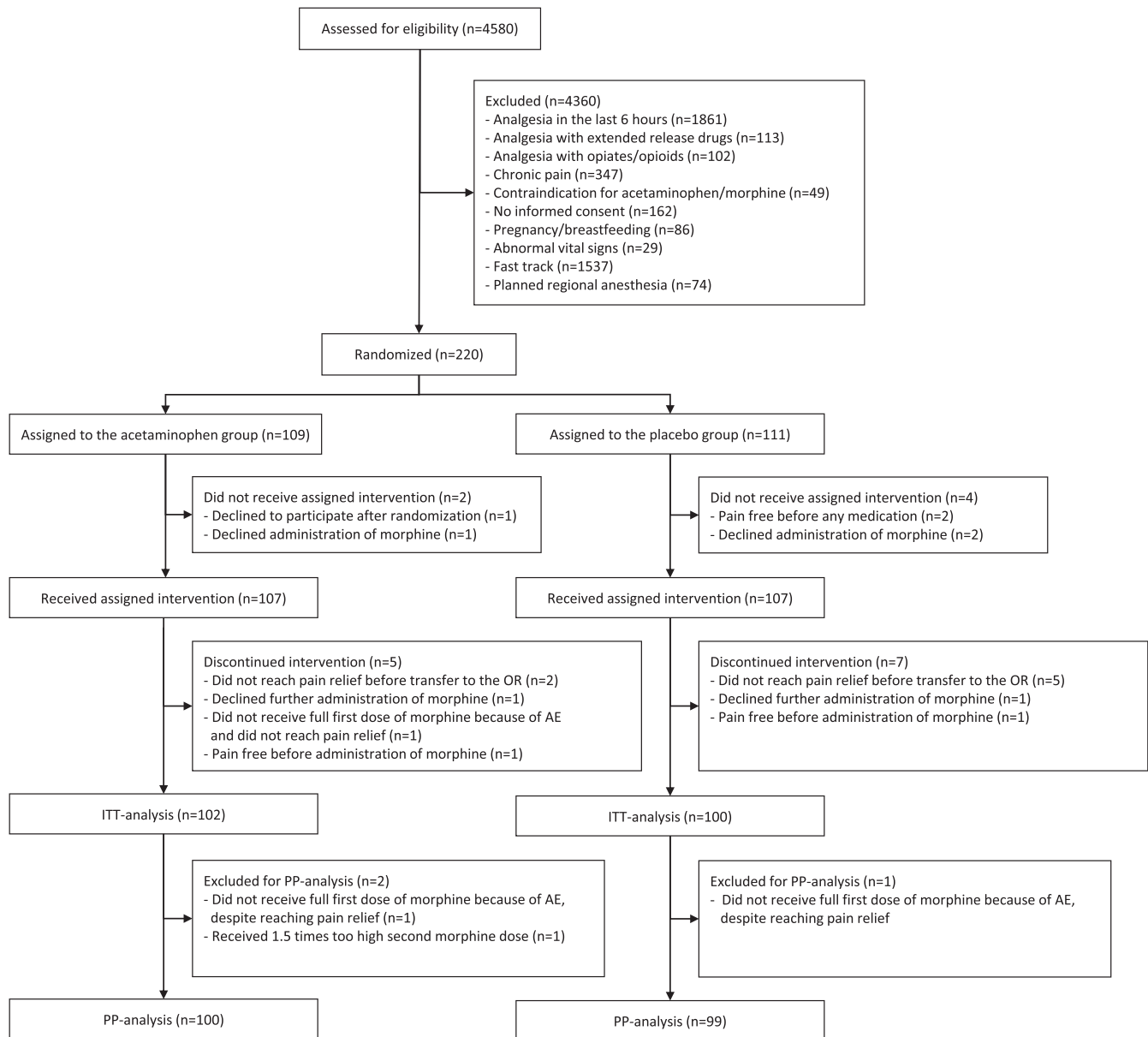


FIGURE 1 Study flow chart. AE, adverse event; ITT = intention to treat; NRS, numeric rating scale; OR, operating room; PP = per protocol. Pain relief = pain < 4 NRS

fracture of the clavicle. The planned outpatient treatment could not take place because a severe orthostatic reaction occurred, leading to unplanned hospitalization. No intervention was required and the patient could be discharged the next day. Of the 42 AEs recorded in the placebo group, 24 (57.1%) were rated as moderate and none as severe. The proportion of moderate or severe AEs did not differ significantly between the two groups (chi-square test, $p = 0.82$).

Subgroup analysis

There was no significant difference in the total morphine dose needed to achieve pain relief according to the location and quality of pain when multiple testing was considered (Table S2).

DISCUSSION

The main findings of this study were excellent pain control using a titrated and individualized morphine analgesia in the majority of ED patients with moderate to severe pain and the absence of a difference between additional acetaminophen or placebo. These results are similar to those of previous studies that showed a lack of superiority of combining hydromorphone with acetaminophen^{22,23} or combining various opioids with acetaminophen.¹³ However, these studies did not take advantage of titrated and individualized opioid therapy, while an older study using the hydromorphone 1 + 1 mg titration approach showed favorable results, but 42% of all patients only needed a single dose, reflecting the inclusion of patients with less severe pain.²⁴

	Patients randomized (n = 220)	Patients included in the primary analysis (n = 202)	
		Acetaminophen (n = 102)	Placebo (n = 100)
Age (years)	46 (18–89)	46 (18–89)	46.5 (18–83)
Sex			
Males	136 (62)	64 (63)	60 (60)
Females	84 (38)	38 (37)	40 (40)
Weight (kg)	82 (45–128)	81 (47–128)	82 (45–120)
Systolic BP (mm Hg)	136 (97–226)	135 (97–205)	137.5 (105–226)
Initial pain NRS	8 (4–10)	8 (4–10)	8 (5–10)
Localization of pain			
Abdominal	75 (34.1)	36 (35.3)	38 (38.0)
Back	17 (7.7)	8 (7.8)	7 (7.0)
Chest	6 (2.7)	2 (2.0)	4 (4.0)
Extremity	46 (20.9)	22 (21.6)	18 (18.0)
Flank	52 (23.6)	27 (26.5)	25 (25.0)
Maxillofacial	1 (0.5)	1 (1.0)	0 (0.0)
Perianal (incl. testicular)	14 (63.6)	6 (5.9)	8 (8.0)
Quality of pain			
Burning	2 (0.9)	1 (1.0)	0 (0.0)
Colicky	27 (12.3)	16 (15.7)	11 (11.0)
Diffuse	14 (63.6)	5 (4.9)	9 (9.0)
Dull	85 (38.6)	45 (44.1)	39 (39.0)
Sharp/stabbing	84 (38.2)	35 (34.3)	41 (41.0)
Additional symptoms			
Nausea	44 (20)	24 (23.5)	17 (17)
Vomiting	18 (8.2)	10 (9.8)	7 (7)
Dizziness	14 (6.4)	8 (7.8)	5 (5)

TABLE 1 Baseline demographic and clinical characteristics of randomized and included patients

Note: Data are reported as median (range) of numeric variables or n (%) of categories.
Abbreviations: BP, blood pressure; NRS, Numeric Rating Scale.

A more recent study combining ibuprofen, followed by acetaminophen alone, or together with oxycodone, showed better analgesia for the combination, but there was no oxycodone group without acetaminophen.²⁵ When comparing acetaminophen with hydromorphone, pain relief was more effective with the opioid—the trade-off being more side effects—but opioid reduction using a combination was not attempted.²⁶

Given the lack of direct comparability with studies using state-of-the-art titrated and individualized morphine therapy (with or without acetaminophen) in patients presenting to the ED with acute pain, a comparison with postoperative pain may be of value. According to a Cochrane review, the amount of opioids needed could be reduced to up to 25% when acetaminophen was added for pain control—with a similar rate of unwanted side effects.¹² However, it seems unlikely that such side effects can be massively reduced in an emergency cohort that often suffers from nausea and vomiting at presentation and before initiation of therapy.²³ Furthermore, it is debatable whether these most frequent side

effects are dose-dependent, as they can occur even at very low doses.²⁷

Overall, it remains unclear why acetaminophen seems to have an opioid-sparing effect in postoperative use but not in patients presenting to the ED with moderate to severe acute pain. However, given the data on fixed-dose opioids^{13,22,23} or titrated and individualized morphine in this study (not providing evidence of differences in efficacy or side effects), it seems unlikely that acetaminophen would have an effect in ED patients. Furthermore, in ED patients with moderate to severe acute pain, initial analgesia with acetaminophen alone may delay administration of opioids and consecutive pain relief and should therefore not be considered standard treatment.

LIMITATIONS

We are aware that this study has its limitations. First, we included patients presenting with pain of different origin, location, and quality.

TABLE 2 Primary and secondary outcomes

Outcomes	Acetaminophen	n	Placebo	n	Difference (95% CI)	p-value
Primary						
Total morphine dose for first pain relief (mg/kg), mean \pm SD ^a						
ITT	0.15 \pm 0.07	102	0.16 \pm 0.07	100	-0.01 (-0.03 to 0.01)	0.22
PP	0.15 \pm 0.07	100	0.16 \pm 0.07	99	-0.01 (-0.03 to 0.01)	0.15
Total morphine dose for first pain relief (mg), mean \pm SD ^a						
ITT	12.0 \pm 5.8	102	13.0 \pm 6.2	100	-1.0 (-2.7 to 0.6)	0.23
PP	12.0 \pm 5.7	100	13.1 \pm 6.1	99	-1.1 (2.7 to 0.6)	0.18
Secondary						
Total amount of morphine at 4 h (mg/kg), mean \pm SD ^b						
ITT	0.19 \pm 0.09	87	0.19 \pm 0.10	90	-0.01 (-0.03 to 0.02)	0.68
PP	0.19 \pm 0.09	87	0.19 \pm 0.10	90	-0.01 (-0.03 to 0.02)	0.68
Total amount of morphine at 4 h (mg), mean \pm SD ^b						
ITT	15.1 \pm 7.5	87	15.5 \pm 8.6	90	-0.36 (-2.80 to 2.03)	0.78
PP	15.1 \pm 7.5	87	15.5 \pm 8.6	90	-0.36 (-2.80 to 2.03)	0.78
Time to pain relief (min), median (95% CI) ^c						
ITT	30 (17 to 31)	105	30 (30 to 35)	106	1.21 (0.92 to 1.60) ^d	0.18
PP	26 (16 to 31)	102	30 (30 to 35)	104	1.23 (0.93 to 1.63) ^d	0.14
Time to pain recurrence (min), median (IQR) ^e						
ITT	48 (33 to 107)	40	61.5 (35 to 145)	38		0.38

Note: Pain relief = pain < 4 NRS.

Abbreviations: HR, hazard ratio; IQR, interquartile range; ITT, intention to treat; NRS, Numeric Rating Scale; PP, per protocol.

^aData available for 202 patients.

^bData available for 177 patients (25 patients had early transport to the operating room).

^cData available for 211 patients in the ITT population and for 206 patients in the PP population.

^dHR (95% CI).

^eData available for 78 patients with pain recurrence.

TABLE 3 AEs during observation

	Overall ^a (n = 91)	Acetaminophen n = 37	Placebo (n = 54)	% Acetaminophen, ^b 41% (31%-52%)	p-value ^c
Numbness	4 (4.4)	3 (8.1)	1 (1.8)	75 (19-99)	0.63
Dizziness	16 (17.6)	6 (16.2)	10 (18.5)	37 (15-65)	0.45
Nausea	46 (50.5)	18 (48.6)	28 (51.9)	39 (25-55)	0.18
Vomiting	15 (16.5)	7 (18.9)	8 (14.8)	47 (21-73)	1.00
Hypotension	3 (3.3)	1 (2.7)	2 (3.7)	33 (1-91)	1.00
Respiratory depression	7 (7.7)	2 (5.4)	5 (9.3)	29 (4-71)	0.45

Note: Data are reported as n (%) unless otherwise specified.

^aData available for 212 patients (106 in each group). Multiple symptoms were counted; the numbers of patients affected were 24 in the acetaminophen and 34 in the placebo group, respectively.

^bProportion (%) of events observed in the acetaminophen group (with 95% CI).

^cp-values from exact binomial tests comparing the observed proportion to that expected under the null hypothesis (50%) based on the proportion of evaluable patients that were in the acetaminophen group.

It is possible that acetaminophen may have morphine-sparing potential in certain subgroups, as has been shown in postoperative patients. However, our group size was too small to perform subgroup analyses. Second, we only included patients at two sites, both in

academic EDs in cities with a similar population. External validity is therefore limited. Third, we did not include patients with mild to moderate pain, but rather with severe pain (around 8/10 NRS) and administered about 12 mg (or 0.15 mg/kg) of morphine for pain relief.

Totally administered doses of about 1.6 mg (or 0.2 mg/kg) within 4 h could be considered high. However, a dose of 0.1 mg/kg has been shown to lack an effect in most ED patients.²⁸ Doses of 0.15 mg/kg have been shown to be statistically—but not clinically—superior.⁴ We can only speculate whether results might be similar in patients with less pain or in other locations (about half of our patients suffered from abdominal or flank pain). Fourth, we had a number of exclusion criteria, particularly previous analgesia, and were therefore only able to recruit about 5% of all patients presenting at daytime, in spite of extensive screening. We did not screen at night, which could also be cause to an inclusion bias, as patients presenting at night could be different. Fifth, despite a nonsignificant difference in the two groups, the lower CI in the acetaminophen group in the time-to-pain-relief analysis could theoretically indicate a shorter time to pain relief. Finally, we did not assess other patient-related outcomes besides pain, realizing that pain is not all that matters to patients.

CONCLUSION

We conclude that there is no evidence to support the hypothesis that one intravenous dose of acetaminophen has an additional effect on pain control or a morphine-sparing effect. However, the pain management used was highly effective, with 80% of all patients reporting pain relief within 60 minutes of starting therapy. We therefore cannot exclude a ceiling effect due to the efficacy of titrated intravenous morphine. In emergency patients with acute and moderate to severe pain we therefore recommend the use of titrated intravenous morphine and abstain from additional intravenous acetaminophen.

AUTHOR CONTRIBUTIONS

Bruno Minotti and Robert Sieber conceived and designed the study. Bruno Minotti, Robert Sieber, Alexander Ott, and Roland Bingisser performed the interventions and the measurements. Sabine Gusewell performed the statistical analysis. All authors discussed and interpreted the results. Bruno Minotti and Gregory Mansella wrote the first draft of the manuscript, and all authors contributed substantially to the final version. Roland Bingisser supervised the project.

ACKNOWLEDGMENTS

The authors acknowledge the following: Emergency Department, Cantonal Hospital of St. Gallen—Alexandra Atzl, Peter Düster, Kathrin Genta, Bodo Giannone, Karin Hasler, Alessandro Jessula, Stefan Loos, Rosa-Maria Marquez-Pinilla, Angelina Meier, Susanne Morf, Fabian Napieralski, Jens Nitzsche, Lena Öhrström, Hans-Jürgen Richter, Jörg Scheler, Peggy Schmeink, Elke Schmidt, Dieter von Ow, Evelyn Dähler and all medical office assistants of the emergency department, Elisabeth Heeb Steiner and all nurses of the emergency department; Sabine Gusewell, Clinical Trial Unit, Cantonal Hospital of St. Gallen, St. Gallen, Switzerland, for statistical analysis; Emergency Department, University Hospital Basel—Nadja Handschin, Tobias Käppeli, Alexandra Malinowska, Oliver Müller, Marco Rüegg, Sarah Thiel, Marc Schläfli, and all nurses of the emergency department.

CONFLICT OF INTEREST

All authors declare no conflict of interest.

ORCID

Bruno Minotti  <https://orcid.org/0000-0002-4820-9968>

REFERENCES

- Todd KH, Ducharme J, Choiniere M, et al. Pain in the emergency department: results of the pain and emergency medicine initiative (PEMI) multicenter study. *J Pain*. 2007;8:460-466.
- Bingisser R, Dietrich M, Nieves Ortega R, Malinowska A, Bosia T, Nickel CH. Systematically assessed symptoms as outcome predictors in emergency patients. *Eur J Intern Med*. 2017;45:8-12.
- Busse JW, Sadeghirad B, Oparin Y, et al. Management of Acute Pain from non-low Back, musculoskeletal injuries: a systematic review and network meta-analysis of randomized trials. *Ann Intern Med*. 2020;173:730-738.
- Birnbaum A, Esses D, Bijur PE, Holden L, Gallagher EJ. Randomized double-blind placebo-controlled trial of two intravenous morphine dosages (0.10 mg/kg and 0.15 mg/kg) in emergency department patients with moderate to severe acute pain. *Ann Emerg Med*. 2007;49:445-453, 453.e1-2.
- Chang AK, Bijur PE, Gallagher EJ. Randomized clinical trial comparing the safety and efficacy of a hydromorphone titration protocol to usual care in the management of adult emergency department patients with acute severe pain. *Ann Emerg Med*. 2011;58:352-359.
- Wong A, Potter J, Brown NJ, Chu K, Hughes JA. Patient-reported outcomes of pain care research in the adult emergency department: a scoping review. *Australas Emerg Care*. 2021;24:127-134.
- Stephan FP, Nickel CH, Martin JS, Grether D, Delport-Lehnen K, Bingisser R. Pain in the emergency department: adherence to an implemented treatment protocol. *Swiss Med Wkly*. 2010;140:341-347.
- Bertrand S, Meynet G, Taffé P, et al. Opiophobia in emergency department healthcare providers: a survey in Western Switzerland. *J Clin Med*. 2021;10:1353.
- Rowland KD, Fuehrer J, Motov SM, Vilke G, Rosenbaum SB, Quenzer F. Should antiemetics be given prophylactically with intravenous opioids while treating acute pain in the emergency department?: clinical practice paper approved by American Academy of emergency medicine clinical guidelines committee. *J Emerg Med*. 2020;58:706-709.
- Bounes V, Charriton-Dadone B, Levraut J, et al. Predicting morphine related side effects in the ED: an international cohort study. *Am J Emerg Med*. 2017;35:531-535.
- Remy C, Marret E, Bonnet F. Effects of acetaminophen on morphine side-effects and consumption after major surgery: meta-analysis of randomized controlled trials. *Br J Anaesth*. 2005;94:505-513.
- McNicol ED, Ferguson MC, Haroutounian S, Carr DB, Schumann R. Single dose intravenous paracetamol or intravenous propacetamol for postoperative pain. *Cochrane Database Syst Rev*. 2016;2016:Cd007126.
- Blok Z, Ridderikhof ML, Goddijn H, Berendsen M, Hollmann MW. Intravenous acetaminophen does not have an opioid sparing effect in emergency department patients with painful conditions. *Am J Emerg Med*. 2021;39:1-5.
- Lvovschi V, Aubrun F, Bonnet P, et al. Intravenous morphine titration to treat severe pain in the ED. *Am J Emerg Med*. 2008;26:676-682.
- Riou B, Aubrun F. Titrated doses are optimal for opioids in pain trials. *Lancet*. 2016;388:961-962.
- Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010;340:c332.
- medStandards. Accessed January 24, 2022. <https://www.medstandards.ch>

18. SR 810.305—Ordinance on Clinical Trials with the exception of clinical trials medical devices (Clinical Trials Ordinance, ClinO). September 20, 2013. Accessed January 24, 2022. <https://www.fedlex.admin.ch/eli/cc/2013/643/en>
19. Arnold BF, Hogan DR, Colford JM Jr, Hubbard AE. Simulation methods to estimate design power: an overview for applied research. *BMC Med Res Methodol*. 2011;11:94.
20. Masoumi K, Forouzan A, Asgari Darian A, Feli M, Barzegari H, Khavanin A. Comparison of clinical efficacy of intravenous acetaminophen with intravenous morphine in acute renal colic: a randomized, double-blind, controlled trial. *Emerg Med Int*. 2014;2014:571326.
21. Liang L, Cai Y, Li A, Ma C. The efficiency of intravenous acetaminophen for pain control following total knee and hip arthroplasty: a systematic review and meta-analysis. *Medicine (Baltimore)*. 2017;96:e8586.
22. Chang AK, Bijur PE, Ata A, et al. Randomized clinical trial of intravenous acetaminophen as an analgesic adjunct for older adults with acute severe pain. *Acad Emerg Med*. 2019;26:402-409.
23. Bijur PE, Friedman BW, White D, et al. Randomized clinical trial of intravenous (IV) acetaminophen as an adjunct to IV hydromorphone for acute severe pain in emergency department patients. *Acad Emerg Med*. 2020;27:717-724.
24. Chang AK, Bijur PE, Lupow JB, Gallagher EJ. Randomized clinical trial of the 2 mg hydromorphone bolus protocol versus the "1+1" hydromorphone titration protocol in treatment of acute, severe pain in the first hour of emergency department presentation. *Ann Emerg Med*. 2013;62:304-310.
25. Friedman BW, Irizarry E, Feliciano C, et al. A randomized controlled trial of oxycodone/acetaminophen versus acetaminophen alone for emergency department patients with musculoskeletal pain refractory to ibuprofen. *Acad Emerg Med*. 2021;28:859-865.
26. Barnaby DP, Chertoff AE, Restivo AJ, et al. Randomized controlled trial of intravenous acetaminophen versus intravenous hydromorphone for the treatment of acute pain in the emergency department. *Ann Emerg Med*. 2019;73:133-140.
27. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. *Pain Physician*. 2008;11:S133-S153.
28. Bijur PE, Kenny MK, Gallagher EJ. Intravenous morphine at 0.1 mg/kg is not effective for controlling severe acute pain in the majority of patients. *Ann Emerg Med*. 2005;46:362-367.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Minotti B, Mansella G, Sieber R, Ott A, Nickel CH, Bingisser R. Intravenous acetaminophen does not reduce morphine use for pain relief in emergency department patients: A multicenter, randomized, double-blind, placebo-controlled trial. *Acad Emerg Med*. 2022;00:1-9. doi: [10.1111/acem.14517](https://doi.org/10.1111/acem.14517)