Addiction

RESEARCH REPORT

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Randomized controlled trial comparing the effectiveness and safety of intranasal and intramuscular naloxone for the treatment of suspected heroin overdose

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ABSTRACT

Aims Traditionally, the opiate antagonist naloxone has been administered parenterally; however, intranasal (i.n.) administration has the potential to reduce the risk of needlestick injury. This is important when working with populations known to have a high prevalence of blood-borne viruses. Preliminary research suggests that i.n. administration might be effective, but suboptimal naloxone solutions were used. This study compared the effectiveness of concentrated (2 mg/ml) i.n. naloxone to intramuscular (i.m.) naloxone for suspected opiate overdose. **Methods** This randomized controlled trial included patients treated for suspected opiate overdose in the pre-hospital setting. Patients received 2 mg of either i.n. or i.m. naloxone. The primary outcome was the proportion of patients who responded within 10 minutes of naloxone treatment. Secondary outcomes included time to adequate response and requirement for supplementary naloxone. Data were analysed using multivariate statistical techniques. **Results** A total of 172 patients were enrolled into the study. Median age was 29 years and 74% were male. Rates of response within 10 minutes were similar: i.n. naloxone (60/83, 72.3%) compared with i.m. naloxone (69/89, 77.5%) [difference: −5.2%, 95% confidence interval (CI) −18.2 to 7.7]. No difference was observed in mean response time (i.n.: 8.0, i.m.: 7.9 minutes; difference 0.1, 95% CI −1.3 to 1.5). Supplementary naloxone was administered to fewer patients who received i.m. naloxone (i.n.: 18.1%; i.m.: 4.5%) (difference: 13.6%, 95% CI 4.2–22.9). **Conclusions** Concentrated intranasal naloxone reversed heroin overdose successfully in 82% of patients. Time to adequate response was the same for both routes, suggesting that the i.n. route of administration is of similar effectiveness to the i.m. route as a first-line treatment for heroin overdose.

Keywords Heroin, intranasal, naloxone, opioid, overdose, resuscitation.

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INTRODUCTION

Heroin overdose is a major cause of death in some countries [1–4]. In most instances, timely treatment with naloxone, an opiate antagonist, reverses opioid toxicity. In the community setting, paramedics administer naloxone routinely for suspected opioid overdose via the intramuscular (i.m.) and/or intravenous (i.v.) routes [5–7]. Administration of the drug by these routes to populations such as injecting drug users carries some risk. Injecting drug users are often infected with blood-borne viruses such as human immunodeficiency virus (HIV), hepatitis B (HBV) and hepatitis C (HCV) [8–10], and in spite of best practice guidelines designed to minimize needlestick injury among health workers, needlestick injuries occur, allowing for the possibility of blood-borne virus transmission. Among health care workers, 4% of HIV infections and 40% of HBV and HCV infections occur after occupational exposure [11].

There is growing interest in intranasal (i.n.) administration of naloxone [12–17]. The benefits of i.n. administration include ease of access, greatly reduced

needlestick injury risk and the potential for peer and non-health professional administration. Its use in acute overdose is supported by a number of small cohort studies [18–22]. To date, there has only been one randomized trial comparing i.n. and i.m. administration [22]. It found i.m. administration resulted in shorter response time than i.n. administration (mean 6 minutes versus 8 minutes), but the i.n. route was successful for 74% of patients. The preparation used for i.n. administration in that study (2 mg in 5 ml) far exceeded recommendations for i.n. use of drugs that specify volumes of less than 1 ml per nostril [12]. It was, however, the only preparation available at the time of that study. That raised the question of whether concentrated, small-volume dosing would improve the effectiveness of i.n. naloxone.

The aim of this study was to determine the effectiveness and safety of concentrated (2 mg/ml) i.n. naloxone compared to i.m. naloxone for treatment of suspected opiate overdose in the pre-hospital setting. Specifically, the study sought to compare the two preparations in terms of response times, side effects, need for a second dose of naloxone and final outcomes.

METHODS

Participants

This was a prospective, randomized, unblinded trial conducted in Melbourne, Victoria, Australia. Patients requiring treatment by six designated branches of Metropolitan Ambulance Service (MAS, Victoria) for suspected opiate overdose during the period from 1 August 2006 to 31 January 2008 were considered for enrolment. We chose these branches as they were located in areas with higher incidence of heroin overdose, known historically to capture more than half of the heroin overdoses in the metropolitan region [23].

Patients were eligible for enrolment if they suffered a suspected opiate overdose [altered conscious state, pinpoint pupils, respiratory depression (respirations < 10)], were unrousable as defined by Glasgow Coma Score (GCS) $\leq$12 and had no major facial trauma, blocked nasal passages or epistaxis. The GCS score was chosen as the measure of sedation because it is the parameter used operationally in the ambulance service within which our study was conducted [24].

We were aiming for a consecutive sample. However, paramedic staff turnover meant that not all eligible patients were enrolled during the study period. Paramedics required training in the study protocol and use of the atomization device before enrolling participants. This meant that potential participants, who were treated by paramedics who had not been trained, could not be enrolled into the study. During the study period there were approximately 1300 heroin overdose attendances, defined as a patient with a positive response to the administration of naloxone by paramedics, in metropolitan Melbourne [25].

Melbourne Health Human Research Ethics Committee (HREC) approved the study. Requirement for individual patient consent was waived. Subjects were informed of their participation by way of an information letter after regaining consciousness which allowed them to withdraw themselves from the study or seek further information.

Procedure

Allocation of mode of administration (i.n. or i.m.) was achieved by block randomization using an online computer program to achieve a random sequence of allocations. Block randomization was performed to achieve equal distribution of allocations (i.n. or i.m.) to each study site. The nature of pre-hospital emergency care and the urgency of treatment for this condition prohibits more sophisticated double-treatment randomization techniques.

Randomization envelopes, present in each ambulance, were designed by the study investigators to conceal the randomization group. The allocation notice was positioned between the study information sheet and the envelope was made of thicker, non-transparent paper. This was designed to prevent paramedics choosing the randomization arm selectively for potential subjects. All envelopes were identical from the outside. All envelopes were numbered sequentially according to the block randomization procedure, and all envelopes were accounted for at monthly intervals and at the end of the study.

After determining eligibility, a randomization envelope was opened at the scene, allocating patients to receive either i.n. naloxone 2 mg or i.m. naloxone 2 mg. Supportive care (primarily breathing support) was administered simultaneously, in accordance with ambulance clinical practice guidelines for this condition.

Administration by i.m. injection was by standard MAS practice using a pre-packaged 'min-i-jet'™ preparation containing naloxone solution (2 mg/5 ml). Naloxone for i.n. administration was constituted in a tamper-evident vial as a preparation of 2 mg in 1 ml, manufactured specifically for the study and complying with national medication quality and safety standards. At the scene, contents of the vial were withdrawn into a luer-lock syringe, and the syringe was then attached to a mucosal atomization device (MAD®). Paramedics were instructed to depress the syringe rapidly during i.n. administration to achieve adequate atomisation. Study participants received 1 mg (0.5 ml) in each nostril.

Standard supportive care, including airway and breathing support as needed, continued throughout the

data collection period until either recovery or transport to hospital. All patients who failed to respond to either form of naloxone treatment after 10 minutes were eligible for a 'rescue' dose of 0.8 mg i.m. naloxone. The 10-minute recommendation was chosen for consistency with treatment recommendations already laid down in the relevant ambulance service protocols [26].

Measurements

Paramedics entered study information into an electronic patient case record (e-PCR), as per the Victorian Ambulance Clinical Information System (VACIS). The e-PCR is the tool used by paramedics to document emergency care administered for all cases. The data for this study were extracted by explicit review of these files. Information collected included demographic data [age, gender, vital signs (including respiratory rate, pulse, GCS)], suspicion of other drugs/alcohol taken, specific location, other people present, resuscitative measures (basic life support, airway management), naloxone administration (dose, route, time of administration, difficulty during administration, requirement for secondary naloxone), response times, side effects and final outcome (self-care, hospitalization, death). Data were entered directly into a Microsoft Access database developed specifically for this study. All data entries were checked for accuracy by an independent blinded research assistant. A third researcher arbitrated discrepant data extraction (three cases only).

The primary outcome of interest was the proportion of patients with an adequate response within 10 minutes of naloxone administration. Response was defined as effective and spontaneous respirations at a rate ≥ 10 per minute and/or GCS ≥ 13. Patients who received a supplementary dose were classified automatically as not achieving an adequate response within 10 minutes. This end-point was chosen to be consistent with current ambulance practice guidelines, where secondary naloxone is recommended for inadequate response after a 10-minute period [25]. While, for many clinicians, reversal of respiratory depression is the key outcome, improvement in level of consciousness, indicating the reversal of over-sedation responsible for respiratory depression, has been used by previous studies in this field [18,19] as an indicator of successful treatment.

Secondary outcomes included time to adequate response, hospitalization, adverse event rate and requirement for 'rescue' naloxone due to inadequate primary response as judged by the treating paramedics.

Adverse events were grouped into three categories including drug-related (vomiting, nausea, seizure, sweating, tremor, acute pulmonary oedema, increased blood pressure, tremulousness, seizures, ventricular tachycardia and fibrillation, cardiac arrest, agitation and paraesthesia), administration-related (nasal obstruction, nasal deformity) and study-related (epistaxis, ruptured septum, spitting, coughing, leakage of solution from nasal passages).

Data analyses

Descriptive analyses [proportion, mean, median, effect size difference with 95% confidence interval (CI)] were conducted using Intercooled Stata version 8.2 [27] to describe the demographic data and compare groups (i.n. and i.m.) for observed differences (drug use, alcohol use). Primary outcomes were compared by univariate analysis including observed difference and odds ratio (OR) with 95% CI, hazard ratio (HR) and χ^2 analysis. Correlates included in the multivariate models (logistic regression, Cox regression) were age, gender and concomitant alcohol and/or drug use.

Response time was compared using Kaplan–Meier survival analysis. A clinically significant difference in response time was defined as 1 minute. This end-point was based on the likelihood of oxygen de-saturation after 1 minute as a result of respiratory depression. For all patients, entry time was defined as 1 minute after administration by either route; exit time was the earliest of (i) adequate response; or (ii) rescue naloxone; or (iii) last recorded observation. Only the first of these exit times was regarded as an event, and the latter two were considered as censored observations.

Based on previous studies [18,19,22], we needed to recruit at least 84 patients per group to detect a difference in proportions for successful response to naloxone treatment of 11% (100% versus 89%) with power 80% (Intercooled Stata version 10.0) [28]. With this sample, and assuming similar results of around 95% success for both groups, the width of the 95% CI for difference in risk will be $\pm$ 6.4%.

RESULTS

Two hundred and sixty-six patients were treated for suspected heroin overdose at the enrolment sites during the study period; 13 patients were not considered for study enrolment. A further 75 patients were not eligible, as shown in the participant flow diagram (Fig. 1), including 20 patients who could not be included because paramedics at the site had not been trained in the study protocol. Of the remaining 178 patients, six patients were excluded from participation for the following reasons: equipment for intranasal administration was missing for three patients and three patients became alert prior to naloxone administration (two in the i.n. group and one in the i.m. group). These six patients were excluded from

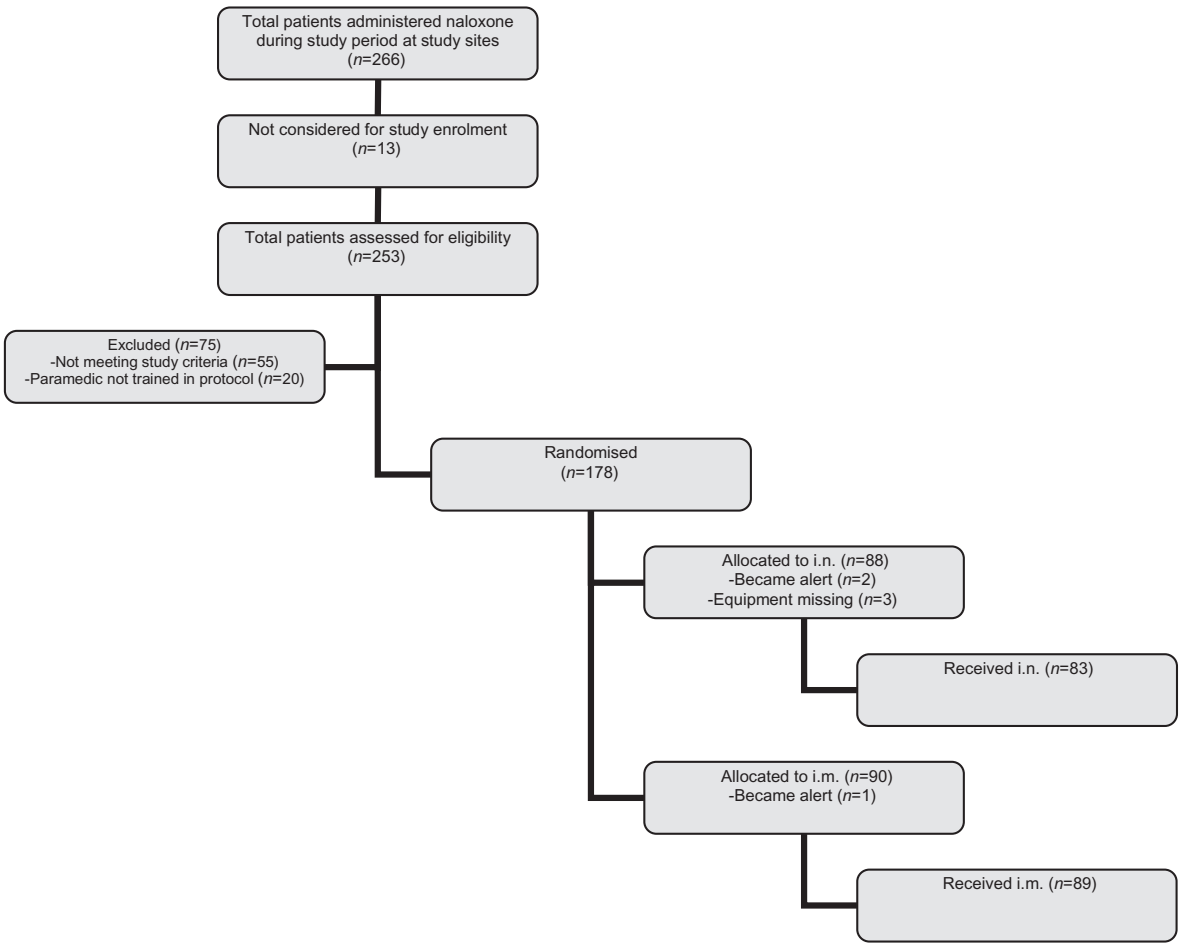

Figure 1 Participant flow diagram. i.m.: intramuscular; i.n.: intranasal

final data analysis. Hence, data were not analysed on an 'intention-to-treat' basis but, rather, analysed by the treatment they received.

The final sample consisted of 172 patients who received i.n. (83 patients) or i.m. (89 patients) naloxone.

The characteristics of the patients are shown in Table 1 according to their allocated treatment. Patients were broadly similar for age, gender and treatment time. The median age was 29 years, and 74% were male. An important difference in baseline characteristics was observed, with more patients in the i.n. group suspected of concomitant drug use compared to the i.m. group [i.n.: 21.7%, i.m.: 9.0%, difference 12.7% (95% CI 2.0, 23.4)].

Study outcomes are shown in Table 2. One hundred and twenty-nine patients (75%) achieved an adequate response within 10 minutes from initial naloxone treatment, 60 (72.3%) in the i.n. group and 69 (77.5%) in the i.m. group [difference −5.2% (95% CI −18.2, 7.7%)]. Mean response time (minutes) was similar between the two groups [i.n.: 8.0, i.m.: 7.9, HR 0.8 (95% CI 0.6, 1.2)], as shown in Fig. 2. The absence of significant difference was supported by multivariate analysis for adequate response within 10 minutes [OR 0.7 (95% CI 0.3, 1.5)] and actual response time [HR 0.84 (95% CI 0.6, 1.2)].

Table 1 Comparison of characteristics for patients treated for heroin overdose with intranasal or intramuscular naloxone.

Variable	*Intranasal (%) n = 83*	*Intramuscular (%) n = 89*
Age (mean years)	30.6	31.8
Treatment time[a] (mean minutes)	13.1	13.4
Male	64 (77.1)	63 (70.8)
Concomitant alcohol	25 (30.1)	31 (34.8)
Concomitant drugs	18 (21.7)	8 (9.0)[b]
Concomitant alcohol ± drugs	39 (47.0)	33 (37.1)
Public use	42 (50.6)	47 (52.8)

[a]Time from ambulance call to administration of naloxone treatment.
[b]Observed difference 12.7% (95% confidence interval 2.0, 23.4).

Rescue naloxone was administered more often to patients in the i.n. group (18.1%) compared with those

Table 2 Comparison of outcomes for patients treated by intranasal (i.n.) or intramuscular (i.m.) naloxone.

Outcome	*i.n. (83)* *n (%)*	*i.m. (89)* *n (%)*	*Difference (95% CI)*	*Univariate analysis* *OR (95% CI)*	*Multivariate analysis* *OR (95% CI)*
Adequate response ≤ 10 minutes	60 (72.3)	69 (77.5)	−5.2%, (−18.2, 7.7)	0.8, (0.4, 1.5)	0.7, (0.3, 1.5)
Rescue naloxone for inadequate response	15 (18.1)	4 (4.5)	13.6%, (4.2, 22.9)	4.7, (1.6, 14.1)	4.8, (1.4, 16.3)*
Hospitalization	24 (28.9)	23 (25.8)	3.1%, (−10.3, 16.4)	1.2, (0.6, 2.3)	1.3, (0.6, 2.7)
Minor adverse event	16 (19.3)	17 (19.1)	0.2%, (−11.6, 11.9)	1.0, (0.5, 2.2)	1.1, (0.5, 2.5)
				HR (95% CI)	HR (95% CI)
Mean response time (minutes)	8.0	7.9	0.1 (−1.3, 1.5)	0.8, (0.6, 1.2)**	0.84, (0.6, 1.2)***

*$P = 0.01$; **$P = 0.29$; ***$P = 0.29$. HR: hazard ratio in i.n. group, relative to i.m. group; OR: odds ratio for each outcome in i.n. group, relative to i.m. group; CI: confidence interval.

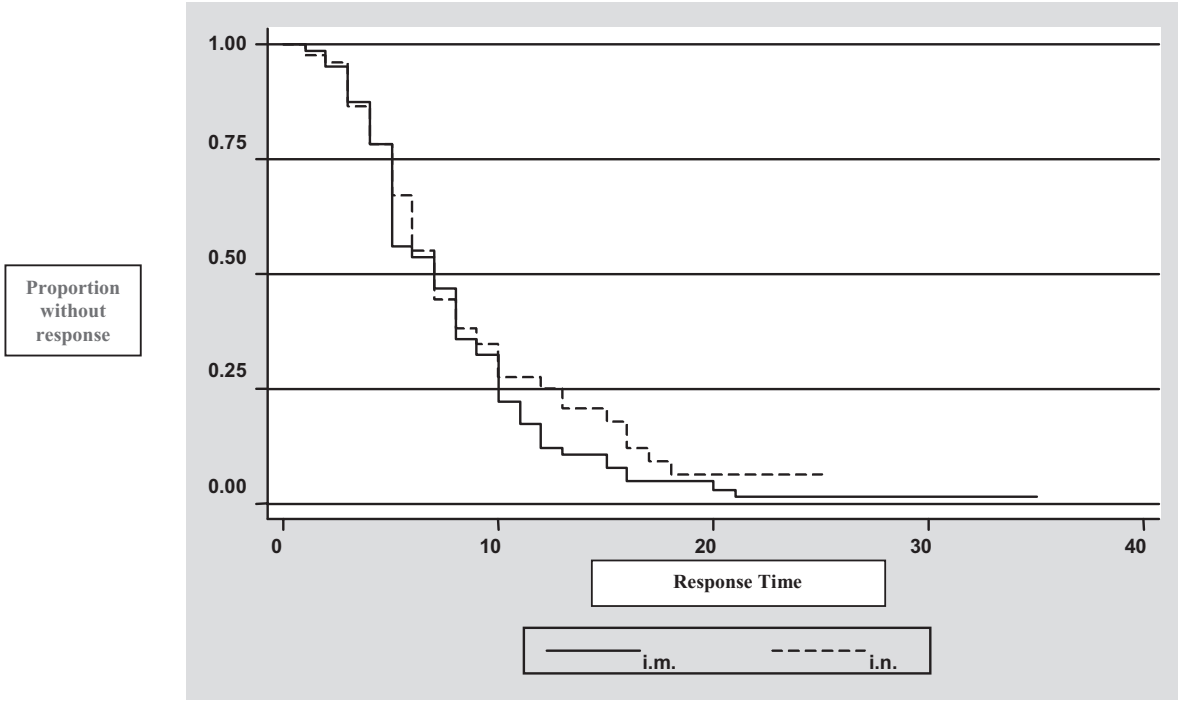

Figure 2 Kaplan–Meier survival curve comparing response times for patients who receive intranasal (i.n.) or intramuscular (i.m.) naloxone

in the i.m. group (4.5%) [difference 13.6% (95% CI 4.2, 22.9%)]. After controlling for age, gender and suspected concomitant alcohol and/or drugs, this difference remained statistically significant [OR 4.8 (95% CI 1.4, 16.3)]. Twenty-four patients did not achieve an adequate response at 10 minutes and were not administered secondary naloxone (i.n.: 8/23, i.m.: 16/20). Average response from initial naloxone treatment was 16 minutes for these cases. It is our assumption that paramedics chose to wait for a response after the 10-minute cut-off, and patients responded without secondary naloxone administration. However, we did not collect information regarding reasons for not administering naloxone for these cases.

There was one major adverse event. A patient who received i.m. naloxone had a *grand mal* epileptic seizure, was given i.v. diazepam, and was transferred subsequently to hospital for further management. Minor adverse events were similar between the two groups (i.n.: 19.3%, i.m.: 19.1%; difference 0.2% 95% CI −11.6, 11.9), as were hospitalization rates (i.n.: 28.9%, i.m.: 25.8%; difference 3.1% 95% CI −10.3, 16.4). No difference was observed in agitation and/or violence (i.n.: 6.0%, i.m.: 7.9%), nausea and/or vomiting (i.n.: 8.4%, i.m.: 7.9%) and headache (i.n.: 4.8%, i.m.: 3.3%) after naloxone treatment. To our knowledge there were no needlestick injuries during i.m. administration of naloxone during the study period.

DISCUSSION

Emergency medical service (EMS) personnel are at an increased risk of blood-borne virus exposure when providing treatment to injecting drug users, a population with an increased prevalence of HIV, and HBV and HBC [29–31]. Administration of medication via non-parenteral routes is one means of reducing needlestick injury risk. This study has shown that administration of naloxone via the i.n. route, using a concentrated solution, to patients with suspected heroin overdose in the pre-hospital setting is a safe and effective treatment option, with similar response rates, response times and side-effect profile to i.m. administration.

Previous studies have reported success rates for i.n. naloxone between 74 and 91% [18,19,22]. In these studies, successful treatment was defined as an adequate response to i.n. naloxone without the requirement to administer secondary naloxone treatment. Taken together with this study, they provide strong evidence that i.n. naloxone is effective for initial treatment of heroin overdose in the community.

Current ambulance protocols for naloxone in most jurisdictions recommend i.m. administration [26,32]. The protocol for the ambulance service involved in this study involves naloxone administration using a pre-packaged syringe and needle (min-i-jet™), which means that needlestick injury protection is reliant upon paramedics adhering to good practice around the management of needles; i.n. administration of naloxone offers clear advantages here in terms of a reduction in needlestick injury risk. Given our findings, it would appear that i.n. naloxone is a viable therapy that reduces the possibility of needlestick injury among paramedics when compared to parenteral alternatives.

While the finding that approximately a quarter of patients in each group did not respond to naloxone is important, it should be noted that there was no statistically significant difference between the groups with regard to the proportion of non-responders. Lack of response to naloxone therapy after ambulance response has been reported (20–63%) [18,19,22]. Non-response may reflect simple misclassification (heroin overdose is notoriously difficult to define) [33], but may reflect other causes such as the possibility that the delay between overdose and the attendance of the ambulance reduces adequate response, with greater delays possibly being associated with more advanced respiratory depression. Polydrug use and other physical comorbidity may also be relevant [34]. Irrespectively, the non-response we observed highlights the importance of pre-hospital supportive care (by bystanders followed initially by EMS personnel) that remains an essential component in preventing deaths.

Response to i.m. naloxone treatment was slower in this study (8 minutes) in comparison to previous research (6 minutes) [22]. It is unclear why this is so, as the naloxone preparation and protocol for i.m. administration were identical in both studies, but there may have been differences between studies regarding the type and quantity of drugs used by participants prior to overdose. Response to i.n. administration was the same as reported previously [22], despite the change in concentration.

A concentrated preparation of naloxone has not been investigated previously. For optimal absorption and effectiveness, it is advised that medication for i.n. administration be prepared in volumes of less than 1 ml per nostril [12]. A suitable preparation for nasal administration (<1 ml per nostril) of a dose equivalent to that used in this study is not currently available in Australia or overseas. Naloxone for i.n. administration was manufactured specifically for this study under the legislative authority as a registered clinical trial. Previous studies using dilute preparations have reported success rates between 74 and 91% [18,19,22]. The success rate in this study is not significantly better than these, so it cannot be concluded that the concentrated solution is more effective. That said, smaller volumes are easier to administer and lend themselves more effectively to pre-packaged devices. In addition, there were no reports of excess fluid expulsion from the nose or coughing by study subjects in this current study, as was observed in previous research [22].

Although patients who received i.n. naloxone were 4.8 times (95% CI 1.4, 16.3) more likely to receive rescue naloxone, this finding needs to be considered from a clinical perspective. Administration of rescue naloxone to patients included in our study was a subjective decision made by paramedics at the scene, and was very dependent upon the individual paramedic and their comfort waiting for an adequate response, the patient's respiratory and conscious state and patient request for further naloxone. Paramedics were encouraged to administer secondary naloxone if an inadequate response was observed after 10 minutes. It is possible that a response might have been observed for some patients if a longer observation period had occurred. Also, randomization was not blinded. A double-blind study design would have eliminated this limitation. Paramedics might have administered secondary naloxone to patients who received the i.n. allocation due to apprehension about the effectiveness of the i.n. treatment option. However, the possibility that patients who receive i.n. naloxone may require rescue naloxone more often cannot be ruled out by our study.

The fact that 72% of the i.n. group responded within 10 minutes highlights the potential of i.n. naloxone to be used for peer administration. Naloxone distribution

programmes using parenteral naloxone have been instituted in some places [32,35], and favourable reports of lives saved have been reported [35]. The preferred route for peer naloxone administration is an important issue, and has been reported in a separate study [36]. Nasal administration for peer naloxone distribution was preferred (74%) by current heroin users ($n = 99$) in a study performed in Melbourne (Australia) during 2007 [36]. Administration via the i.n. route may be a simpler option for those without professional health care training and largely eliminates infection risk. An opioid overdose prevention programme in Boston (USA) distributes an intranasal naloxone spray to potential bystanders [37]. They report that after 15 months from programme commencement there have been 74 successful overdose reversals, and few problems with the i.n. spray.

Our study responds to the need for well-designed randomized clinical trials in the drug and emergency medicine research fields. It does, however, have some limitations that should be considered when interpreting the results. The study may have been strengthened by a double-blinded study design; however, the pre-hospital setting for research poses challenges that require flexibility and simplicity in study design [38]. Not all patients were enrolled into the study, although we encouraged paramedics to consider all patients treated for heroin overdose for recruitment. Our study did not include all ambulance sites in metropolitan Melbourne, hence only 266 were considered for recruitment. This might have resulted in a systematic bias in enrolment. We were also unable to measure for opioid, polydrug or alcohol load. Hence, heroin overdose was not confirmed. Tolerance to heroin has been shown to be influenced greatly by alcohol and polydrug use [39–41]. Paramedics document routinely evidence of polydrug and/or alcohol consumption prior to the event, but there may have been some unidentified cases. Our sample size calculations were made on data that was available at the time of study design. This over-estimated significantly the success rates of both routes of administration and posed a potential threat to the study's power. This is countered by the almost identical response times, so a clinically significant difference in effectiveness is unlikely.

In conclusion, we have shown that naloxone administered via the i.n. route is an effective and safe intervention for the initial management of heroin overdose. However, the concentrated preparation we used was not more effective than the less concentrated version used in a previous study. The i.n. option offers rescuers a needleless option as first-line treatment and opens opportunities for wider distribution of naloxone for peer and non-health care administration. A low adverse event rate was found for both (i.n. and i.m.) routes.

Declarations of interest

None.

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