

RESEARCH REPORTS

THE EFFECT OF FENTANYL COMPARED TO MORPHINE ON PAIN SCORE AND CARDIORESPIRATORY VITAL SIGNS IN OUT-OF-HOSPITAL ADULT STEMI PATIENTS

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ABSTRACT

Objective: ST-elevation myocardial infarction (STEMI) is a leading cause of mortality in Australia. Paramedics treating adults with STEMI in the out-of-hospital environment can use fentanyl or morphine to manage the patient's pain, although there is little research comparing the efficacy and safety of these drugs. Therefore, the objective of this study was to compare the effects of fentanyl to morphine on cardiac chest pain and cardiorespiratory vital signs in adult STEMI patients in the out-of-hospital environment.

Methods: We conducted a retrospective analysis of records of 1902 STEMI cases attended by Queensland Ambulance Service paramedics during the 4-year interval from 2013 to 2016. We compared pain score, blood pressure, respiratory rate, and pulse rate between patients administered intravenous fentanyl and intravenous morphine. We used a two-way mixed effects model (drug, time) to assess for main and interaction effects, and where the interaction effect was significant, applied Mann-Whitney U tests to further analyze between-group differences at each time point.

Results: We observed a significant main effect of time on pain score ($p < 0.001$), respiratory rate ($p < 0.05$), and pulse rate ($p = 0.025$), such that these variables all decreased over time. Additionally, we observed a significant drug-time interaction for systolic and diastolic blood pressures (both $p < 0.01$), such that blood pressures decreased over time in the morphine, but not fentanyl, group.

Conclusion: We compared the effects of fentanyl to morphine on cardiac chest pain and cardiorespiratory vital signs in out-of-hospital adult STEMI patients and observed differences in blood pressures only. Morphine appeared to have a depressive effect on systolic and diastolic blood pressure, whereas fentanyl did not. An unanticipated behavioural finding of this research is that, in the absence of a definitive guideline, paramedics appear to use fentanyl when patients may be at risk of developing hypotension.

INTRODUCTION

Acute coronary syndrome including ST-elevation myocardial infarction (STEMI) was the leading cause of death in Australia in 2021, accounting for approximately 11% of all deaths (Australian Bureau of Statistics, 2021). The predominant cause of STEMI is a disruption to epicardial blood flow, with associated chest pain

being a key diagnostic feature (Baruah & Hartley, 2023). When attending a patient with STEMI, the paramedics' primary goal is to ensure early access to thrombolytic therapy while controlling the patient's pain and reducing their likelihood of experiencing adverse effects from myocardial hypoxia until their transition to definitive care (Chew et al., 2016). To achieve this goal, current Australian ambulance protocols recommend treatment with aspirin, oxygen, nitroglycerine, thrombolytic drugs, and either fentanyl or morphine for analgesia (Chew et al., 2016).

Fentanyl and morphine are both opioid analgesics. While previous research has investigated the efficacy and safety of each drug (Fleischman et al., 2011; Galinski et al., 2005; Huang et al., 2022; Stoeckel et al., 1982; Thompson et al., 1995; Watso et al., 2022; Weldon et al., 2016), much of this research has used healthy volunteers (Huang et al., 2022; Stoeckel et al., 1982; Thompson et al., 1995; Watso et al., 2022). Comparatively few studies have directly compared these two drugs that are the mainstay of analgesia in paramedicine. For example, a study by Fleischman et al. (2011), compared the efficacy and safety of fentanyl and morphine in the out-of-hospital setting, but this study faced limitations due to the lack of standardized patient conditions. Treating a patient with STEMI presents a unique challenge for paramedics because the pathology can create hemodynamic instability leading to an increased risk of adverse events. As such, it is particularly problematic that research has not yet investigated whether fentanyl or morphine is more appropriate for use in adult STEMI patients. A 2016 study (Weldon et al.) investigated the effects of fentanyl and morphine on individuals experiencing suspected ischemic chest pain. Importantly, this study did not require confirmation of the specific underlying pathology. Additionally, there are concerns about the study's statistical power, and it remains uncertain whether the study excluded patients who received treatments that could potentially introduce confounding variables. This existing literature underscores the need to compare fentanyl and morphine more comprehensively and with attention to detail. Particularly, assessing their safety and efficacy in adult STEMI patients is likely to be crucial for guiding drug selection and enabling paramedics to confidently choose the best analgesic for this haemodynamically vulnerable population.

The limited information available suggests that both fentanyl and morphine offer comparable analgesic effects (Fleischman et al., 2011; Galinski et al., 2005; Weldon et al., 2016). While morphine has been shown to be associated with decreases in blood pressure in healthy volunteers (Watso et al., 2022), fentanyl does not seem to produce the same effect (Huang et al., 2022). However, both fentanyl (Stoeckel et al., 1982) and morphine (Thompson et al., 1995) have been reported to produce respiratory depression in healthy adults. Given these findings, the lack of research investigating the suitability of fentanyl versus morphine for adult STEMI patients is concerning, given the specific challenges posed by this medical condition.

The aim of this research is to compare the effects of paramedic-administered fentanyl and morphine on cardiac chest pain and cardiorespiratory vital signs in out-of-hospital adult STEMI patients. Building upon the limited existing research, our central hypothesis is that we will observe no differences in pain score between fentanyl and morphine groups. Based on the data reported for healthy volunteers, we anticipate that the morphine but not fentanyl group will exhibit decreases in systolic and diastolic blood pressures, and there will be no difference in the change in respiratory rate between groups.

By comparing the efficacy and safety of fentanyl and morphine in adult STEMI patients in the out-of-hospital paramedicine environment, this research aims to contribute key data to support paramedics in selecting the most appropriate analgesia for adult STEMI patients and inform the future development of clinical guidelines.

METHODS

STUDY DESIGN AND SETTING

We conducted a retrospective observational analysis of a state-wide (Queensland Ambulance Service) sample of STEMI patient case data recorded by registered paramedics while providing patient care during the 4-year interval from 1 January 2013 to 31 December 2016 inclusive. This was a unique time period, during which both fentanyl and morphine were preferred analgesic options for acute coronary syndrome, allowing a direct comparison in the one study. Each case in the dataset represented 1 STEMI patient. No cases of non-cardiac ST elevation were included in the dataset. All case records in the dataset were stored and maintained by the Queensland Ambulance Service. This research was approved by the Charles Sturt University Human Ethics Committee (protocol number H20058) and the Queensland Ambulance Service Research and Innovation Committee (Ref: 20/00383).

PARTICIPANTS

The Queensland Ambulance Service provided a preliminary dataset that included 2721 de-identified records of cases attended in the study interval where the patient was an adult (18 to 75 years) with confirmed STEMI. We applied further inclusion and exclusion criteria to the preliminary dataset, as presented in Table 1, to reduce possible bias related to confounding treatments and patient criticality.

	Inclusion	Exclusion
Age	≥18 years and <75 years	<18 years or ≥75 years
Diagnosis	Confirmed STEMI	Any comorbid pathology
Analgesic	Morphine OR fentanyl	Combination of morphine and fentanyl Any other pain relief
Administration	Intravenous only	Intraosseous or intramuscular or combination
Dose Information	Recorded	Unavailable
Contact time	≥20 minutes	<20 minutes
Sets of Observations	Recorded at ≥2 time points	Recorded at <2 time points
Confounding Treatment	None	Treated with opioid in last 24 hours Treated with regular (daily) opioid and/or drug(s) for neuralgia
Criticality		Pulse rate <40 beats per minute Pulse rate >160 beats per minute Respiratory rate <8 breaths per minute
Other		Corrupted data

Table 1. Criteria for inclusion or exclusion of adult STEMI case record in analysis.

In all cases included in the study, clinically appropriate doses of intravenous fentanyl or intravenous morphine were administered by a registered paramedic as part of providing patient care. To control for possible effects of other interventions, we excluded cases where the patient appeared to be in a hemodynamically or respiratory critical condition because of the high likelihood the patient would have been treated with adrenaline, amiodarone, atropine, or fluids, which are known to confound our variables of interest. After applying our inclusion and exclusion criteria (Table 1), 1902 cases remained for analysis. For a summary of the characteristics of each group, see Table 2.

MEASURES

The outcome variables selected for analysis were pain score (0-10 numbered rating scale), pulse rate (beats per minute), systolic blood pressure (millimeters of mercury [mmHg]), diastolic blood pressure (mmHg), and respiratory rate (breaths per minute). All outcome variables were recorded by registered paramedics, according to standard practice at the time of the study, as part of providing patient care.

STATISTICAL ANALYSIS

All data were checked for normality using the Shapiro-Wilk statistic. Dependent data (pain score, pulse rate, systolic blood pressure, diastolic blood pressure, respiratory rate) were analyzed using a two-way mixed effects model (Factors: Time, Drug) to assess for main and interaction effects. For variables where we identified a statistically significant interaction effect, we then performed Mann-Whitney U tests to assess between-group differences at each time point. The threshold for statistical significance was set at $p < 0.05$. All analyses were conducted using Jamovi (Ver 2.3.21.0).

RESULTS

Mean age, initial pain score, and initial respiratory rate were not significantly different between the fentanyl and morphine groups (all $p > 0.05$). Initial systolic blood pressure, initial diastolic blood pressure, and initial pulse rate were lower in the fentanyl group than the morphine group (all $p < 0.001$; Table 2).

PAIN SCORE

The change in pain score over time for the fentanyl compared to morphine groups is shown in Figure 1. The main effect of drug and the drug-time interaction effect for pain

	Fentanyl	Morphine
N (males, females)	688 (567, 121)	1214 (944, 270)
	Mean ± SD	Mean ± SD
Age (years)	59 ± 10	57 ± 10 †
Initial Pain Score (0-10)	7 ± 2	7 ± 2 †
Initial Pulse Rate (bpm)	75 ± 2	78 ± 2 *
Initial SBP (mmHg)	130 ± 26	139 ± 26 *
Initial DBP (mmHg)	88 ± 18	84 ± 18 *
Initial RR (breaths per minute)	18 ± 3	18 ± 3 †
Time from T0 to first dose (minutes)	14.9 ± 9.4	15.3 ± 10.0 †
Number of doses	3.3 ± 1.6	3.2 ± 1.5 †
Dose-dose interval (minutes)	13.0 ± 7.1	13.5 ± 7.3 †
Note: bpm, beats per minute; DBP, diastolic blood pressure; T0, 0-minute time point; mmHg, millimeters of mercury; RR, respiratory rate; SBP, systolic blood pressure; SD, standard deviation; * $p < 0.05$; † $p > 0.05$.		

Table 2. Characteristics of fentanyl and morphine groups.

score were not statistically significant ($p = 0.210$; $p = 0.116$). The main effect of time was significant, such that the mean pain score decreased from 7/10 at 0 minutes to 4/10 at 60 minutes ($p < 0.001$).

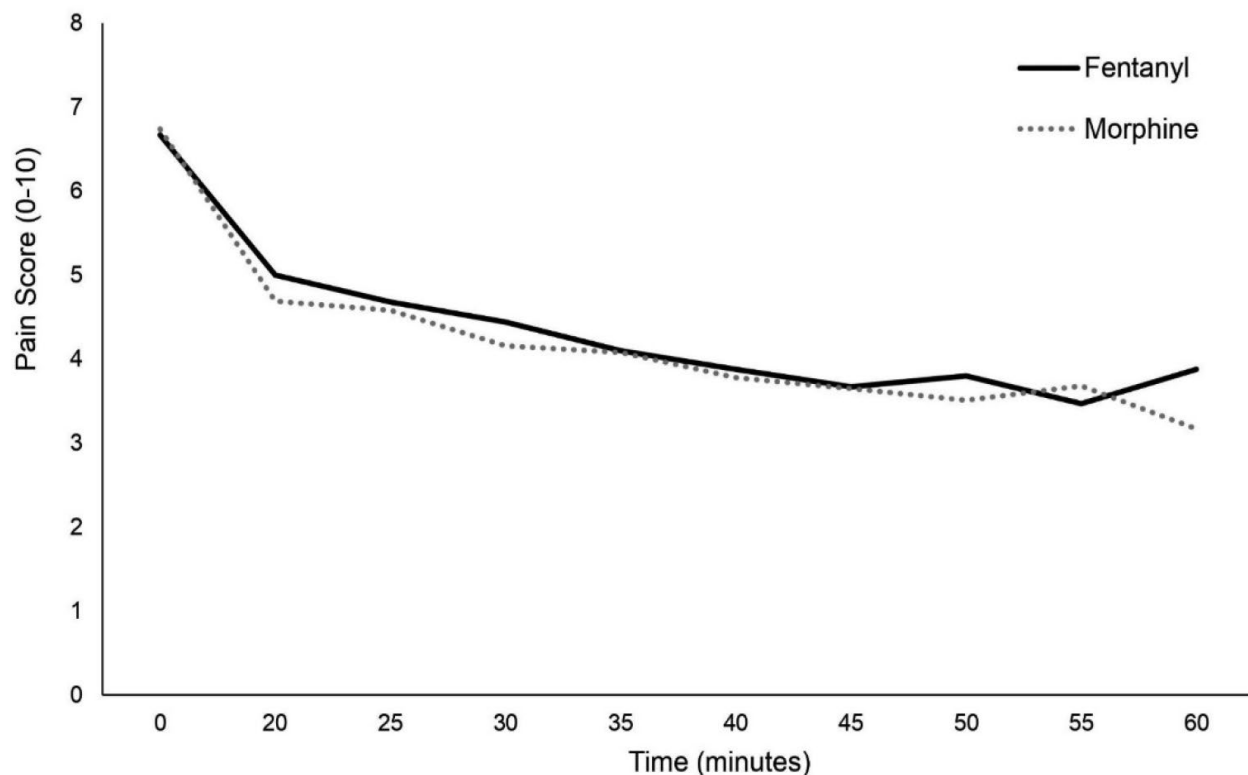


Figure 1. Change in pain score over time for adults with ST-elevation myocardial infarction administered intravenous fentanyl compared to intravenous morphine.

BLOOD PRESSURE

Figure 2 presents the change in systolic and diastolic blood pressure over time for the fentanyl and morphine groups.

SYSTOLIC BLOOD PRESSURE

The main effect of the drug, the main effect of time, and the drug-time interaction effect on systolic blood pressure were statistically significant (all $p < 0.001$). When analyzing between-group differences at each time point from 0 to 60 minutes, systolic blood pressure was significantly lower in fentanyl compared to morphine at 0 minutes ($\bar{x}_{\text{fentanyl}} = 130\text{mmHg}$; $\bar{x}_{\text{morphine}} = 139\text{mmHg}$; $p < 0.001$), 20 minutes ($\bar{x}_{\text{fentanyl}} = 132\text{mmHg}$; $\bar{x}_{\text{morphine}} = 139\text{mmHg}$; $p < 0.001$), and 30 minutes ($\bar{x}_{\text{fentanyl}} = 130\text{mmHg}$; $\bar{x}_{\text{morphine}} = 133\text{mmHg}$; $p = 0.036$). Systolic blood pressure at all other time points was comparable (all $p > 0.05$).

DIASTOLIC BLOOD PRESSURE

The main effect of the drug, the main effect of time, and the of drug-time interaction effect on diastolic blood pressure were significant (all $p < 0.001$). With respect to the between-group differences at each time point from 0 to 60 minutes, diastolic blood pressure was significantly lower in the fentanyl group than the morphine group at 0 minutes

($\bar{x}_{\text{fentanyl}} = 83\text{mmHg}$; $\bar{x}_{\text{morphine}} = 88\text{mmHg}$; $p < 0.001$), 20 minutes ($\bar{x}_{\text{fentanyl}} = 83\text{mmHg}$; $\bar{x}_{\text{morphine}} = 88\text{mmHg}$; $p < 0.001$), 25 minutes ($\bar{x}_{\text{fentanyl}} = 83\text{mmHg}$; $\bar{x}_{\text{morphine}} = 85\text{mmHg}$; $p = 0.026$), and 30 minutes ($\bar{x}_{\text{fentanyl}} = 82\text{mmHg}$; $\bar{x}_{\text{morphine}} = 85\text{mmHg}$; $p = 0.003$). No other significant differences in diastolic blood pressure were observed (all $p > 0.05$).

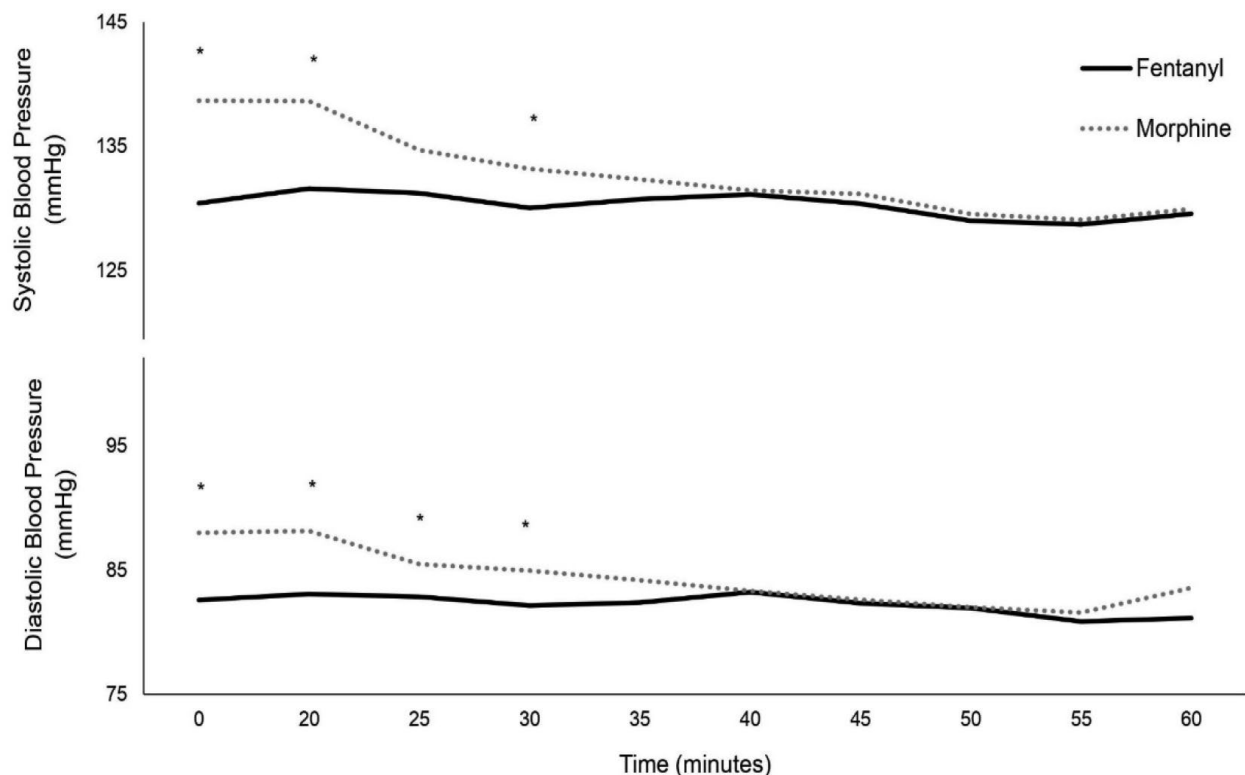


Figure 2. Change in blood pressure over time for adults with ST-elevation myocardial infarction administered intravenous morphine compared to intravenous fentanyl. Note: mmHg, millimeters of mercury; *, $p < 0.05$.

RESPIRATORY RATE

The change in respiratory rate over time for the fentanyl and morphine groups is shown in Figure 3. The main effect of drug, and the interaction effect of drug and time on respiratory rate were not statistically significant ($p = 0.135$; $p = 0.533$). The main effect of time on respiratory rate was significant, with the respiratory rate decreasing from 18.3 breaths per minute at 0 minutes to 17.6 breaths per minute at 60 minutes ($p < 0.001$).

PULSE RATE

The change in pulse rate over time for fentanyl compared to morphine is shown in Figure 4. The main effect of the drug on pulse rate and the main effect of time on pulse rate were both significant ($p < 0.001$; $p = 0.025$, respectively). However, the drug-time interaction effect on pulse rate was not statistically significant ($p = 0.185$).

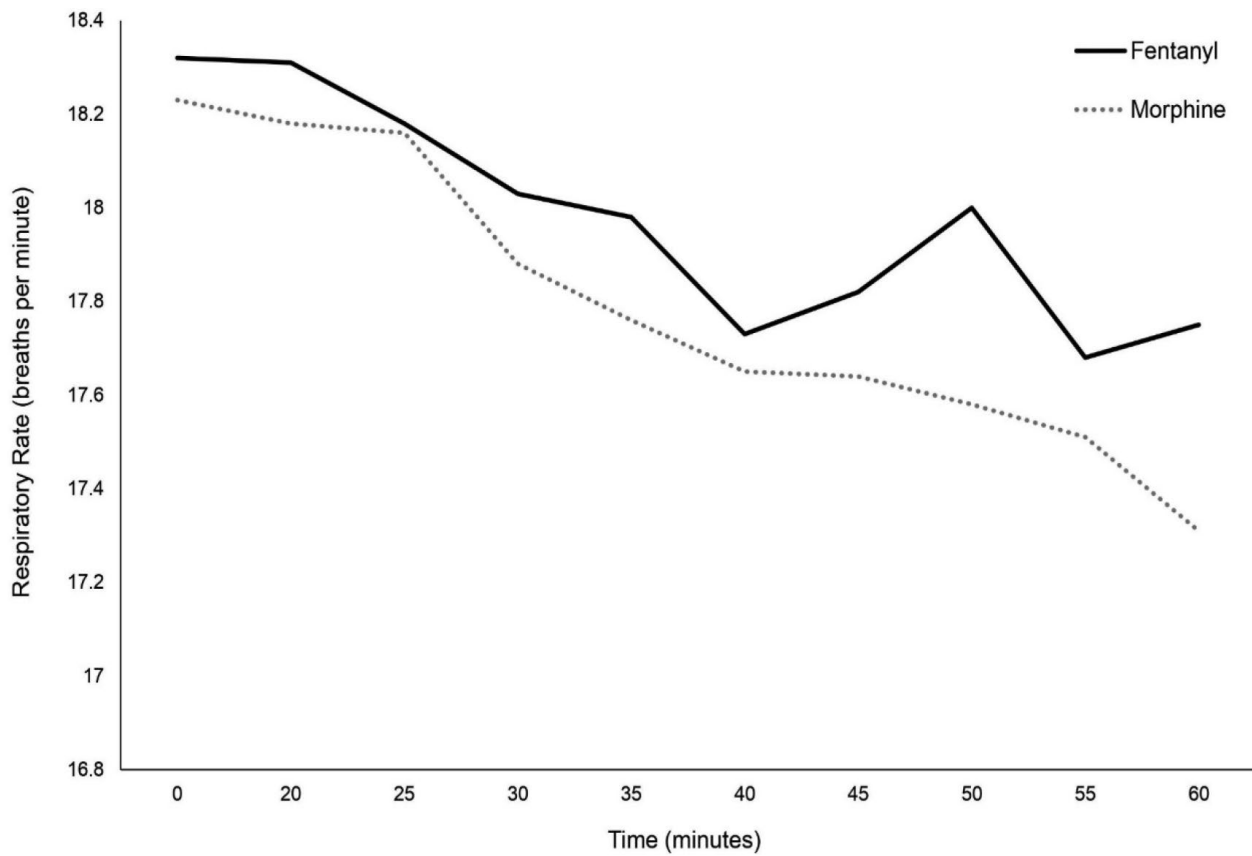


Figure 3. Change in respiratory rate over time for adults with ST-elevation myocardial infarction administered intravenous fentanyl compared to intravenous morphine.

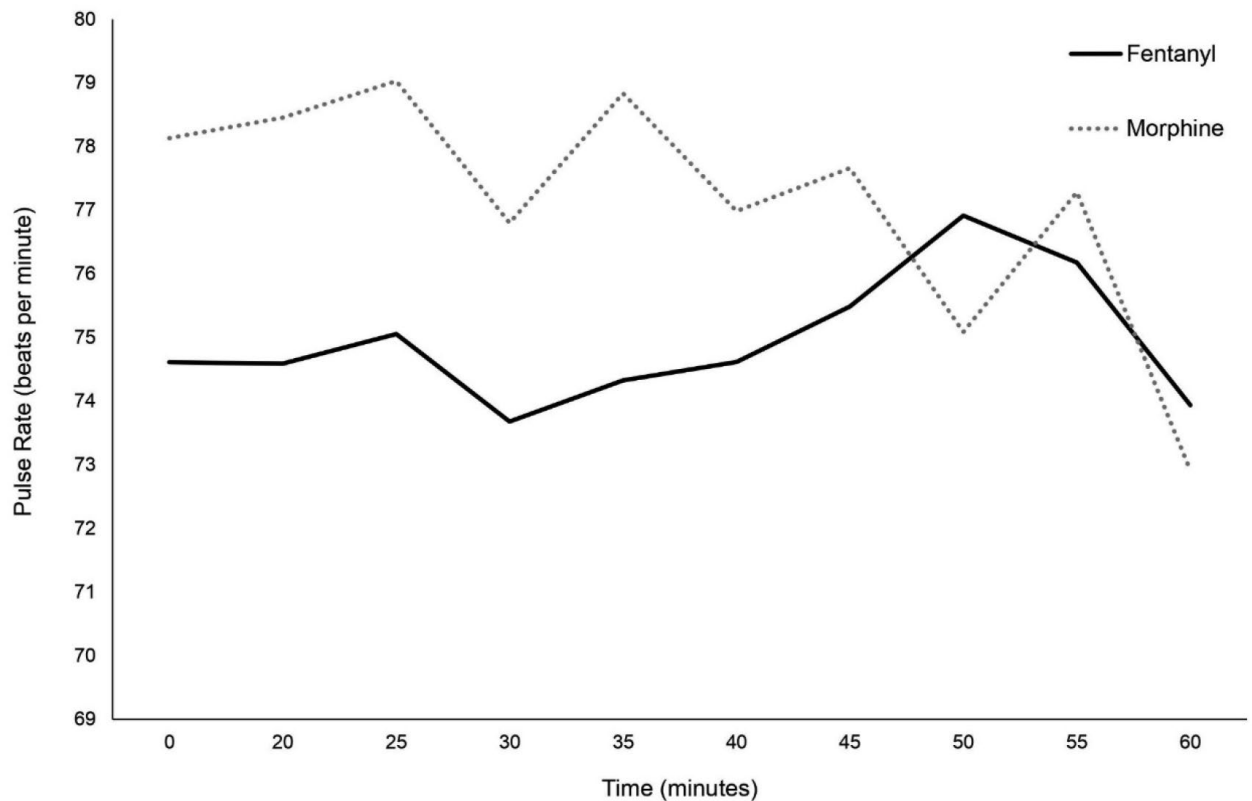


Figure 4. Change in pulse rate over time for adults with ST-elevation myocardial infarction administered intravenous fentanyl compared to intravenous morphine. Note: * $p < 0.05$.

DISCUSSION

The purpose of this research was to compare the effects of fentanyl to morphine on cardiac chest pain and cardiorespiratory vital signs in adult STEMI patients in the out-of-hospital paramedicine environment. Consistent with our first hypothesis, we found that pain score across the 0 to 60-minute study interval was comparable between the fentanyl and morphine groups. Also consistent with our second hypothesis, we observed differences in systolic and diastolic blood pressures between the two groups and decreased respiratory rate over time across both groups.

PAIN SCORE

The decrease in pain score over time was comparable between the fentanyl and morphine groups, with pain score in both groups decreasing from 7/10 to 4/10 between 0 and 60 minutes. This finding is consistent with the small volume of previous research showing that fentanyl and morphine offer equivalent analgesic effects (Fleischman et al., 2011; Galinski et al., 2005; Weldon et al., 2015). Additionally, according to Rowbotham (2001), a decrease in pain score of 2 points or more is likely to reflect a clinically meaningful improvement in the patient's experience of pain. As such, paramedics can use either fentanyl or morphine to achieve clinically meaningful pain reduction for adult STEMI patients and analgesic effect is not a factor that would indicate the use of one drug over the other for this population.

CARDIORESPIRATORY VITAL SIGNS

BLOOD PRESSURE

Both systolic and diastolic blood pressures were significantly lower in the fentanyl than morphine group at 0, 20, and 30 minutes, with diastolic blood pressure also lower in the fentanyl group at 25 minutes. Most interestingly, we found that both systolic and diastolic blood pressures were 6% lower in the fentanyl (130/83mmHg) than morphine (139/88 mmHg; both $p < 0.05$) group at 0-minutes, prior to drug selection and administration. This unanticipated and novel finding suggests that paramedics may be selecting fentanyl over morphine for patients who are at risk of becoming hypotensive. Between 2013 and 2016 when data were collected, both fentanyl and morphine were preferred analgesic options for ACS (Queensland Ambulance Service, 2017) and as such, we did not expect to observe differences in blood pressures at the 0-minute time point. However, the statistical significance of these differences suggests that paramedics may be systematically selecting fentanyl over morphine when the patient's blood pressure is lower. While both groups' blood pressures were within the normal range (Gabb et al., 2016), the fentanyl group were at risk of becoming hypotensive if their blood pressures decreased. As such, our results suggest that paramedics are potentially administering fentanyl preferentially when they observe the patient is at risk of becoming hypotensive.

This novel behavioural finding, whereby paramedics appear to administer fentanyl preferentially when a patient is at risk of developing hypotension, is particularly positive. A systematic review conducted by Duarte et al. (2019) has reported that the use of morphine in patients with acute coronary syndrome is linked to an increased risk of major adverse cardiovascular events and in-hospital mortality. Considering this previous research, the use of fentanyl in patients with low-normal blood pressures that we observed

in our data likely led to patients experiencing reduced risk for adverse events associated with opioid administration. Queensland paramedics appear to be making a positive clinical decision to administer fentanyl to patients at risk of becoming hypotensive, validating the high level of trust in paramedics reported in the Australian community (Australian Government Productivity Commission, 2022). This finding also supports the importance of conducting further qualitative research into the factors that inform clinical decisions in the absence of definitive guidelines, given that, at the time of data collection, either drug was equally recommended. Such research may be crucial to inform the development of best-practice guidelines that support paramedics to continue making informed, safe, and effective clinical decisions for their patients.

We did not observe any significant differences in systolic or diastolic blood pressures between groups after the 30-minute time point. This finding is likely related to two factors: pharmacokinetic and pharmacodynamic differences between the two drugs; and paramedics' selection of fentanyl for patients at risk of developing hypotension as described above. The speed of onset for fentanyl and morphine are reportedly 4–6 minutes and 20 minutes respectively (Alexander, 2023). Therefore, given the mean administration time for both drugs was 15 minutes, we expect that any changes in blood pressure would occur by the 20-minute observation for the fentanyl group, and the 35-minute observation for the morphine group. The difference between blood pressures in the fentanyl group at the 0-minute (130/83 mmHg) and 20-minute (132/83 mmHg) time points was unlikely to be clinically significant, and blood pressures for the fentanyl group remained within the normal range across the entire 60-minute study interval (Gabb et al., 2016).

In contrast, blood pressures in the morphine group decreased between the 0-minute (139/88 mmHg) and 30-minute (133/85 mmHg) time points. While mean blood pressures in the morphine group remained within normal range (Gabb et al., 2016), a difference of the same magnitude in the fentanyl group would have resulted in mean blood pressures in the fentanyl group becoming hypotensive. These results suggest that paramedics selected the appropriate analgesic for their patients, leading to patients in both groups maintaining normotension despite the disparate effects of the 2 drugs on blood pressures.

RESPIRATORY RATE

Despite evidence indicating that administration of intravenous fentanyl (Stoekel et al., 1982) or intravenous morphine (Thompson et al., 1995) can cause respiratory depression in healthy adults, we observed negligible changes in respiratory rate. Respiratory rate decreased by 0.5 breaths per minute in the fentanyl group, and by 0.9 breaths per minute in the morphine group, across the study interval ($p < 0.05$). Although these differences were statistically significant, they are unlikely to have clinical significance because mean respiratory rate for both groups at all time points in the study interval was within the normal range (Braun, 1990). Our findings, therefore, suggest that, contrary to popular opinion, respiratory rate should not be the primary factor determining whether to administer fentanyl or morphine to adult STEMI patients in the out-of-hospital paramedicine environment.

PULSE RATE

Similarly, we observed that mean pulse rate for both groups at all time points during the study interval remained within normal range (Ostchega et al., 2011). Additionally, the drug-time interaction effect was not significantly different between groups, suggesting that the change in pulse rate over time for each group was comparable. Therefore, pulse rate should not be the determining factor when administering fentanyl or morphine to adult STEMI patients.

CLINICAL APPLICATIONS

Taken together, our results suggest that blood pressure, and not respiratory rate, should be the primary factor determining whether fentanyl or morphine is to be administered for adult STEMI patients in the out-of-hospital paramedicine environment. This data is particularly valuable as it supports paramedics to have confidence in their decision to administer fentanyl to adult STEMI patients who are at risk of becoming hypotensive. Fentanyl and morphine appear to offer comparable, clinically significant reductions in cardiac chest pain for STEMI patients, and both medications result in similar, clinically insignificant reductions in the respiratory rate in this population. It appears that the key difference between fentanyl and morphine is their effect on blood pressure. We observed a 6% greater decrease in systolic and diastolic blood pressures associated with the administration of morphine compared to fentanyl. As such, when a decrease in blood pressure would cause an adult STEMI patient to become hypotensive, paramedics should preferentially administer fentanyl. While previous studies (Huang et al., 2022; Watso et al., 2022) suggested that this finding should be expected, this study has added value by confirming that results from healthy populations do translate to the hemodynamically precarious population of adult STEMI patients.

Additionally, given the unique challenge presented by STEMI pathology, it is likely to be particularly important that paramedics administer fentanyl over morphine for patients at risk of developing hypotension in this population. Hypotension can have considerable detrimental effects for patients with STEMI, further compromising myocardial perfusion and leading to decreased cardiac output, impaired organ perfusion, and an increased risk of cardiac arrhythmias (Kontos et al., 2015; Menon & Hochman, 2002). Therefore, selecting fentanyl, which has a smaller impact on blood pressure than morphine, will likely lead to improved patient outcomes by avoiding the risks associated with morphine-induced hypotension while offering a comparable reduction in pain for adult STEMI patients. We recommend that paramedics consider blood pressure as a key determining factor guiding the choice of analgesic for adult STEMI patients to minimise the risk of adverse effects.

LIMITATIONS

While we are confident in the clinical applicability of our results, it is important to note that we did not compare possible differences in the equivalent dose of analgesic received by each group. In practice, paramedics administer clinically appropriate doses of medications according to their education, relevant guidelines, and professional judgement. While it is possible that the fentanyl and morphine groups in our study did not receive equivalent doses, and this may have influenced the results, we determined that increasing experimental control by adjusting results based on possible dose differences would

reduce the practical applicability of our conclusions. We recommend further research investigates the possibility that differences in appropriate doses between the two drugs contributes to the results we observed in this study. Additionally, we were unable to control for possible differences in non-pharmacological approaches to pain reduction, such as assisting the patient to a position of comfort or providing reassurance. Given all patients were attended by registered paramedics, it is likely that these approaches were consistently applied. However, we were unable to confirm this, and acknowledge the possibility of confounding as a limitation of the study.

In conclusion, the aim of this study was to compare the effects of fentanyl and morphine on pain and cardiorespiratory vital signs in adult STEMI patients. We found that, with respect to our variables of interest, fentanyl and morphine seem to have comparable effects on all variables except blood pressures, where morphine appears to lead to a greater decrease in systolic and diastolic blood pressure over time. We also observed an unanticipated behavioural finding - that paramedics seem to selectively administer fentanyl over morphine when the patient is at risk of hypotension - and this appears to be effective in mitigating the chance of inducing hypotension in these patients. Further qualitative research into the factors paramedics consider when selecting fentanyl or morphine is worthwhile, as is research into patient outcomes when patients are at risk of developing a worsening condition. Through our analysis, we have determined that fentanyl is likely to be a more optimal choice than morphine for patients at risk of developing hypotension.

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