Comparison of Fentanyl and Morphine in the Prehospital Treatment of Ischemic Type Chest Pain

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Abstract

In the treatment of acute coronary syndromes, reduction of sympathetic stress and catecholamine release is an important therapeutic goal. One method used to achieve this goal is pain reduction through the systemic administration of analgesia. Historically, morphine has been the analgesic of choice in ischemic cardiac pain. This randomized double-blind controlled trial seeks to prove the utility of fentanyl as an alternate first-line analgesic for ischemic-type chest pain in the prehospital setting. Successive patients who were treated for suspected ischemic chest pain in the emergency medical services system were considered eligible. Once chest pain was confirmed, patients received oxygen, aspirin, and nitroglycerin therapy. If the ischemic-type chest pain continued the patient was randomized in a double-blinded fashion to treatment with either morphine or fentanyl. Pain scale scores, necessity for additional dosing, and rate of adverse events between the groups were assessed every 5 minutes and were compared using t-testing, Fisher's Exact test, or Analysis of Variance (ANOVA) where appropriate. The primary outcome of the study was incidence of hypotension and the secondary outcome was pain reduction as measured by the visual analog score and numeric rating score. A total of 207 patients were randomized with 187 patients included in the final analysis. Of the 187 patients, 99 were in the morphine group and 88 in the fentanyl group. No statistically significant difference between the two groups with respect to hypotension was found (morphine 5.1% vs. fentanyl 0%, $p = 0.06$). Baseline characteristics, necessity for additional dosing, and other adverse events between the two groups were not statistically different. There were no significant differences between the changes in visual analog scores and numeric rating scale scores for pain between the two groups ($p = 0.16$ and $p = 0.15$, respectively). This study supports that fentanyl and morphine are comparable in providing analgesia for ischemic-type chest pain. Fentanyl appears to be a safe and effective alternative to morphine for the management of chest pain in the prehospital setting. **Key words:** chest pain; prehospital; morphine; fentanyl; acute pain

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Introduction

Ischemic-type chest pain is the most common chief complaint resulting in transport to hospital.[1,2] Currently, both fentanyl and/or morphine may be carried by EMS systems with morphine being predominantly used to treat suspected ischemic-type chest pain. Given the large patient volume, there are operational and patient safety-related advantages of utilizing a single narcotic agent.

In acute coronary syndromes (ACS), sympathetic stress and catecholamine release is associated with myocardial irritability, arrhythmia, and infarct size.[3] As a result, analgesia is an important therapeutic goal, which is achieved with either fentanyl or morphine. Historically morphine has been the analgesic of choice in ischemic cardiac pain.[4] Morphine is endorsed by the American Heart Association in ST segment elevation myocardial infarction with a class 1 indication; however, its use in acute coronary syndromes may be associated with increased mortality.[5]

The modern era of cardiac care creates the demand for rapid diagnostic and treatment times involving all aspects of ACS care.[6] First medical contact to treatment is a well-established time for benchmarking, quality improvement, and most importantly patient outcomes. It follows that a rapid onset of action of any cardiac treatment including analgesia is ideal. Because of its immediate onset of action and lower histamine release, allowing for more hemodynamic stability, intravenous fentanyl may be a better option than morphine in the pre-hospital setting.[7]

The goal of this study was to evaluate the utility of fentanyl as a superior alternate first line analgesic for ischemic chest pain in the pre-hospital setting. We tested the hypothesis that the administration of fentanyl in this setting would result in a lower incidence of hypotension compared with morphine.

Methods

Case Identification

This was a prospective double-blind randomized controlled trial of morphine vs. fentanyl in the treatment

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of ischemic type chest pain in the pre-hospital setting. Successive patients aged 18 years or over, treated for ischemic type chest pain in the emergency medical services system in Winnipeg, Manitoba were screened for enrollment in the study. The Winnipeg Fire Paramedic Service is an urban EMS system providing care for a population of 708,400 and employs a two-tiered approach to 911 dispatch information of which ischemic type chest pain calls receive a combined basic life support (BLS) and advanced life support (ALS) provider response. Transport to hospital occurs via ambulance with both BLS and ALS providers attending to the patient. During the study the BLS provider assessed for eligibility and obtained consent while the ALS provider delivered the study drugs and collected clinical data.

In order to be eligible for participation, the patient was required to meet the following inclusion criteria: (1) typical ischemic type chest pain not relieved by oxygen, acetylsalicylic acid (ASA), and nitroglycerin; (2) initial systolic blood pressure greater than 100 mmHg; and (3) initial oxygen saturation greater than 95%. Electrocardiogram interpretation was not used for inclusion eligibility to allow for inclusion of a wide spectrum of acute coronary syndrome patients including those with acute myocardial infarction. Exclusion criteria was as follows: (1) patients under the age of 18; (2) known pregnancy; (3) cognitive impairment; (4) known allergy to either fentanyl or morphine; (5) traumatic injury; and (6) patients with evidence of right ventricular infarct identified by the presence of ST segment elevation in V4R on prehospital electrocardiogram.

Upon arrival of the ALS paramedic and once chest pain suggestive of myocardial ischemia was confirmed, patients received supplemental oxygen at four liters per minute via nasal prongs, chewable ASA 160 mg, and nitroglycerin spray 0.4 mg sublingually every five minutes to a maximum of three doses. This treatment sequence is per Winnipeg Fire and Paramedic prehospital chest pain protocol. A nitroglycerine patch 0.2 mg/hr was also applied. If the patient continued to have pain despite the aforementioned therapy and they met all inclusion criteria and no exclusion criteria, they were approached and consented for enrollment. Given that the study patient population was expected to be heterogeneous in terms of criticality, informed consent was obtained using a summary consent process. An initial brief written consent was obtained on scene followed by a complete consent document once transferred to hospital. The complete consent document was not refused by any patients.

Data Collection

A standardized data collection tool was initiated for all patients enrolled. The patients' demographic information including age, gender, estimated height, and weight as well as clinical findings including blood pressure, heart rate, respiratory rate, and pain scores were recorded. Adverse events were also documented. Specifically adverse events were defined as but not limited to apnea, severe respiratory depression (defined as desaturation below 90%), nausea, emesis, and decreased level of consciousness. Hypotension as an adverse event was defined as any episode of systolic blood pressure less than 90. Severe adverse events were deemed present if the patient required ventilation with bag valve mask or intubation, and/or if the narcotic reversal agent, naloxone was given for apnea.

A routine survey of ambulance patient care reports containing the Winnipeg Fire and Paramedic diagnosis code for chest pain or myocardial infarction was undertaken to identify eligible subjects who were not initially considered for the study.

Trial Medication

Study drugs were supplied in coded preloaded syringes by an outside agency pharmacy and were identical in appearance. Patients were randomized to double blind treatment according to A or B alternative:

A: 1 Patients less than 75 years of age and greater than 50 kg, an intravenous injection of 5 mg of morphine was given every 5 min as needed to a maximum of four injections.
A: 2 Patients greater than or equal to 75 years of age and/or less than or equal to 50 kg, an intravenous injection of 2.5 mg of morphine was given every 5 min as needed to a maximum of four injections.
B: 1 Patients less than 75 years of age and greater than 50 kg, an intravenous injection of 50 mcg of fentanyl was given every 5 min as needed to a maximum of four injections.
B: 2 Patients greater than or equal to 75 years of age and/or less than or equal to 50 kg, an intravenous injection of 25 mcg of fentanyl was given every 5 min as needed to a maximum of four injections.

Randomization occurred in a block design with four syringes per block. Each syringe contained either morphine or fentanyl mixed with normal saline to result in a total volume of 8 mL. An external pharmacy performed the reconstitutions, as well as randomizations and consecutive coding based on a computer generated randomization list. Each patient received an ordered numeric code and received the medication in the corresponding prepackaged syringe to ensure allocation concealment. Morphine was dosed at 2.5 mg per 1 mL and fentanyl at 25 mcg per 1 mL. For patients greater than or equal to 75 years and less than or equal to 50 kg, 1 mL increments were drawn up for total dosing. For patients greater than 50 kg and less

than 75 years 2 mL increments were drawn up for total dosing.

Pain Assessment

A previously validated visual analogue scale (VAS) was used to assess pain relief.[8] Study parameters were recorded at baseline and at 2, 4, 6, 10, and 15 minutes after the administration of the study drug. Patients were also asked to rate their pain on a Numerical Rating Scale (NRS) where 0 was no pain and 10 was the most severe pain.

Outcome Measures

The primary outcome was the incidence of hypotension. Secondary outcomes were pain relief as measured by the visual analogue scale and numeric rating score as well as alteration in hemodynamic and respiratory status as measured by repeated vital signs. Adverse events previously defined were also recorded.

Ethics

The study received approval from The University of Manitoba Biomedical Research Ethics Board.

Statistical Methods

Subjective and objective clinical findings were categorized as discrete unordered variables. Descriptive statistics were used to summarize the data. Baseline differences between treatment groups were analyzed with a Student's t–test. The response variables were measured repeatedly over time and were analyzed using a repeated measurements analysis of variance (ANOVA) model. We estimated morphine would have a 10% adverse event rate for hypotension[4,9] and that it would drop to 1% with fentanyl. Using an alpha of 0.05 and a power of 80%, we anticipated that we would need approximately 96 patients in each arm for a total of 192 patients. As the incidence of hypotension is low with fentanyl, we hypothesized that it would have this advantage over morphine for chest pain. Studies have reported variable results on blood pressure with fentanyl, but it is generally around 1%. Fleischman et al.[15] reported only 2 cases of fentanyl-related hypotension in 363 patients (i.e., 0.6% incidence) receiving fentanyl for out-of-hospital analgesia[9]; while Thomas et al. reported an incidence of 1.9% in 213 patients.[15] Thus, for our sample size calculations, we estimated the incidence of hypotension to be approximately 1%. Analysis was per protocol and therefore was restricted to participants who fulfilled all aspects of eligibility, interventions, and outcome assessment.

RESULTS

Between February 13, 2005 and June 25, 2006, ALS Paramedics treated 1,264 patients for ischemic type chest pain in the Winnipeg Emergency Medical Services system. Upon review of all patient care reports, 1,057 patients were not eligible on the basis of: (1) patient refusal (12.5%); (2) lack of inclusion criteria (50.8%); (3) presence of exclusion criteria (7.5%); (4) no IV access (3.8%); (5) unable to consent (9.7%); and (6) other reasons (15.7%). The majority of patients in the category of "other reason" were excluded due to close proximity to a hospital; transport time less than 5 minutes (Figure 1).

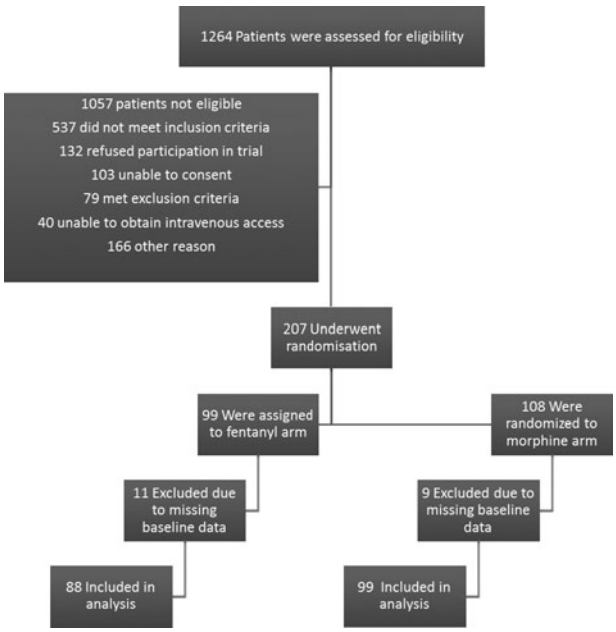

FIGURE 1. Overview of patient eligibility and enrollment.

During the study period 207 patients were randomized to either the fentanyl or morphine protocol. Of

TABLE 1. Baseline characteristics of patients

	Morphine	Fentanyl	*p*-value
Number of patients	99	88	
Age (years)	66.1 ± 15.8	64.5 ± 16.0	0.49
Weight (kg)	79.4 ± 19.6	78.43 ± 17.6	0.73
Range (kg)	36–150	40–140	
Height (cm)	170.3 ± 9.1	171.1 ± 8.6	0.53
Percent male	53%	53%	0.90
Size of dose received	1.7 ± 0.5	1.7 ± 0.5	0.84
Systolic blood pressure (mmHg)	141 ± 22	144 ± 21	0.33
Diastolic blood pressure (mmHg)	82 ± 14	83 ± 14	0.50
Heart rate	84 ± 23	87 ± 18	0.36
Respiratory rate	19 ± 4	20 ± 3	0.76
Numerical Rating Scale, NRS	5 ± 2	5 ± 2	0.89
Visual Analog Scale, VAS (cm)	4 ± 2	4 ± 2	0.76
Excluded - absence of baseline data	8	12	0.35

Statistical significance was analyzed by a 2-sided Student's t-test or Fisher's Exact where appropriate.

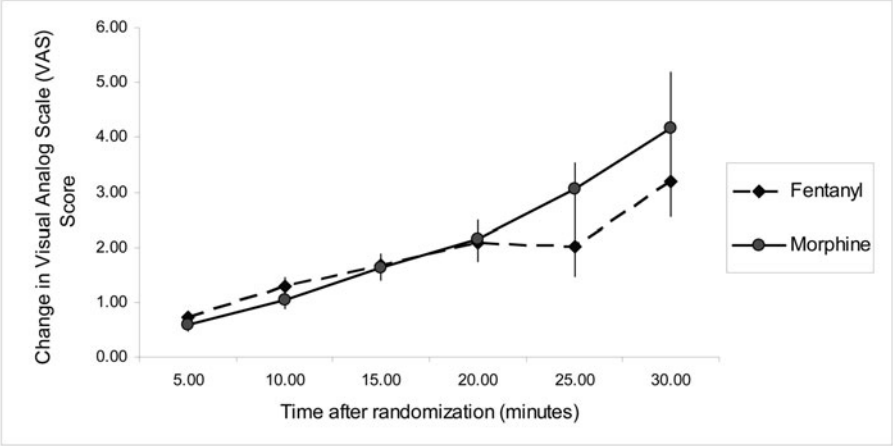

FIGURE 2. Progression of change in Visual Analog Scale (VAS) score. The greatest numerical but not statistical difference was found at 25 minutes ($p = 0.16$) by Kruskal-Wallis One-way Analysis of Variance.

these patients, 20 patients (12 from fentanyl arm, 8 from morphine arm) were excluded due to lack of baseline data, leaving a study population of 187 patients.

The morphine and fentanyl groups did not differ significantly with respect to age, weight, baseline vital signs, or baseline pain scores (Table 1).

The change in overall VAS scores is shown in Figure 2. There was no significant difference between changes in VAS scores from baseline between either morphine or fentanyl ($p = 0.47$). Morphine appeared better 20 minutes after initiation of therapy, but this was not significant. In addition, there were no differences between changes in NRS, MAP, heart rate, or respiratory rate for either treatment arm (Figures 3–6).

From Table 2, it can be seen that there was no significant difference in the report of adverse events in both groups with nausea being the predominant side effect encountered. There were no cases of apnea in either treatment arm. All of the cases of hypotension were within the morphine arm (5.1% vs. 0%, $p = 0.06$). The necessity for additional narcotic doses was equivalent for both regimens (Table 3). There was a trend, however, toward more drug being required in the fentanyl arm in the first 5 to 9 minutes from the initiation of study drug ($p = 0.08$).

DISCUSSION

The progress of modern cardiac care has resulted in emergency medical systems being held to strict time standards in the treatment of ischemic chest pain. Therapeutic interventions from first medical contact must be rapid in order to stay in pace with time to thrombolytic and percutaneous coronary intervention goals. The more rapid onset of fentanyl is consistent with the practice of reducing treatment times in modern prehospital ACS care. Historically, out of hospital pain management has been suboptimal,[10,11] which may be related to the slow onset of action of morphine.

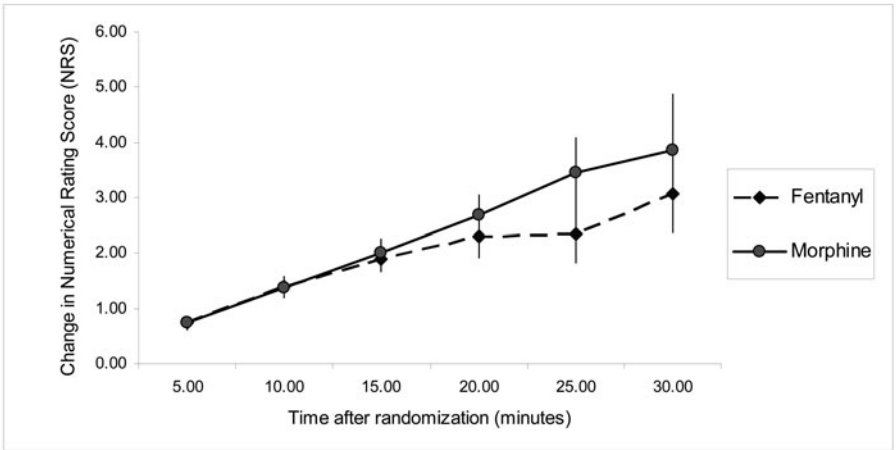

FIGURE 3. Progression of change in the Numerical Rating Scale (NRS) score. The greatest numerical but not statistical difference was found at 25 minutes ($p = 0.15$) by Kruskal-Wallis One-way Analysis of Variance.

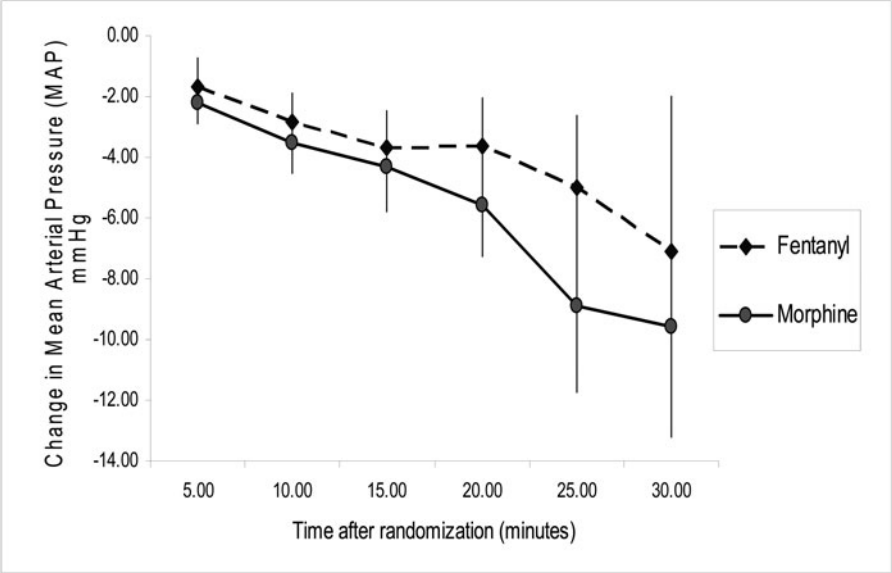

FIGURE 4. Progression of change in Mean Arterial Pressure (MAP). The greatest numerical but not statistical difference was found at 20 minutes ($p = 0.48$) by Kruskal-Wallis One-way Analysis of Variance.

Fentanyl is an ideal agent in this setting with an immediate onset of action and less side effects than the traditionally used morphine. Although a similar study was performed using alfentanil,[12] and multiple studies have addressed the utility of fentanyl in an undifferentiated prehospital population,[7,13–15] to the best of our knowledge this is the first study to compare intravenous morphine and intravenous fentanyl in the setting of prehospital ischemic-type chest pain.

In many emergency medical systems, fentanyl is commonly used to treat traumatic pain, while morphine has been the historic choice for ischemic-type chest pain likely due its inclusion in the American Heart Association guidelines for Acute Coronary Syndromes.[16] The rationale for this assignment of opiates is poorly supported and there is evidence that the use of morphine in the setting of ACS may increase infarct size and result in increased mortality.[5] Morphine's hemodynamic effects are theorized to influence myocardial oxygen consumption resulting in deleterious effects on outcome in ACS.[5] The histamine-releasing properties of opiates from mast cells appear to be distinct from that of known opiate receptors.[17] Although fentanyl has a similar pharmacokinetic profile as morphine, it is the preferred agent if hemodynamic instability results from morphine's histamine-releasing properties.[18] As shown in Table 2, our findings support this, as 5 patients who had received morphine had sustained episodes of hypotension whereas no fentanyl patient had evidence of hypotension. Although these values are not statistically significant, the trend does support the belief

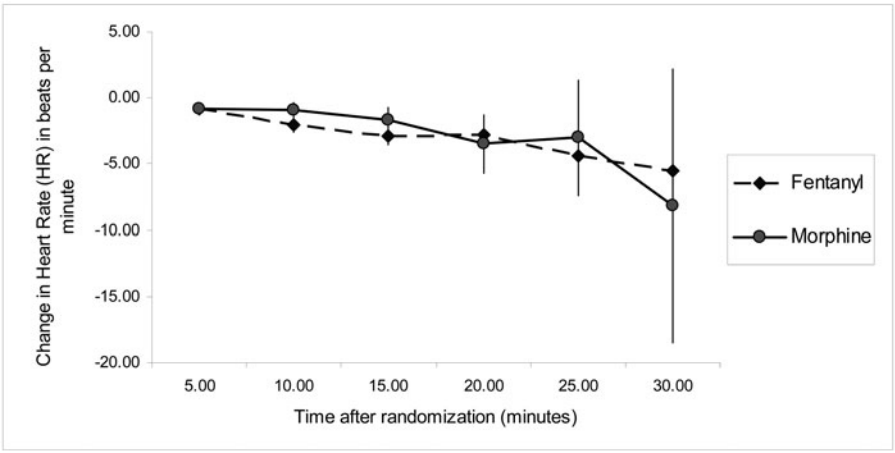

FIGURE 5. Progression of change in heart rate. The greatest numerical but not statistical difference was found at 15 minutes ($p = 0.09$) by Kruskal-Wallis One-way Analysis of Variance.

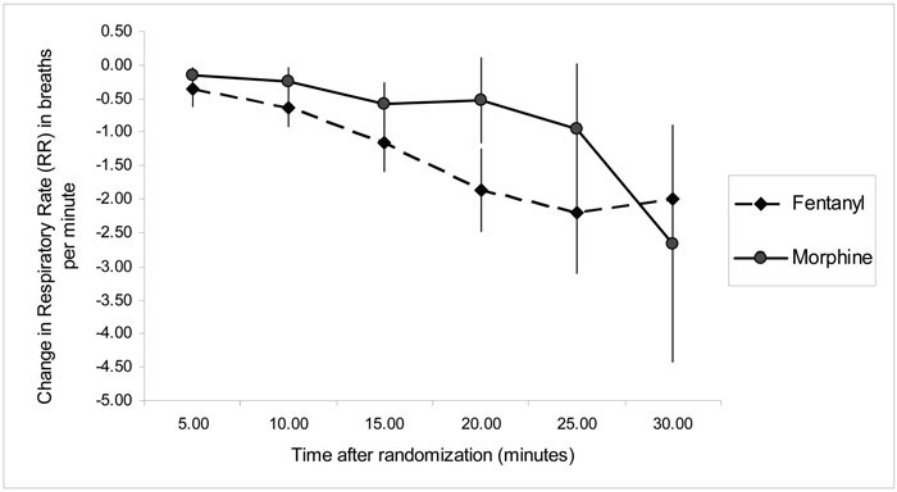

FIGURE 6. Progression of change in respiratory rate. The greatest numerical but not statistical difference was found at 20 minutes ($p = 0.13$) by Kruskal-Wallis One-way Analysis of Variance.

that fentanyl is a more hemodynamically stable analgesic option. The avoidance of hypotension in ischemic chest pain patients is a major therapeutic goal.

In addition to blood pressure considerations, respiratory depression is often of concern in the administration of opioid analgesia. No patient in this study sustained any episodes of apnea and there was no statistical difference in respiratory rate reduction between the two groups as outlined in Table 4.

*A prio*r study performed in Helsinki comparing the narcotic alfentanil, which is similar to fentanyl, to morphine,[12] found similar results to our own. More specifically, morphine was as effective as alfentanil with respect to a reduction in pain scores and adverse effects.[4] A more similar and recent retrospective study in 355 patients also found comparable results when morphine and fentanyl were examined directly in a countywide EMS program for out-of-hospital analgesia.[15] A decrease in pain scores and adverse effects from either narcotic were found to be similar, however, their study design was limited by being a retrospective, before- and after-comparison.

There are advantages operationally, to utilizing a single narcotic for EMS services. The streamlining of narcotic delivery allows for reduced costs associated with tracking and storage and the potential for a reduction of divergence. Paramedic familiarity with a single agent improves accuracy of delivery, and reduces the potential for medication error.

A single opiate analgesic that has a rapid onset, is easily titrated and that can be delivered via many routes is desirable. Fentanyl meets all of these criteria and in addition is administrable via the intranasal route. The intranasal route of administration is invaluable in patient populations where initiating an intravenous line may not be desirable such as the pediatric and palliative care population.

LIMITATIONS

The population included in this study, was a heterogeneous chest pain population. Patients did not require definitive EKG evidence of infarct or ischemia but did require symptoms consistent with ischemic chest pain as opposed to chest pain related to other pathologic processes. We believe that this represents a

TABLE 2. Comparison of adverse events at any time point after the dose out to 30 minutes.

	Morphine (99)	Fentanyl (88)	*p*-value
Nausea	18.2% (18)	12.5% (11)	0.32
Apnea	0%	0%	1.00
Emesis	2.0% (2)	1.1% (1)	1.00
Requirement for dimenhydrinate	9.1% (9)	8.0% (7)	0.80
Hypotension (SBP < 90 mmHg)	5.1% (5)	0%	0.06

Statistical significance was analyzed by a 2-sided Fisher's Exact.

TABLE 3. Necessity for an additional dose of narcotic by treatment arm.

Time interval	Morphine (212*)	Fentanyl (195*)	*p*-value
1–4 mins	29%	26%	1.00
5–9 mins	76%	92%	0.08
10–14 mins	80%	71%	1.00
15–19 mins	51%	71%	0.79
20–24 mins	45%	76%	0.55
25–30 mins	57%	25%	1.00

Statistical significance was analyzed by a 2-sided Fisher's Exact.
*the denominator here is for the total number of patients within all the assessment periods (i.e. number of events assessed at 1–4 min, 5–9 min, etc.).

TABLE 4. Adverse events

Monitoring adverse parameter:	Fentanyl (mean ± SD)	Morphine (mean ± SD)	Between narcotics	Reduction over time overall
Heart Rate reduction	–5.5 ± 6.7 by 30 min	–8.1 ± 27.3 by 30 min	$p = 0.81$	$p = 0.23$
Respiratory Rate reduction	–2.0 ± 2.8 by 30 min	–2.7 ± 4.3 by 30 min	$p = 0.74$	$p = 0.52$
Mean Arterial Pressure reduction	–7.1 + 17.0 by 30 min	–9.6 + 8.0 by 30 min	$p = 0.87$	$p = 0.04$

Mean = the Least Squares mean as calculated by the ANOVA; SD = standard deviation.

real world approach to prehospital analgesia and supports the generalizability of our results to other EMS systems

A limitation of this study was the exclusion of patients who lacked baseline data, which resulted in an available case analysis as opposed to intention to treat. Imputation of data would require multiple assumptions in particular because the majority of the data is continuous and outcomes were measured as changes from baseline. Although exclusions are always a concern it is important to note that the rate of exclusion was no different between study arms (Table 1).

During the study 1264 chest pain patients were screened for enrollment and 1,057 did not meet inclusion criteria or did meet inclusion criteria but were not enrolled for logistical or other reasons. The low enrollment number may affect external validity of the study results; however, these were unavoidable within our current design but are an important consideration for future studies

The EMS system where the study was conducted is an urban centre with off-line medical control. The results may not be applicable to systems with other modes of medical control. We do believe the results may be relevant to other settings including rural patient populations and potentially the in-hospital patient population.

A final limitation would be the lack of hospital outcome data for the presence or absence of adverse events.

CONCLUSION

Fentanyl appears to be a safe and effective alternative to morphine for the management of chest pain in the prehospital setting. This study demonstrates that fentanyl and morphine are comparable in providing analgesia for ischemic type chest pain in the prehospital setting.

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