**EFFECTIVENESS AND SAFETY OF LARGE BOLUS INTRAMUSCULAR NALOXONE FOR OPIOID POISONING IN THE EMERGENCY DEPARTMENT: A RANDOMISED CONTROLLED TRIAL**

**Study Short Title**

Large Bolus IM Naloxone for Opioid Poisoning in the ED

**Background**

*What is known about topic?*

Opioid poisoning is increasing1 and is the single largest cause of drug related deaths worldwide.2 Naloxone, a competitive mu-opioid receptor antagonist that is a specific antidote for opioid poisoning, has been available since the 1960s.3 It rapidly reverses the effects of opioid toxicity including life-threatening respiratory depression and coma.

In opioid tolerant patients the administration of naloxone can precipitate acute withdrawal. The vast majority of cases of acute opioid withdrawal, though unpleasant, is relatively benign. Symptoms includes yawning, piloerection, shivering, nausea, vomiting, tachycardia, hypertension and agitation.4 Severe acute behavioural disturbance or aggression is uncommon.5, 6 Rarely, seizure, pulmonary oedema, arrhythmia and myocardial infarction have been reported.2, 7

Naloxone can be administered by multiple routes with the most commonly used being the intravenous, intramuscular and intranasal routes. Doses can vary widely from 0.04mg to 2mg and depend partly on physician preference and often on trial and error.8 The optimal initial dose and route of administration is not clear as there is little research defining the best regimen to reverse opioid toxicity.

Current consensus advocates for using the lowest dose of naloxone that can achieve the reversal of respiratory depression without precipitating any symptoms of opioid withdrawal. 2, 4, 9 To achieve this a titrated intravenous naloxone regimen of 0.04mg – 0.1mg is given every 2 to 3 minutes. This is how naloxone is most commonly prescribed in the hospital setting. The intravenous route is used as it is more titratable and more predictable,4 allowing a lower overall dose to achieve reversal of respiratory depression while minimising the precipitation of withdrawal symptoms.4 But this approach risks inadequate reversal of respiratory depression – which can be life-threatening – in an effort to avoid acute opioid withdrawal that is largely mild and well tolerated.

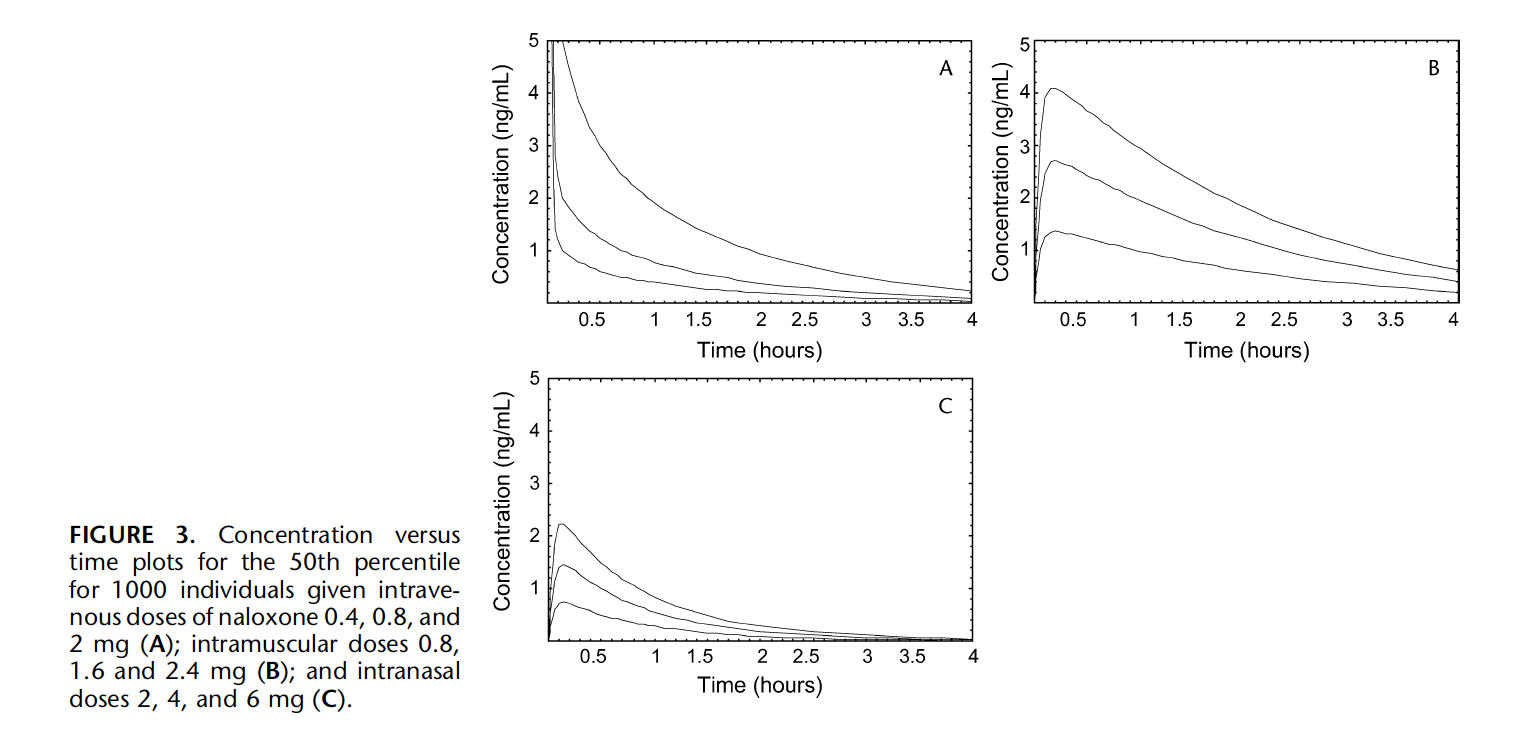
In the pre-hospital and community settings gradual titration is less practical and the intravenous route may not be possible. In these settings, a large bolus of 1.6mg to 2mg of intramuscular or intranasal naloxone is usually preferred. These doses are given as they more reliably reverse the opioid toxicity in a single administration. Although these higher doses are thought to pose a higher risk of precipitating opioid withdrawal, the evidence supporting this assumption is not clear, as severe opioid withdrawal – with pulmonary oedema – has been reported following a single 0.1mg intravenous dose of naloxone in the post-operative period.10

*Why are we doing this study?*

Finding the optimal naloxone regimen is important. Opioid toxicity remains a significant cause of morbidity and mortality in Australia.

Our unit recently conducted a retrospective series of 117 presentations to the emergency department with suspected heroin poisoning that received naloxone.11 Those administered pre-hospital naloxone mostly received 1.6mg of naloxone via the intramuscular route. Those who received naloxone in the emergency department mostly received low dose titrated boluses of intravenous naloxone. In our series, the patients who received the 1.6mg intramuscular bolus of naloxone had a lower rate of a subsequent naloxone infusions compared to the patients who received titrated low dose intravenous aliquots (10% in intramuscular group v 39% in intravenous group). The rate of severe withdrawal was very low and similar in both groups.

Our retrospective study suggested that 1.6mg naloxone administered intramuscularly was more effective at treating opioid toxicity than titrated low dose intravenous naloxone, while having a similar adverse event profile. It is possible that this can be explained by the pharmacokinetic profile of intramuscular naloxone. A study on healthy volunteers demonstrated that the intramuscular route delivers a slower and more sustained rise in naloxone concentrations compared to the intravenous route12 – which may translate to improved effectiveness The attenuated peak concentration may also explain why the rates of severe opioid withdrawal were similar despite the high intramuscular dose.



*Figure A plots intravenous naloxone at doses of 0.4mg, 0.8mg and 2mg while Figure B plots intramuscular naloxone doses of 0.8mg, 1.6mg and 2.4mg in a model of naloxone concentration over time in healthy volunteers.12*

The findings of our retrospective study were at odds with traditional medical teaching2-4, 8 which advocates for the use of titrated low doses of intravenous naloxone in the emergency department to limit the precipitation of withdrawal. This follow-up study is a randomised controlled trial investigating the effectiveness and safety of 1.6mg naloxone in the management of opioid toxicity in the emergency department.

This study seeks to investigate two different naloxone treatment regimens, both of which are used routinely in the management of opioid poisoned patients in an effort to determine which, if any, is more effective and which, if any, is associated with fewer symptoms of opioid withdrawal.

A recent audit of naloxone administration in the Princess Alexandra Hospital over the first 4 months of 2020 revealed there were 49 administrations. Of these 21 (43%) were delivered via the intramuscular route, 13 (27%) by the intravenous route and 15 (30%) by both the intramuscular and intravenous route. This highlights how heterogenous prescribing practices are currently for naloxone dosing.

**Aims**

To investigate the effectiveness and safety of 1.6mg of intramuscular naloxone administered to patients with suspected opioid poisoning and respiratory depression (defined as a respiratory rate < 10 and/or oxygen saturations < 93%).

**Hypothesis**

* Administering an initial 1.6mg intramuscular bolus of naloxone results in a lower rate of recurrence of respiratory depression and subsequent delivery of a naloxone infusion compared to titrated 100mcg intravenous aliquots of naloxone.
* Administering 1.6mg naloxone does not result in a higher rate of clinically significant features of opioid withdrawal (tachycardia, hypertension, vomiting, severe acute behavioural disturbance, pulmonary oedema, myocardial infarction, seizure) compared to titrated 100mcg intravenous aliquots of naloxone.

**Research Plan**

**Study group**

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| --- | --- | --- |
| Dr Katherine Isoardi | Emergency Physician and Clinical Toxicologist | Princess Alexandra Hospital |
| Dr Keith Harris | Emergency Physician and Clinical Toxicologist | Princess Alexandra Hospital |
| Prof Geoff Isbister | Emergency Physician and Clinical Toxicologist | Calvary Mater Newcastle Hospital |

**Study design and setting**

This is a blinded randomised control trial performed at the Princess Alexandra Hospital Emergency Department.

**Participants**

**Inclusion criteria**

* Adult patients > 17 years old presenting to the Princess Alexandra Hospital Emergency Department that require naloxone to reverse respiratory depression (defined as a respiratory rate < 10 or oxygen saturations < 93%) due to suspected opioid poisoning.

**Exclusion criteria**

* Patients in which intravenous access is unable to be obtained
* Patients who have iatrogenic poisoning following opioid administration for acute pain
* Patients who are intubated and ventilated for management of concurrent conditions such as aspiration pneumonitis or to facilitate management of co-ingestions agents.
* Patients in police or corrections custody

**Enrolment, Randomisation and Blinding**

Emergency department medical and nursing staff will be informed of and educated on the study. Current practice at the PAH emergency department is to notify the clinical toxicology team of all patients entering the opioid care pathway in the resuscitation bay. The clinical toxicologist on call will identify suitable patients.

If eligibility is confirmed, the clinical toxicologist will direct emergency staff to open a sequentially numbered opaque sealed study envelope which will be kept in the medical resuscitation bay, Resus 1. Resus 1 will be stocked with 5 study envelopes.

The study envelope has a study number, study datasheet and either 2 syringes of 800mcg of naloxone in 2mL or 2 identical syringes of 2mL normal saline, so that the treating staff are blinded. The syringes will be labelled with the study number only. The study envelopes will be created by an emergency department pharmacist who will randomly allocate consecutive study numbers with blocks of 4 (e.g. AABB, ABAB, BAAB, etc.) to treatment or control arms, guided by a randomisation spreadsheet.

We considered stratification of randomisation for patients that received naloxone in the pre-hospital setting, but due to the risk of errors in allocation in a resuscitation environment it was decided against such a stratification.

Randomisation allocation will be unblinded only following the completion of recruitment and data collation.

**Study Intervention**

1. All patients with respiratory depression (RR < 10 or oxygen saturations < 93%) following opioid poisoning receive 0.1mg IV naloxone
2. Patients are discussed with the clinical toxicologist on call to confirm eligibility for the study before being randomised to receive either 1.6mg naloxone (intervention arm) or saline placebo (control arm) through the opening of a study envelope
3. Following this, both groups receive standard care which consists of further intravenous naloxone is dosed at 0.1mg q3min IV if there is ongoing respiratory depression until the patient has a respiratory rate ≥ 10 and oxygen saturations ≥ 93% representing a reversal of the initial respiratory depression.
4. Patients then continue to be managed by the established opioid poisoning care pathway [Appendix A] which ensures the patient is on continuous oximetry and regular nursing observations are performed (q5min for 15 minutes following any naloxone administration, then q15min thereafter while in the resuscitation bay).
5. If there is a recurrence of respiratory depression evidenced by a RR <10 or oxygen saturations < 93%, intravenous aliquots are repeated until the patient has a respiratory rate ≥ 10 and oxygen saturations ≥ 93%. At this stage a naloxone infusion is commenced at 2/3 the total dose required to reverse the respiratory depression.
6. The study datasheet [Appendix B] mimics the observation chart on the standard opioid poisoning care pathway, and this is completed by nursing staff managing the patient.
7. Once the patient is alert, they receive a study information brochure and are informed of their participation in the study. They are given the opportunity to withdraw their consent or to seek further information.

**Data Collection**

The study datasheet will be entered into a password-protected Excel spreadsheet. The study spreadsheet and a scanned copy of the datasheet will be stored securely on a Queensland Health password-protected server.

Further data pertaining to baseline demographics, risk assessment, medication received (naloxone, droperidol) and disposition will be obtained from the patient’s iEMR.

Patients will be allocated a study code NLX#. No identifiable information will be used on the study spreadsheet. A separate password-protected Excel file will link the study code with the patient's URN to enable patients to be re-identified if further analysis is required (for example if requesting by a journal reviewer). This file will also be stored securely on a Queensland Health password-protected server. Following the close of the study this file (linking patient URN and study code) will be deleted.

**Study Outcomes**

Primary

* Proportion of patients with recurrence of opioid toxicity (defined as respiratory rate <10 and/or oxygen saturations <93%) in the 4-hour period following the intramuscular administration of either 1.6mg naloxone or saline.

Secondary

* Proportion of patients receiving a naloxone infusion
* Proportion of patients with reversal of opioid toxicity (defined as respiratory rate ≥10 and oxygen saturations ≥93%) at 10 minutes following naloxone administration.
* Total number of IV naloxone administrations
* Rate of any clinically significant features of withdrawal (tachycardia, hypertension, vomiting, acute behavioural disturbance, myocardial infarction, arrhythmia, pulmonary oedema, seizure, subjective opioid withdrawal score)

**Sample Size and Feasibility**

Based on our recent retrospective series11 which reported a difference in the rate of naloxone infusions of 39% in the titrated IV naloxone group compared to 10% in the large bolus IM naloxone group following suspected poisoning and using an α value of 0.05 and a 1-β value of 95%, giving a sample size of 51 in each group (102) with a 24% adjustment for potentially non-opioid poisoned patient being recruited to the study, resulting in a total sample of 126.

In the first 6 months of 2020 there were 69 patients with opioid poisoning who presented to the Princess Alexandra Hospital and received naloxone. Based on our retrospective series 60% of these patients receive naloxone in the emergency department with the other 40% receiving it in the field and needing no further naloxone. This would mean approximately 80 patients each year would be eligible for the study. It is likely the required sample size could be recruited in two years.

**Statistical analysis**

Data will be analysed with descriptive statistics with continuous variables reported as medians, interquartile ranges and ranges. Dichotomous variables will be reported as proportions with 95% confidence intervals. Differences in groups will be assessed by Chi squared or Fisher’s exact test. A *P*-value of <0.05 will be considered statistically significant. A pre-defined subgroup for analysis is those that received naloxone in the pre-hospital setting prior to arrival to the Emergency Department.

Analysis will be performed in GraphPad Prism 9.0.1 for Mac OS (GraphPad Software, La Jolla, CA, USA).

**Ethical considerations**

A ‘consent to proceed’ model will be used for the provision of consent in this project. Patients with opioid intoxication lack capacity when they present with sedation and respiratory depression.

Current practice is for patients who are intoxicated with opioids with respiratory depression to receive the reversal agent naloxone. The dose is determined by the managing clinician. Doctors may elect to give naloxone either intravenously or intramuscularly, at a small titrated, or large bolus dose depending on preference. They administer the reversal agent under a duty of care afforded by the urgent provisions of the Guardianship and Administration and Administration Act (QLD) 2000 as an opioid poisoned patient lacks capacity to consent.

Once the patient’s toxicity is reversed with naloxone and they have regained their capacity to provide consent, they will be notified of their participation in the study, be given a study information sheet. They will be approached by a member of the study team and offered the opportunity to consent to proceed in the study or to withdraw from the study.

**Study monitoring**

The conduct of the research project will be carefully monitored by the Principal Investigator (Katherine Isoardi) in terms of the volume of participants recruited and the acceptability of recruitment by meeting the inclusion criteria. Any adverse events will be reviewed according to the degree of seriousness and frequency. In the event of a serious adverse event this will be reviewed by the PI consultation with the safety monitor (Prof Geoff Isbister) who will have complete access to the study data but will not be involved in the study treatment. Serious adverse events will be brought to the attention of the ethics committee.

**Budget**

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| --- | --- | --- | --- |
| Item | Cost per unit | Amount | Total |
| Identical naloxone vials for study kit | $60/kit | 100 kits | $6,000 |
| Saline placebo vials for study kit | $30/kit | 100 kits | $3,000 |
|  |  | TOTAL | $9,000 |

**Budget justification**

* Slade has provided the following quote for the provision of the drugs for the study kits.
* We will have 74 extra kits beyond our sample size to account for withdrawal of consent, protocol violations and breakages.

**Milestones**

|  |  |  |
| --- | --- | --- |
| Milestone | Estimated Commencement | Estimated Completion |
| Ethics submission | Submitted for November 2020 HREC meeting | 6 months |
| Study education and promotion | April 2021 | 2 months |
| Patient recruitment | May 2021 | 24 months |
| Data analysis | May 2023 | 3 months |
| Presentation/Manuscript | August 2023 | 6 months |

**Clinical Significance of Proposed Research**

Opioid poisoning is rising and results in significant harm. Emergency department management of acute poisoning has changed very little over the last five decades and is based on expert opinion. There is little research defining the best way to reverse opioid toxicity. Current consensus is that titrated low doses of naloxone is a superior approach. But this risks inadequately treating life-threatening respiratory depression due to misplaced concern regarding precipitating acute opioid withdrawal – which is usually mild and well tolerated.

There are many practical advantages of using a single bolus of a large dose of intramuscular naloxone, including the ease of administration and less resource allocation compared to titrated intravenous naloxone and the administration of a naloxone infusion.

If we are able with this study to demonstrate the effectiveness and safety of 1.6mg intramuscular naloxone it could change the way emergency clinicians manage opioid poisoning.

**Research translation**

This study will be presented at a national emergency conference (ACEM Annual Scientific Meeting) and an international toxicology conference (EAPCCT Annual Scientific Meeting). It will also be published in a peer review journal such as Annals of Emergency Medicine.

Results of this study will guide the management of opioid poisoned patients across Metro South. Currently both options (1.6mg naloxone IM or 0.1mg naloxone IV) are advised as management options for the treatment of opioid toxicity in the MSH Prescribe. If 1.6mg IM naloxone proves more effective, with an acceptable safety profile, it will be advocated as a first line option in the management of opioid poisoning.

It is expected, that the result will guide other toxicological guidelines such as the Therapeutic Guidelines: Toxicology and Toxinology when it is next revised.

**Clinical originality and innovation**

This study follows on from our retrospective series which had an unexpected finding – with 1.6mg IM naloxone appearing more effective and equally safe as low dose titrated IV naloxone. This challenges the commonly accepted medical dogma that naloxone is best delivered in a low dose, titrated IV regimen that has been advocated for decades.

There is surprisingly no well-designed research looking at the best dosing regimen of naloxone for the management of opioid toxicity in the emergency department. If we are able with this study to demonstrate the effectiveness and safety of 1.6mg intramuscular naloxone it could change the way emergency clinicians manage opioid poisoning.

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