Article ID: WMC005225 ISSN 2046-1690

Does Naloxone Infusion Improve Recovery from Delirium in Intensive Care Unit? A Worth Exploring Project Into An Uncharted Domain

Peer review status:
No

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Article ID: WMC005225

Article Type: Research Protocol

Submitted on:15-Nov-2016, 03:10:19 AM GMT **Published on:** 15-Nov-2016, 06:59:41 AM GMT

Article URL: http://www.webmedcentral.com/article_view/5225

Subject Categories:CRITICAL CARE

Keywords: Naloxone, Intensive Care Unit, Delirium, Intensive Care Delirium Screening Checklist, Ramsay Agitation Sedation Scale, Face-Legs-Activity-Cry-Consolability Scale

How to cite the article: Gupta D, Pallekonda V. Does Naloxone Infusion Improve Recovery from Delirium in Intensive Care Unit? A Worth Exploring Project Into An Uncharted Domain. WebmedCentral CRITICAL CARE 2016;7(11):WMC005225

Source(s) of Funding:

Not Applicable

Competing Interests:

Not Applicable

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Abstract

Hypoactive delirium is difficult to differentiate from over-sedation and is often treated as such. However, hyperactive delirium with its agitation component is easily identified and differentiated by the Intensive Care Unit (ICU) personnel. This type of delirium irrespective of its underlying etiologies or risk factors may be reflective of overactive and dysrhythmic brain activity with potential excitatory neurotransmitters playing a role in the pathophysiology. Naloxone has been shown to decrease excitatory neurotransmitters in the cerebrospinal fluid. Based on this background, it would be worthwhile to investigate whether this low-dose continuous naloxone infusion has any role in decreasing the total duration of delirium in critically ill patients. Therefore, the objective of envisaged randomized placebo-controlled prospective study would be to assess if continuous low-dose naloxone infusion improves the recovery parameters of delirious patients in the ICU. The optimistic hope and expectation for the abovementioned results from the envisaged project is because although naloxone infusion has attained status of standard care to avoid and potentially treat perioperative spinal cord insult and injury, the naloxone infusion use for brain (the other or better half of the central nervous system) has NOT been explored at all until recently when Chinese researchers investigated into hepatic disease related brain dysfunction being managed by naloxone infusion. Therefore this uncharted domain should be explored and what can be a better model than hyperactive delirium model in ICU patients wherein trends in the response of agitation component to naloxone infusion will NOT only be easily recordable clinically but also if validated, can offer an additional tool in the armamentarium of ICU specialists for difficult to manage critically delirious patients. To summarize, naloxone infusion role in managing delirium is easy to explore and worth researching so that this non-costly drug may be able to find an alternate use (if validated) that would be able to prevent unprecedented losses/costs (personal, institutional and systematic) involved while managing delirious patients.

Origin of hypothesis

In Intensive Care Units (ICUs), patients may exhibit ICU delirium that is defined as acute brain dysfunction with multi-factorial etiopathogenesis and yet potentially reversible[1]. Delirium can be grouped into three major groups: hyperactive delirium with a marked agitation component, hypoactive delirium with a marked sedation component and mixed delirium. Hypoactive delirium is difficult to differentiate from over-sedation and is often treated as such. However, hyperactive delirium with its agitation component is easily identified and differentiated by the ICU personnel. This type of delirium irrespective of its underlying etiologies or risk factors may be reflective of overactive and dysrhythmic brain activity with potential excitatory neurotransmitters playing a role in the pathophysiology.

Naloxone has been shown to decrease excitatory neurotransmitters in the cerebrospinal fluid[2]. Low dose naloxone (1mcg/kg/hr) has been used to reverse the paraplegia and prevent neurological dysfunction in spinal cords exposed to ischemia and other insults during thoracoabdominal aneurysm surgeries[3-4]. This low-dose infusion of naloxone does not seem to interfere with the analgesia provided by the simultaneously administered parenteral opioids[5]. Similar to spinal cord protection, naloxone may offer advantages in cerebral protection since the spinal cord is a continuum of the central nervous system axis with brain at its apex. There have been studies in hepatic encephalopathy showing that naloxone decreases neurological dysfunction and cognitive deficits in patients who are delirious secondary to hepatic disease[6-7].

Based on this background, it would be worthwhile to investigate whether this low-dose continuous naloxone infusion has any role in decreasing the total duration of delirium in critically ill patients. Therefore, the objective of envisaged randomized placebo-controlled prospective study would be to assess if continuous low-dose naloxone infusion improves the recovery parameters of delirious patients in the ICU.

Envisaged Materials and Methods

After institutional review board approval, a written and informed consent for inclusion in the study would be needed from the surrogates of the patients aged 18 years old and above who would present to ICUs and would have been newly diagnosed with delirium. The consent would be taken from the surrogates as the patients would be delirious and incapable to provide consent to the study. The number of participants would have to be decided based on the statistical power of analysis for the sample population, frequency of available eligible participants with consenting surrogates in the general population catered by the researching facility, and the panoramic supportive resources of the researching ICUs. In all eligible patients, the study would be introduced to the patients' surrogates (legally authorized representatives) and to the primary caregiver ICU consultants/specialists and the primary surgical specialists for the patients so that all concerned would be on-board with the study protocol. The exclusion criteria would be as shown below:

1. Age less than 18 years
2. Male Patients with Body Mass Index >42 kg/m/m
3. Female Patients with Body Mass Index >37 kg/m/m
4. Patients whose Authorized Representatives could only give Telephonic Consents
5. Patients presenting with Delirium Tremens
6. Patients having airway devices/mechanical ventilation
7. Patients receiving Epidural Opioids Infusion
8. Patients suffering from Cancers as Primary Diagnosis
9. Patients who would have been Opioid Dependent
10. Patients who would have been Benzodiazepene Dependent
11. Patients who would have been allergic to Naloxone
12. Patients who would have been allergic/intolerant to Haloperidol
13. Patient who would have had long QTc interval on electrocardiogram
14. Patients who would have been allergic/intolerant to Hydromorphone
15. Patients who would have been pregnant or lactating
16. Patients who would have had End Stage Renal Disease
17. Patients who would have had Severe Liver Disease
18. Patients who would have been taking cocaine, methamphetamine, cyclic antidepressants, calcium channel blockers, beta-blockers, digoxin, clonidine

Additionally, based on online public information portal of naloxone manufacturing company (Amdipharm Mercury Company Limited, London, United Kingdom)[8], the risks associated with naloxone would be discussed with the surrogates prior to obtaining their informed consents for inclusion of their patients in the study as follows:

1. Very common occurrence defined as at least 10% chances for: nausea
2. Common occurrence defined as at least 1% chances for: giddiness, headache, high heart rates, low or high blood pressures, vomiting and pain
3. Uncommon occurrence defined as at least 0.1% chances for: tremulousness, sweating, heart rhythm abnormalities, low heart rates, diarrhea, dryness of mouth, high breathing rates, vessel wall insult/injury
4. Rare occurrence defined as at least 0.01% chances for: seizures, tension
5. Very rare occurrence defined as less than 0.01% chances for: allergic reactions, skin hypersensitivity reactions, fluid on lungs, fibrillation and arrest of heart

All eligible ICU patients who would have been spontaneously breathing and would NOT have any invasive airway devices would be pre-screened for new onset delirium with Intensive Care Delirium Screening Checklist[9] (ICDSC, by Bergeron et al[10]; Score ≥4). Once diagnosed to be delirious, the facility-specific standard treatment protocol for ICU delirium would be initiated in those patients. After screening for the exclusion criteria and informed consent from the surrogates of those patients, the patients would be randomly divided into two groups:

Study Group: Naloxone infusion @ 1mcg/kg/hr (based on Lean Body Weight) for 72 hrs

Control Group: Saline Placebo infusion for 72 hrs

250-ml infusion bags containing naloxone would be prepared with 2.5mg naloxone per 250ml (2500mcg per 250ml and effectively 0.1ml=1mcg). This bag would be infused @ 1mcg/kg/hr (0.1cc/kg/hr) and the residual medication would be discarded every 24hrs. In the control group, the placebo saline infusion (with 250-ml saline bags) would be infused @ 0.1cc/kg/hr to maintain randomization and blinding of the observers. No additional intravenous access would be required for the study; but the study drug infusion would be continuously administered through a dedicated and most distal side-port of already existing intravenous line. This randomization would be according to computer generated random numbers list and would be done by the pharmacy when preparing the drugs

before the infusion in the patient. The clinical observers would be blinded to the actual drug infused in the study patients (naloxone vs placebo saline).

Besides the standard non-pharmacological protocol for delirium management in ICU, a standard pharmacological protocol for delirium management in ICU would be used as following:

1. Assess ICDSC score every 12 hours to evaluate the progression or resolution of delirium
2. Assess Ramsay Agitation Sedation Scale[11] (RASS, by Sessler et al[12]) Score every 6 hours to appropriately medicate with Haloperidol 5mg IV Push for RASS Score 0 to -1 (Haloperidol Dose would not be increased more than 5mg and it would not be repeated more frequent than 6 hours)
3. Assess Face, Legs, Activity, Cry, Consolability Scale[13-14] (FLACC, initially by Merkel et al[15] for young children and recently by Voepel-Lewis et al[16] for all age group non-verbal critically ill patients; Copyright © 2002, The Regents of The University of Michigan) Score every 2 hours to appropriately medicate with Hydromorphone 0.5mg IV Push for FLACC Score < 5 (Hydromorphone dose would be increased to 1mg or 2mg every 2hours but not more frequent than every 2hours)
4. Sedative agents (Midazolam or Lorazepam) would be avoided

The following parameters would be recorded in all patients: age, sex, height, weight, reason for admission to ICU, possible reasons for the incidence of delirium in ICU, pre-delirium characteristics (days in the ICU, days of mechanical ventilation if any in ICU, amount of all medications used in the ICU including infusions, amount of blood and related products transfused in the ICU). Subsequently, the following characteristics would be assessed during the infusion of study medications: total hours before the infusion stopped (72 hours or less), total amount of haloperidol given, total amount of hydromorphone given, any complications related to the medications. During those hours (72hours or less), the ICDSC score every 12 hours, RASS Score every 6 hours, and FLACC Score every 2 hours would be recorded too. Additionally, the intra-delirium characteristics would be recorded too (days in the ICU, amount of all medications used in the ICU including infusions, amount of blood and related products transfused in the ICU). The detailed data collection sheet as envisaged is shown in Table 1.

Study would be stopped in a patient:

1. If the patient would be unresponsive to the standard protocol for delirium management (unresponsiveness defined as high RASS scores and/or high FLACC scores and/or high ICDSC scores even after 12hours of institution of standard protocol)
2. If the patient would deteriorate for any reason, requiring mechanical ventilation with invasive airway devices like endotracheal tube
3. If the patient's family or surrogate would withdraw the patient from the study
4. If the patient would still be delirious after 72 hours of study infusion
5. If the patient would become awake alert and oriented before the completion of 72 hours of study infusion

There would be no funds required except the additional pharmacy costs for study drug (naloxone) and control drug (saline) infusions both of which are usually not costly. Rest of the involvement in terms of caregiver providers (primarily nursing staff) and their wages would anyway be covered under the standard nursing management for ICU delirium patients except the institution of naloxone/saline infusion as a specific addition due to this study.

Statistical Analysis

The primary outcome would be the comparison between the two groups about total hours before the infusion would have been stopped (72 hours or less) due to patient becoming awake alert and oriented. The secondary outcomes would be the comparison between the two groups about total amounts of haloperidol and hydromorphone given. Between the two groups, an ANOVA (Analysis of Variance) would be used to compare the continuous data like age, height and weight; days in the ICU, and amounts of medications and blood products used; and changes in ICDSC scores, RASS scores and FLACC scores trended over entire study period. Between the two groups, Chi square analysis would be used to compare categorical data like patients' sex. A p value < 0.05 would be considered statistically significant.

Expected line of results

Based on abovementioned envisaged materials and methods, the expected results would be on the line of best case scenario: Decreased total hours of ICU delirium period accompanied with decreased haloperidol requirements while managing those decreased hours of delirium WITHOUT the need for increased hydromorphone requirements during the uneventfully safe administration of naloxone infusion as compared to the saline infusion. The study results would be mostly applicable to general population although the envisaged study would have excluded extremely obese patients to maintain homogeneity of naloxone (and other medications) total body weight based dosage administrations and would have been limited to include only the male patients up to BMI 42

kg/m/m and only the female patients up to BMI 37 kg/m/m so as to avoid the patients with greater than above-mentioned BMI values wherein lean body mass of patients cease to linearly increase with total body weight and rather plateaus or declines after peaking at the above-mentioned gender-specific BMI cut-off (transitioning) values[17].

The optimistic hope and expectation for the abovementioned results from the envisaged project is because although naloxone infusion has attained status of standard care to avoid and potentially treat perioperative spinal cord insult and injury[3-5], the naloxone infusion use for brain (the other or better half of the central nervous system) has NOT been explored at all until recently when Chinese researchers investigated into hepatic disease related brain dysfunction being managed by naloxone infusion[6-7]. Therefore this uncharted domain should be explored and what can be a better model than hyperactive delirium model in ICU patients wherein trends in the response of agitation component to naloxone infusion will NOT only be easily recordable clinically but also if validated, can offer an additional tool in the armamentarium of ICU specialists for difficult to manage critically delirious patients.

To summarize, naloxone infusion role in managing delirium is easy to explore and worth researching so that this non-costly drug may be able to find an alternate use (if validated) that would be able to prevent unprecedented losses/costs (personal, institutional and systematic) involved while managing delirious patients.

Acknowledgements

The authors are deeply indebted to: Maria Teresa Palleschi, RN, DNP, APRN-BC CCRN, Clinical Nurse Specialist; Krista A Wahby, Pharm.D, BCCCP, Clinical Pharmacist Specialist; Sheri Testani, MSN, RN, NE-BC, Administrative Director Critical Care and Specialty Services; Farhad Ghoddoussi PhD and George McKelvey PhD for their support to our hypothesized thought processes at Harper University Hospital, Detroit Medical Center, Detroit, Michigan, United States.

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Illustrations

Illustration 1

TABLE 1: ENVISAGED DATA COLLECTION SHEET

TABLE 1: ENVISAGED DATA COLLECTION SHEET:

Research Participant Serial Number:
Group: BLINDED
Age
Sex
Height
Weight
Reason for admission to ICU
Possible reasons for the incidence of delirium in ICU

Pre-delirium characteristics

Days in the ICU
Days of mechanical ventilation if any in ICU
Amount of all medications used in the ICU including infusions
Amount of blood and related products transfused in the ICU

During the infusion of study medications

Total hours before the infusion stopped (72 hours or less)
Total amount of haloperidol given
Total amount of hydromorphone given
Any complications related to the medications
Days in the ICU
Amount of all medications used in the ICU including infusions
Amount of blood and related products transfused in the ICU

	ICDSC Score q12hr	RASS Score q6hr Pre/Post Medication	FLACC Score q2hr Pre/Post Medication
Day 1 (hrs)			
0		/	/
2			/
4			/
6		/	/
8			/
10			/
12		/	/
14			/
16			/
18		/	/
20			/
22			/
24		/	/
Day 2 (hrs)			
2			/
4			/
6		/	/
8			/
10			/
12		/	/
14			/
16			/
18		/	/
20			/
22			/
24		/	/

Day 3 (hrs)			
2			/
4			/
6		/	/
8			/
10			/
12		/	/
14			/
16			/
18		/	/
20			/
22			/
24		/	/