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Author

Rickard, Claire, O'Meara, Peter, McGrail, Matthew, Garner, David, McLean, Alan, Lievre, Peter

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Title:

A randomized controlled trial of intranasal fentanyl versus intravenous morphine for analgesia in the prehospital setting

Authors:

A/Professor Claire Rickard, PhD
School of Nursing & Midwifery, Griffith University

A/Professor Peter O'Meara, PhD
School of Public Health, Charles Sturt University

Matthew McGrail, PhD Candidate
School of Rural Health, Monash University

David Garner, MICA
Rural Ambulance Victoria

Alan McLean, BHlthSc
Clinical and Operational Services, South Australia Ambulance Service

Peter Le Lievre, BBus
Workforce Regulation Section, Department of Health and Aging

Corresponding Author:

A/Prof Claire Rickard
Griffith University School of Nursing & Midwifery
Kessels Road, Nathan, 4111, Queensland, AUSTRALIA
Tel: +61 7 3735 5406, Fax: +61 7 3735 7984
Email: rickard_claire@yahoo.com.au

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ABSTRACT (150 words)

Study Objective

To compare intranasal fentanyl (INF) with intravenous morphine (IVM) for prehospital analgesia.

Methods

Randomized, controlled, open-label trial. Consecutive adult patients (n=258) requiring analgesia (Verbal Rating Score (VRS) >2/10 non-cardiac or >5/10 cardiac) were recruited. Patients received INF 180mcg +/- 2 doses of 60 mcg at ≥ 5 minute intervals, or IVM 2.5-5mg +/- 2 doses of 2.5-5mg at ≥ 5 minute intervals. The endpoint was the difference in baseline/destination VRS.

Results

Groups were equivalent (p=NS) for baseline VRS [mean (SD): INF 8.3 (1.7), IVM 8.1, (1.6)] and minutes to destination [mean (SD): INF 27.2 (15.5), IVM 30.6 (19.1)]. Patients had a mean (95%CI) VRS reduction of: INF 4.22 (3.74-4.71), IVM 3.57 (3.10-4.03), p=0.08. Higher baseline VRS (p<0.001), no methoxyflurane use (p<0.01), and back pain (p=0.02) predicted VRS reduction. Safety and acceptability were comparable.

Conclusions

There was no significant difference in the effectiveness of INF and IVM for prehospital analgesia.

A randomized controlled trial of intranasal fentanyl versus intravenous morphine for analgesia in the prehospital setting

1. Introduction

Severe pain is a frequent complaint in the prehospital setting, yet management may be suboptimal [1]. Intravenous morphine (IVM) has traditionally been used by Australian paramedics as the “gold standard” treatment for severe pain. IVM relies on successful venous cannulation which may be unpleasant or technically impossible in some patients, and carries a risk of needlestick injuries to staff. In addition, a small number of patients will experience adverse events including nausea, hypotension and respiratory depression.

Some believe fentanyl is preferential to morphine due to its rapid peak, short duration of action and non-histamine release, leading to reduced side-effects, particularly hypotension [2]. Intravenous fentanyl has been shown an effective alternative to IVM in the prehospital setting [3-7], however, the limitations of the intravenous administration route remain.

Recently, intranasal fentanyl (INF) has become available and provides an alternative analgesic that does not rely on venous access. In addition, the nasal route allows rapid delivery of treatment. INF has been found an effective analgesia in the inpatient hospital setting [8-16], but to our knowledge there has been no prior trial in the prehospital setting.

The aim of this study was to compare INF and IVM for prehospital analgesia.

2. Materials and methods

We performed a prospective, multi-center, randomized, open-label controlled study. The study included two ambulance services in Australia: Rural Ambulance Victoria, and South Australia (SA) Ambulance Service. The ambulances were staffed by two paramedics, one of whom was an Intensive Care paramedic.

The Standing Committee on Ethical Research in Humans of Monash University approved the study. The need for written informed consent was waived in consideration of the emergency setting. Patients received a brief verbal explanation as consistent with standard practice for administration of the two drugs and consent was implied by acceptance of the drug. Patient recruitment occurred sequentially between November 2003 and May 2005. A sample size of 200 patients per group was planned to allow the detection of a VRS rating difference of 1 between groups with 80% power at alpha 0.05.

A random number table was used to prepare opaque sealed envelopes which were opened if a patient met all inclusion and no exclusion criteria. The inclusion criteria consisted of age 18-65 years and severe pain defined as a Verbal Rating Score (VRS) $>5/10$ for patients with cardiac type pain or discomfort persisting 5 minutes or more after glyceryl trinitrate administration, or VRS >2 for patients with non-cardiac pain. The VRS was a 10-point scale: 0 = pain free, 10 = worst pain ever. Exclusion criteria were consistent with our pre-existing policy of contraindications for opiate therapy. These were hypoxia ($SpO_2 \leq 85\%$), hypotension (systolic BP ≤ 110 mmHg), heart rate <50 bpm or >150 bpm, altered conscious state (GCS <15), vomiting, a known allergy to morphine, fentanyl or other opiates, opiate use in past 24 hours, or patients unable to provide a VRS. Patients were enrolled as a consecutive sample.

This was an open-label study with doses consistent with pre-study clinical use. Patients allocated to INF received an initial (T0) dose of fentanyl citrate 180mcg. This involved 0.6 mls drawn into a 1ml syringe with a mucosal atomisation device. The charged atomizer was inserted loosely into one nostril (aimed backwards at the centre of nasal cavity) and 0.3 mls (90 mcg) fluid was atomised. This was repeated immediately in the opposite nostril. If the VRS remained ≥ 3 , then two further increments of fentanyl citrate 60mcg (0.2ml) at ≥ 5 minutely intervals (T1, T2).

Patients randomized to IVM received an initial (T0) dose of morphine sulphate 2.5 - 5mg IV diluted to 1mg/ml in normal saline. If the VRS remained ≥ 3 then two further doses of 2.5-5mg were given ≥ 5 minutely (T1, T2).

For patients in both groups, rescue analgesia (T3) was available at 15 minutes if the VRS remained ≥ 3 . Rescue for both groups was intravenous morphine 2.5-5mg at ≥ 5 minute intervals to a maximum of 20mg.

In both groups, all patients with chest pain or discomfort thought to be cardiac-related routinely received glyceryl trinitrate 0.3-0.6mg buccal/sub-lingual repeated at ≥ 5 minute intervals, up to a total of 3 times the initial dose within 30 minutes. In both groups, patients with non-cardiac pain were also permitted to have methoxyflurane of up to 2 doses of 3 mls via Pentrox™ inhaler.

Pain score using the VRS was the primary outcome measured [1]. This measure was selected for its recognition as a validated research tool in the emergency setting, and for its simplicity and familiarity to paramedics [17,18]. The VRS was recorded at baseline, before each dose of analgesia, and at destination. The timing of all analgesia was recorded.

All INF and IVM doses were noted by paramedics for patient tolerance (yes/no). For analysis, poor tolerance was defined as a composite measure comprising: (i) doses rated as “no” for tolerance by paramedics, (ii) doses unable to be administered due to technical difficulties or refusal by patients, and (iii) doses after which subsequent treatment was withheld due to suspected adverse effects. Adverse events for all patients were recorded. INF treatments were rated as clinically acceptable (yes/no) to the treating paramedic.

The treating paramedics collected all data. An instruction sheet was distributed and education provided at study onset to aid correct completion of the form. Once completed, the forms were placed into a locked box ready for data entry at the relevant ambulance service and then sent in a de-identified format to the statistician.

All analysis was performed using the Statistical Package for the Social Sciences (SPSS®, Version 12.0, Chicago, U.S.A.). Analyses between groups were carried out on the basis of treatment given, using two tailed *t* tests for differences in continuous variables, χ^2 tests for differences in proportions and Mann-Whitney U tests for

differences in ordinal variables. The primary outcome measure was the difference in VRS (an ordinal scale) from baseline to destination (Mann Whitney-U). Bonferroni's correction was applied for multiple comparisons of VRS at differing timepoints. To be evaluable for the primary analysis, it was decreed *a priori* that patients must complete the study protocol. To ensure this approach was not biased, an intention to treat analysis was also performed on all randomized patients to assess for the effect of drop-outs. All patients who received study drug (partial or completed protocol) were included in the secondary analysis of patient tolerance and adverse events. Ordinal regression was used to analyse the combined effect of variables on the change in VRS. Only variables with p-values < 0.20, in bivariate analysis against the main dependent outcome, were considered for the regression model. Rejected variables were considered after the final regression model was built. A p-value of 0.05 was considered statistically significant for all variables with the exception of VRS comparisons (p=0.01).

3. Results

The original sample size of 400 was not achieved within the available timeframe and a total of 258 patients were randomized during the study period. Of these, 227 completed the study protocol and were evaluable. Protocol violations included failing to meet the inclusion criteria (usually on age criteria), failure to receive the allocated treatment (usually IVM patients unable to be cannulated), or failure to complete allocated treatment. There was one randomised (INF) patient who was erroneously treated in the alternative (IVM) group. Refer to Figure 1 for a depiction of patient flows through the study.

Table 1 shows the baseline characteristics of randomized patients. There were 14% more male patients in the IVM group than the INF group (p=0.05); all other baseline factors were equivalent between groups. The average initial VRS across the sample was 8.2. Specifically, 32% had a VRS of 10, 37% VRS 8-9, 24% VRS 6-7 and 8% VRS 3-6.

There were 127 INF and 100 IVM patients evaluable. Good pain relief was achieved on average for patients in both treatment groups, and there was no significant difference in the number of patients who required the second or third doses, or rescue analgesia. As seen in Table 2, the groups did not differ for VRS at baseline,

destination, or for the change in VRS between these two timepoints (primary outcome measure). Intention to treat analysis (n=258) of the change in VRS between groups did not change this conclusion (INF 4.21, IVM 3.65, p=0.10). INF patients received their second and third doses significantly earlier (1.6 and 5.0 minutes respectively) than IVM patients; rescue doses in this group were also given earlier, although this was not statistically significant.

Overall, patients with back pain had the largest absolute reduction of pain scores. Of the 37 patients in this cohort, INF patients experienced, on average, a reduced VRS of 5.41, whilst the IVM patients experienced an average reduced VRS of 3.67 (p=0.05). A breakdown of the VRS results by dominant problem is seen in Table 3.

Bivariate analysis led to the following variables being excluded from the regression model: Chest Pain; Abdomen Pain; Other Pain; Age; Sex; Weight; GTN; use of rescue analgesia. Backward stepwise regression then excluded Fracture/Dislocation. The most significant contributor was initial pain score, with a higher initial score predicting greater decrease in pain by destination. Back pain was also significantly associated with a greater reduction in pain score than patients with other complaints. Analysis by group without the back pain cohort, led to a more similar treatment effect between groups (VRS reduction INF 3.97, IVM 3.55, p=0.31). Patients who received methoxyflurane achieved significantly worse pain reduction. Treatment group continued to be non-significant. See Table 4 for the regression model. This statistical model accounted for 18.7% of variation in the change in VRS.

There were 62 recorded adverse events associated with 51 of the 232 patients who received one or more doses of their allocated drug. A review of the adverse events that were experienced by 36 (27%) INF patients and 15 (15%) IVM patients is shown in Table 5. Patients with one or more serious adverse events (SAEs) (hypotension, respiratory depression and/or altered level of consciousness) were more prevalent in the INF (n=19, 15%) than the IVM (n=7, 7%) group, although this was not significant (RR 2.09, 95%CI 0.92-4.78, p=0.07). Initial pain scores, use of rescue analgesia, and weight did not differ statistically for patients who had an SAE (data not shown), however, such patients were an average of 6 years older (p=0.03).

Treating paramedics considered INF clinically acceptable for 85% of patients who received the treatment. Poor tolerance was noted in 12 of 319 total INF doses (3.8%) given to 136 patients and 16 of 322 (5.0%) of total IVM doses given to 122 patients.

4. Discussion

In this study we found no significant difference between INF and IVM patients in pain reduction from baseline to destination. That is; INF and IVM were not significantly different in their effectiveness as prehospital analgesia. The average patient in both groups improved from a baseline VRS of 8 out of 10, to a destination VRS of 4, over a journey of approximately half an hour. In addition, there was no significant difference in safety or acceptability measures.

Although the study did not detect a statistically significant difference ($p=0.08$) in effectiveness, it is possible that a larger study would have done so. INF patients had, on average, a greater VRS reduction of 0.65, a difference which we do not consider to be of clinical significance. The 95% confidence intervals indicate that the true effect lies somewhere between a 0.29 better VRS reduction for IVM, to a 1.61 better VRS reduction for INF. The general consensus is that a difference of 1.3 points on the VRS scale is needed for a clinically significant effect [18]. Future research with larger sample sizes is needed; if INF can actually reduce VRS scores by one point or more as compared to IVM, then this would be of clinical benefit. We conclude that INF is at least equally effective as IVM, and future research may find it superior for prehospital analgesia.

To our knowledge this is the first reported study of INF in the prehospital setting. Our favorable results are consistent with, and build upon, studies published in the inpatient setting. RCTs in adult orthopaedic, gynecology and general surgery patients show equivalent postoperative pain relief and side-effect profile to intravenous fentanyl [8,10,12,15], and superior pain relief and patient satisfaction when compared with a multi-drug model [16]. Randomized trials in both adult and pediatric burns patients undergoing wound care have found INF pain reduction and side-effect profiles equivalent to oral morphine [9,14]. In pediatrics, the effectiveness of INF has been demonstrated for analgesia in an emergency department, [13] and for both

analgesia and post-operative agitation when incorporated as anesthesia for ENT surgery [11].

Research into prehospital analgesia has been minimal until relatively recently despite reports that the problem is common, and often poorly managed [1,18-20]. A review of 17 prehospital analgesia studies published 1966-2001 concluded that there was a paucity of data to support practice, with evidence all at level III or IV, and no randomized trials [21]. Our study with its randomized controlled trial design provides evidence to the growing body of knowledge in this area.

The results of this study may be related to elements of study design or patient population. We required that patients complete the protocol to be included in the primary analysis, and it is possible that by excluding the 31 patients who did not, the study validity was impinged. However, we did perform an intention to treat analysis of all randomised patients and this did not alter the study conclusions. The open-label, unblinded design was a limitation as it may have allowed bias to enter the study, with patients or clinicians favouring one or the other treatment. Unfortunately we did not have the resources to undertake a blinded placebo-controlled trial, and also felt that the ethical issues associated with slight delays in analgesia in this setting may have been a concern. We observed shorter duration between dosages of fentanyl than morphine and this may have been due to paramedics' pre-existing beliefs about the efficacy or safety of the drugs, or alternately may reflect fentanyl's short-acting effect. Ideally future trials should be blinded with double-dummy design.

Ideally, in a comparative trial such as this, data would not be 'muddied' by such a high number in the INF group also receiving morphine. However, at trial outset, this 'rescue option' was seen to be ethically required. The fact that the groups had equivalent pain scores at all time points, including just prior to rescue, supports equivalence of effect between groups. The dosing schedule in the trial may have influenced the outcome. If a patient had the 3 available increments they would have received 300mcg of fentanyl or 7.5-15mg morphine. Previous studies reporting INF use in adults have generally used lower doses of approximately 50-170 mcg over comparative (30 minute) periods [9,10,12,15,16]. However, almost all previous studies were of patients in the postoperative period who were concurrently affected

by intraoperative agents, making these doses of little application to the prehospital setting. We note that one quarter of our INF patients and one third of IVM patients required rescue analgesia after completion of the three allocated doses, and there was a low rate of serious adverse events; this suggests that higher or more total doses are required for both regimes. It is noted that most people have limited absorption through one or the other nare at various times throughout the day due to mucous congestion. This may partially explain why doses seemed inadequate. Anecdotally, some Australian ambulance services have since increased their INF dosing schedules above that used in this study with reported beneficial outcomes. Our morphine dose of 2.5-5 mg increments was chosen in line with our pre-existing institutional policies. However, this also appeared inadequate and this is consistent with research suggesting even doses of 0.1-0.15 mg/kg do not provide effective relief [22,23].

This study took an “all-comer” approach to recruitment, and enrolled patients with a variety of clinical complaints and pain locations. Whilst this does reflect the need for standardised treatments in the prehospital setting, and allows broad generalisation of results, it limits the measurement effect in any one patient cohort. Our design aimed to control for the presence of cardiac as opposed to other forms of pain in recognition of the differences inherent in this subgroup. Although our numbers were too small to undertake sub-group analysis, we had hypothesised (based on clinical reports) a priori that back pain patients may benefit more greatly from fentanyl. There were 37 back pain patients in our study and they did show a greater benefit from INF with pain score reduction on average almost 2 points higher on the ten point scale, than that achieved by IVM. This suggests further studies particularly focus on the back pain population, to further explore the observed trend for higher benefit in this group, as well as extension of the research to new populations such as pediatric prehospital care.

We observed that higher baseline VRS and non-use of methoxyflurane predicted improvement in VRS. Whilst interesting, these observations probably add little more than can be logically reasoned. The higher the initial pain score, the greater the range of potential VRS scores for it to fall to, and although a small number of patients’ pain may be intractable, in most cases paramedics will reduce pain severity. Methoxyflurane was administered to just over a third of patients, and these patients

tended to have VRS levels which were resistant to improvement. Typically, methoxyflurane is given to patients with milder pain, and if this is unsuccessful in reducing symptoms, or pain worsens, then opiates are administered. It may also be used in extended cases, such as entrapment in a motor vehicle. This patient subgroup with their resistant or worsening pain, are intuitively going to be more difficult to treat regardless of the opiate (INF/IVM) delivered. Nevertheless, drug interactions are possible, and future research will need to investigate best practice when multiple-drug models are employed for prehospital analgesia.

Our study raises some concerns about the adverse event profile of INF, and this will be an important issue to explore in future research. While the patients in the INF group had more than double the rate of adverse events than IVM, the overall numbers were not statistically significant. However, our sample size may have been inadequate to detect this, and it should be remembered that in an unblinded study such as this, there was potential for bias in monitoring/reporting of events. Fentanyl is generally thought to be a safer option than morphine, with a rapid peak, slower duration of action, less hypotension and rarely associated nausea and vomiting [2]. Anecdotally, nausea and vomiting may remain a problem in the mucosal routes, particularly in children, who may also be uncooperative with this route of treatment. However, it remains a potent narcotic and should be used with caution in regards to respiratory depression and altered level of consciousness. When confined to only serious adverse events involving the respiratory, cardiovascular or neurological system, INF also had a (non-significantly) higher rate. However, only one patient in each group actually had an SAE requiring abandonment of treatment, and it is worth noting that reported adverse events may have actually been related to the patient's underlying condition, rather than the study drug. We do stress that the adverse/side effect data was obtained by paramedics in the field and this data may not be equivalent to that observed, for example, by a trained physician, or a dedicated paramedic researcher who was not busy with clinical care. In addition, the non-blinded nature of the study requires caution in interpretation of these results. Our review of SAE cases found that 65% were likely, and 25% possibly related to the study drug, however, this was done retrospectively and we did not have access to the patients' hospital charts after arrival – these may have contained alternative explanations for the SAE. Previous randomized trials in inpatient surgical populations have observed an equivalent side-effect profile of INF compared with intravenous

fentanyl [8,10,12,15], and with oral morphine [9,14]. In our study, the treating paramedics were not asked to rank adverse events at the time of occurrence as to their likelihood of causation by the study drug; this would be a useful addition to future trials.

The practicalities of intranasal application were borne out in this study, with only one (<1%) report of atomiser malfunction. Of patients allocated to morphine, 7% were unable to be cannulated and a further 2% were cannulated with difficulty. In addition 3% of patients refused morphine, perhaps due to a fear of needles or of the drug itself. This total of 12% of patients unable to be treated with morphine as allocated provides evidence as to the type and number of patients where INF provides practical advantages. Only 1% of fentanyl patients refused to be treated at study outset, although it is worth noting that 2% of those commencing treatment refused further doses, whereas no morphine patient refused subsequent treatment. Anecdotally, mucosal irritation is frequently reported by patients who receive INF. However, the intranasal route of INF allowed pain to be treated rapidly, as opposed to more traditional routes of delivery.

In conclusion, INF is an effective alternative to IVM for use in the pre-hospital setting. Of particular value is the option to provide rapid analgesia to patients where cannulation is undesirable or impossible.

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Legends for Tables/Figures

Table 1. Patient characteristics

Table 2. Treatment effect on VRS

Table 3. Change in VRS by dominant problem

Table 4. Final regression model for the outcome of change in VRS

Table 5. Adverse events for patients with completed or partial treatment

Figure 1. Assignment of participants into Morphine or Fentanyl treatment groups

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