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[Intervention Review]

Naloxone for shock

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ABSTRACT

Background

There is pre-clinical evidence, involving several animal species, suggesting that opioid peptides play a role in the physiopathology of shock (endotoxic, hypovolemic, cardiogenic, spinal, anaphylactic). Many case reports have suggested that naloxone (an opiate antagonist) might be an effective treatment for shock in humans, but others have not supported such a point of view. This controversy led us to undertake a meta-analysis of the available evidence on the efficacy of naloxone as a treatment measure for shock in humans.

Objectives

To evaluate the effectiveness and safety of naloxone in human shock and to estimate the methodological quality of the clinical trials.

Search methods

We searched the Cochrane Injuries Group Specialised Register, CENTRAL (The Cochrane Library), MEDLINE (Ovid SP), PubMed, EMBASE (Ovid SP), ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED), and ISI Web of Science: Conference Proceedings Citation Index-Science (CPCI-S) (to December 2008). In order to identify further studies the reference lists of all included papers were examined and the primary investigators of eligible studies were contacted.

Selection criteria

Randomized controlled trials evaluating naloxone in human shock, regardless of the patient's age (adult, child, or neonate).

Data collection and analysis

Three independent review authors extracted data on study design, intervention, outcomes, and methodological quality.

Main results

Three independent readers reviewed 120 publications and selected six clinical trials. Overall agreement on study selection was perfect (concordance: 100%). The meta-analysis includes six studies involving 126 patients with septic, cardiogenic, hemorrhagic, or spinal shock.

Naloxone therapy was associated with statistically significant hemodynamic improvement (odds ratio 0.24; 95% confidence interval (CI) 0.09 to 0.68). The mean arterial pressure was significantly higher in the naloxone groups than in the placebo groups (weighted mean difference +9.33 mm Hg; 95% CI 7.07 to 11.59). No heterogeneity was found for this outcome. The death rate was lower in the naloxone group (odds ratio 0.59; 95% CI 0.21 was 1.67) but this was consistent with the play of chance. A significant heterogeneity was detected for the latter outcome ($P < 0.05$).

Authors' conclusions

Naloxone improves blood pressure, especially mean arterial blood pressure. However, the clinical usefulness of naloxone to treat shock remains to be determined and additional randomized controlled trials are needed to assess its usefulness.

PLAIN LANGUAGE SUMMARY

Naloxone may improve blood pressure in people who are in shock but more trials are needed to show whether this reduces deaths

When people go into shock, their blood pressure drops and may be too low to sustain life. One theory about the cause of this is the effect of the opiates that the body produces after major blood loss or trauma. Naloxone is a drug that counteracts the effects of opiates. It has been tried as a treatment to reduce the impact of shock. This review of trials found that giving naloxone to people in shock improves their blood pressure. It is not clear whether or not this improves their overall condition or reduces their chances of dying. More trials are needed.

BACKGROUND

The discovery, in 1975, of endogenous opioid peptides (Hughes 1975) has generated abundant research on the potential functional role of opiate receptors and their peptide ligands. Holladay and Faden provided the first experimental evidence for opioid peptide involvement in the physiopathology of circulatory shock (Holaday 1978).

Subsequent research supported the therapeutic efficacy of opiate antagonists used in different experimental shock states (endotoxic, hypovolemic, cardiogenic, spinal, anaphylactic) in several animal species. Since then, many papers have been published on the use of an opiate antagonist (naloxone) in human shock. In most publications naloxone therapy was reported to be effective, but in eight reports it failed to show any kind of hemodynamic improvement (Allolio 1987; Bonnet 1985; Cabrera 1986; DeMaria 1985; Gerad 1983; Montastruc 1985; Rock 1985; Valdiviels 1984). This controversy, and the need to reconsider some of the less expensive technologies given that the immunotherapies have been so disappointing, prompted us to undertake this systematic review.

OBJECTIVES

This systematic review addressed the following questions.

1. What is the quality of the clinical trials dealing with this topic?
2. Is naloxone an effective therapy for shock in human patients?
3. Is there heterogeneity among the pooled studies?
4. How strong is the evidence?
5. Is naloxone a safe and useful therapy for shock in humans?

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials.

Types of participants

Human participants only. Patients were considered to be in shock if they met the criteria as defined in each trial. No uniform definition of shock was used to redefine or reclassify the participants in each trial.

Types of interventions

Dose of naloxone of at least 0.01 mg/kg/dose in one or more bolus injections, or a continuous infusion of at least 0.01 mg/kg/hour for 60 minutes or longer.

Types of outcome measures

Change in death rate, reduction in doses of vasoactive drugs, mean arterial pressure, systolic blood pressure, and heart rate.

Search methods for identification of studies

Searches were not restricted by date, language, or publication status.

Electronic searches

We searched the following electronic databases:

- Cochrane Injuries Group Specialised Register (searched 5 December 2008);
- CENTRAL (*The Cochrane Library* 2008, Issue 4);
- MEDLINE (Ovid SP) (1950 to week 3, November 2008);
- Embase (Ovid SP) (1980 to November (week 49) 2008);
- ISI Web of Science:Science Citation Index Expanded (SCI-EXPANDED) (1970 to December 2008);
- ISI Web of Science:Conference Proceedings Citation Index-Science (CPCI-S) (1990 to December 2008);
- PubMed (searched 5 December 2008; added to PubMed in the last 180 days).

The search strategy can be found in Appendix 1.

Searching other resources

All search results were examined. These included reviews, overviews, editorials, monographs, symposia, book chapters, and clinical studies. We also searched the reference lists of relevant material. Primary investigators of eligible studies were contacted and asked whether they knew of any other study or systematic review on the same topic.

Data collection and analysis

Selection of studies

The literature was independently reviewed by three review authors (Catherine Ann Farrell, France Gauvin, Anne-Marie Guerguerian) who selected studies according to the agreed inclusion criteria, defined a priori. Disagreement regarding inclusion was resolved by a consensus of at least two review authors. Agreement on the decision to include a study was assessed by the percentage of concordance and kappa score (Kramer 1981).

Data extraction and management

Data on the effectiveness of naloxone to treat shock were extracted from the included studies. First, they were displayed in two-by-two contingency tables. Two contingency tables were constructed. The outcome considered in the first was better blood pressure control; the second comprised data on death. We mailed these tables to each primary investigator and requested them to verify the data. Secondly, we extracted data on the three outcomes that were continuous (systolic blood pressure, mean arterial pressure, and heart rate). Following this, we made three new comparison tables.

Assessment of risk of bias in included studies

For all studies included in this review, the completeness of the information required to determine quality (see Chalmers 1981) was assessed independently by three review authors (Jacques Lacroix, Véronique Poirier, Chantal Roy). Disagreements were settled by consensus, which was defined as the agreement of at least two authors. The scoring system used to estimate the quality of the clinical trials is detailed elsewhere (Boeuf 1998). It included the following information: description of patient selection, number of patients assessed and rejected for eligibility, adequate description of therapeutic regimen given, allocation concealment, blinding of patients, blinding of physician to therapy, blinding of physician and patients to results, prior estimate of sample size, stopping rules, testing the adequacy of randomization, testing blinding, testing compliance, biological equivalence, endpoint duplicate

variable, dates of starting and stopping accession, results pre-randomization, statistical tests performed and results detailed, posterior power estimate of observed difference for negative trial, confidence interval calculated, life-table or time-series or repeated measures, timing of events, regression or correlation, appropriate statistical tests used, withdrawals, handling of withdrawals, adequate side effect discussion, proper retrospective analysis.

Data synthesis

For the two main outcomes, we combined data to estimate the odds ratio (OR) and its 95% confidence interval (95% CI) across the studies using a fixed-effect model (Mantel 1959). The cumulative evidence of the pooled studies was evaluated by the method suggested by Collins and Langman (Collins 1987). A correction factor of 0.5 was attributed to zero cells (Roberts 1988). The heterogeneity of treatment effects across the studies was ascertained by a Chi^2 analysis. For some outcomes, we combined continuous data to estimate a weighted mean reduction and its 95% CI across the studies using a fixed-effect model. Following this, a Student t-test was carried out to compare the mean differences.

RESULTS

Description of studies

Study identification and selection

We found 120 papers (published to December 2008) dealing (at first glance) with naloxone and shock; 114 were excluded by adjudicators for the following reasons:
a) animal studies (n = 39);
b) case report, editorial, or review (n = 56);
c) case series (n = 14) (Bone 1982; Bonnet 1985; Canady 1989; Duarte 1992; Gerad 1983; Groeger 1983; Hackshaw 1990; Hughes 1983; Martinon 1982; Peters 1981; Putterman 1986; Rock 1985; Tarelkina 1989; VelizPintos 1985);
d) the cases or controls, or both, were not in shock (n = 5) (Allolio 1987; Desmonts 1978; Estilo 1982; Lightfoot 2000; Oldroyd 1995) (see Characteristics of excluded studies).

Six clinical trials were found that fulfilled the inclusion criteria. Overall agreement on selection of studies was perfect (concordance: 100%). The primary outcome was an increase in blood pressure in five reports (Hughes 1984; DeMaria 1985; Lu 1995; Montastruc 1985; Safani 1989). A decrease in the amount of vasopressor, inotrope, or both was used once (Roberts 1988), and death once (DeMaria 1985). The secondary outcomes considered were changes in blood catecholamine levels (Hughes 1984; Lu 1995) and blood lactic acid levels (Lu 1995). The definitions of shock used by the authors of the selected studies were not homogenous and did not follow the current American College of Chest Physicians (ACCP) definition (ACCP/SCCM 1992). Only one author (Roberts 1988) assessed the illness severity score at baseline: mean APACHE II score of 16.8 in the naloxone group and 18.9 in the control group.

Risk of bias in included studies

Overall agreement for the evaluation of the quality of each study was good (intraclass correlation coefficient 0.70). Scores were averaged between the three review authors. The maximum score of quality would be 104; the score was 61.1 for DeMaria 1985, 43 for Lu 1995, 60.2 for Roberts 1988, and 47.8 for Safani 1989. These are fair-to-good quality scores.

Effects of interventions

Death rate

Death rates ranged from 0% to 60% in the three naloxone groups, and from 45.4% to 66.6% in the three control groups. The pooled odds ratio (OR) comparing naloxone with the control groups was 0.59 (95% CI 0.21 to 1.67). A significant heterogeneity was found for this outcome ($P < 0.05$).

Reduction in dose of vasoactive drugs

In one study that included only 22 patients, the primary outcome measure was a reduction in dose of vasoactive drug (Roberts 1988). The OR was 0.12 (95% CI 0.12 to 1.29).

Mean arterial blood pressure

The mean arterial blood pressure changed from 87.5 ± 8.7 to 99.1 ± 9.1 mm Hg with naloxone, and from 84.3 ± 8.2 mm Hg to 93.8 ± 10.7 mm Hg with placebo in DeMaria 1985; from 64.1 ± 7.7 to 81.2 ± 9.8 mm Hg with naloxone, and from 77.2 ± 10.1 to 66.8 ± 6.3 mm Hg with placebo in Lu 1995; and from 61.3 ± 3 to 74 ± 4 mm Hg with naloxone, and from 62 ± 4 mm Hg to 65 ± 3 mm Hg with placebo in Safani 1989. Overall, the mean arterial blood pressure increased from 70.9 to 84.9 mm Hg with naloxone, and from 74.5 to 75.3 mm Hg with placebo. We were unable to obtain the standard deviations of these results at baseline, thus no statistical analysis was done on the difference between mean arterial blood pressure at baseline and after treatment. However, we were able to compare the mean arterial blood pressure after treatment in the two groups for these three studies: it was statistically higher in the naloxone than in the placebo group (weighted mean difference +9.33 mm Hg; 95% CI 7.07 to 11.59). No significant heterogeneity was found.

Systolic blood pressure

The systolic blood pressure increased from 87.5 ± 8.5 to 95 ± 10.8 mm Hg with naloxone, and from 89 ± 7.7 mm Hg to 99 ± 9.3 mm Hg with placebo in Hughes 1984; from 75.5 to 83.8 mm Hg with naloxone, and from 77.4 to 82.8 mm Hg with placebo in Montastruc 1985; and from 86 ± 4 to 102 ± 7 mm Hg with naloxone, and from 90 ± 4 mm Hg to 100 ± 6 mm Hg with placebo in Safani 1989. On average, the systolic blood pressure increased from 82.8 to 93.6 mm Hg with naloxone, and from 85.5 to 93.9 mm Hg with placebo. We were unable to obtain the standard deviations of these results at baseline, thus no statistical analysis was done on the difference between systolic blood pressure at baseline and after treatment. We compared the systolic blood pressure after treatment in these three studies: it was similar in the naloxone and placebo groups. No significant heterogeneity was found.

Heart rate

The heart rate changed from 109 ± 8 to 106 ± 7 beats/minute with naloxone, and from 102 ± 10 to 106 ± 15 beats/min with placebo in Hughes 1984; from 113 ± 32 to 110 ± 20 beats/min with naloxone, and from 108 ± 14 to 101 ± 19 beats/min with placebo in Lu 1995; from 80 to 75 beats/min with naloxone, and from 87 to 91 beats/min with placebo in Montastruc 1985; and from 114 ± 5 to 112 ± 4 beats/min with naloxone, and from 126 ± 4 to 115 ± 5 beats/min with placebo in Safani 1989. On average, the heart rate decreased from 103.9 to 100.7 beats/min with naloxone, and from 105.8 to 103.35 beats/min with placebo. We were unable to obtain the standard deviations of these results at baseline, thus no statistical analysis

was done. We compared the heart rate after treatment in these three studies: it was similar in the naloxone and placebo groups. No significant heterogeneity was found.

Adverse effects

Adverse effects were monitored in two clinical trials (Roberts 1988; Safani 1989). No serious adverse effects were observed, although four of the 11 patients who received naloxone in Safani 1989 experienced a "mild to moderate degree of agitation" a few minutes after naloxone was given, which was not reported in the placebo group.

DISCUSSION

Principal findings

This systematic review shows that naloxone can increase blood pressure in patients with shock; this was statistically significant (DeMaria 1985; Lu 1995; Safani 1989). Participants receiving continuous infusion of naloxone over a prolonged period appeared to have a lower death rate but this was not statistically significant (DeMaria 1985; Roberts 1988; Safani 1989).

Strengths and weaknesses of the review

The part of this systematic review considering survival as the outcome measure includes a limited number of patients, 59 patients from three clinical trials (DeMaria 1985; Roberts 1988; Safani 1989). The positive trend that we found could easily be reversed if there has been publication bias. This also holds true for the mean arterial pressure outcome (66 patients from three clinical trials) (DeMaria 1985; Lu 1995; Safani 1989).

Strengths and weaknesses in relation to other studies

The literature on the effectiveness of naloxone in treating shock in humans is abundant but controversial, and the methodological quality of the publications is frequently weak. We found 80 publications where 27 were letters or narrative reviews, 28 were case reports, 14 were cases series, five were non-controlled clinical trials, and only six were double-blind randomized studies. Many papers reported positive results. However, almost all the positive papers were case reports (28/28) (Accettelli 1982; Bagrov 1993; Campos 1986; Cattani 1982; Christensen 1986; Cocchi 1984; Cohen 1983; De Groot 1983; Dirksen 1980; Duarte 1992; Gaudette 1986; Gullo 1983; Furman 1984; Higgins 1981; Higgins 1983; Jolivet 1984; Lenz 1981; Parisot 1986; Pourriat 1981; Safani 1985; Siram 1984; Siram 1984; Swinburn 1982; Tiengo 1980; Unzueta 1987; Wright 1980; Xing 1990; Yeston 1983). Among 14 case series, one was negative (Rock 1985) and 13 were positive (Bone 1982; Bonnet 1985; Canady 1989; Duarte 1992; Gerad 1983; Groeger 1983; Hackshaw 1990; Hughes 1983; Martinon 1982; Peters 1981; Putterman 1986; Tarelkina 1989; VelizPintos 1985). Among the six double-blind studies, four reported positive results (Hughes 1984; Lu 1995; Roberts 1988; Safani 1989) while results were not statistically significant in two (Montastruc 1985; DeMaria 1985). Clearly a systematic review was necessary to determine whether naloxone should be considered as a treatment for shock.

No serious adverse events or complications were reported in the six randomized clinical trials included in this systematic review. Most case reports did not prospectively monitor adverse events. In spite of this, there are data suggesting that the use of naloxone is not without risks. Naloxone caused anxiety in septic patients who received 0.3 mg/kg of naloxone (Groeger 1983). It can also be expected that giving naloxone could block the analgesic effect of endogenous and exogenous opioids. Adverse drug reactions such as hypotension, pulmonary edema, and grand mal seizures have been reported with a high-dose regimen of naloxone (Prough 1984; Rock 1985). In healthy volunteers, naloxone decreases tolerance to hypotensive, hypovolemic stress (Lightfoot 2000). A deep level of anesthesia and postoperative analgesia attenuates the physiologic responses to stress (ACCP/SCCM 1992). Naloxone modulates the inflammatory process; blocking these effects could be a double-edged sword. For example, naloxone may increase the risk of acquiring or worsening multiple organ dysfunction syndrome, or contracting nosocomial infections.

Meaning of the review

All types of shock states are associated with an over-production of endorphins, and naloxone might improve shock by its antagonist activity on beta-endorphins. The source of the beta-endorphins involved in shock is a matter of debate. It was thought for a while that beta-endorphins are released into the blood circulation exclusively by the central nervous system, but it was later shown that they are also released locally into inflamed tissue by lymphocytes and macrophages (Jessop 1998). Endorphins mediate the release of nitric oxide, which might cause systemic and local vasodilation. Endorphins can also depress heart function. The exact mechanism involved is unknown, but endorphins enhance the release of cytokines which are cardiac depressants, like interleukin-1.

The data reported in human beings are supported by experimental data. In 1978, a study (Holaday 1978) reported that naloxone rapidly reversed the hemodynamic effects of endotoxic shock in rats. The improvement in hemodynamic status was dose-related, with a minimal dose of 0.1 mg/kg. Several months later the same authors (Faden 1979) obtained the same results with a single dose of 1 mg/kg in a model of hemorrhagic shock (50% blood volume loss) in rats. Many subsequent experimental studies confirmed the therapeutic efficacy of naloxone in various animal species.

AUTHORS' CONCLUSIONS

Implications for practice

The results of this systematic review suggest that naloxone may be an effective treatment of shock. However, the power of these results is weak because the number of patients is small. Therefore, the clinical inferences that can be drawn from this review are limited. Naloxone is not approved by the Food and Drugs Administration (USA) to treat shock. It might be beneficial in some patients but the available evidence does not support the use of naloxone as a standard treatment of shock.

Implications for research

More clinical trials with positive results are needed before one can recommend naloxone as a standard treatment of shock. In these future trials the population selected should only include patients in shock. The patients' baseline status should be assessed by the Acute Physiology and Chronic Health Evaluation (APACHE) score, or the Pediatric Risk of Mortality (PRISM) score (Pollack 1996). Naloxone should be administered early, for a prolonged period, and with a continuous infusion of at least 0.1 mg/kg/h. The

outcome under scrutiny should be death. Finally, clinical research concerning naloxone should also determine the dose-effect curve and the optimal frequency of administration. A study of at least 340 patients in each group is needed to demonstrate a significant difference in mortality for a power of 80%.

In future studies, it would be useful to monitor surrogate outcomes (like blood pressure and heart rate) and secondary outcomes (such as the rate of nosocomial infections or the Multiple Organ Dysfunction score) in the experimental and control groups (Leteurtre 2003; Marshall 1995). Adverse effects, such as anxiety and pain, must be carefully recorded. Adverse drug reactions such as hypotension, pulmonary edema, and grand mal seizures must be reported. Moreover, a cost-benefit analysis should be performed to determine whether the benefits of naloxone outweigh its complications and whether naloxone should be routinely used to treat shock in humans.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

DeMaria 1985

Methods	A placebo-controlled, randomized, double-blind trial of naloxone in patients with septic shock to estimate clinical efficacy.
Participants	Criteria for inclusion (28 patients, and 38 episodes of shock): 1. clinical evidence of shock (low urine output, altered mentation, cold extremities) and systolic blood pressure (SBP) <90 mmHg or <100 mmHg with vasopressor; 2. clinical diagnosis of sepsis with signs and symptoms suggestive of bacteremia or well-established focus of infection; 3. likelihood of clinical stability, so that rates of intravenous infusion and doses of vasopressor agents could remain unchanged for the 1 h study. The patient's general medical care was not changed by participation. Excluded (6 patients, and 15 episodes of shock): 1. from entry if they were pregnant, opiate abusers, or had been treated with opiates in the past 24 h; 2. from analysis if they received corticosteroids. In several patients substantial changes in doses of vasopressor agents or rates of intravenous infusion were made during the study period which rendered analysis of blood pressure changes impossible. Such patients were excluded from the study before the treatment code was broken.
Interventions	Naloxone group (n=10): bolus of 0.4 mg of naloxone every 5 min x 3 doses. Control group (n=13): bolus of sterile vehicle for injection every 5 min x 3 doses.
Outcomes	Primary outcomes 1. Increase in BP > 10% within 60 minutes after administration of the test material. 2. Case fatality: number of deaths at 7 days.
Notes	Medical and surgical intensive care units at Boston City Hospital from March 1982 to March 1983.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Hughes 1984

Methods	A placebo-controlled, randomized, double-blind trial on naloxone in patients with septic shock to evaluate its clinical efficacy.
Participants	Criteria for inclusion: clinical evidence of septic shock with:

Hughes 1984 *(Continued)*

	1. hypotension (SBP<90 mmHg); 2. fever; 3. oliguria (< 15 ml/h/1.73 m^2); 4. positive blood cultures. Conventional therapy of septic shock for every patient: consisting of antibiotics, intravenous fluids to maintain PWP of 12 mmHg and CVP of 11 mmHg, dopamine, and ventilatory assistance.
Interventions	Naloxone group (n=7): bolus dose of naloxone, 30 µg/kg followed by 30 µg/kg/hr for one hour plus a single dose of methyl- prednisolone, 30 mg/kg. Control group: conventional therapy alone (n=7).
Outcomes	1. Change in SBP, cardiac index (CI), systemic vascular resistance (SVR), and heart rate (HR). 2. Change in plasma catecholamine levels. 3. Relationship between catecholamine levels (if increase) and hemodynamics. All outcomes were checked for 60 minutes.
Notes	Section of General Medicine, East Carolina University School of Medicine in Greenville, North Carolina.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Lu 1995

Methods	A controlled randomized trial of naloxone on hemorrhagic shock.
Participants	21 patients with moderate shock included: 1. control group: 9 cases (7 males, 2 females), mean age 59.3 +/- 12.5 years. Upper gastrointestinal hemorrhage 2, liver and spleen rupture 3, ectopic pregnancy 3, multiples fractures 2. 2. naloxone group: 12 cases (10 males, 2 females) mean age 61.1 years. Upper gastrointestinal hemorrhage 2, liver and spleen rupture 5, ectopic pregnancy 3, multiple fracture 2, other 2. No hypertension and no coronary heart disease in both groups.
Interventions	Naloxone group (n=12): 200 ml of normal saline infused in 15 min and bolus of 0.02 mg/kg of naloxone. Control group (n=9): 200 ml of normal saline infused in 15 min.
Outcomes	1. Increase of MAP and SVR. 2. Decrease in blood level of lactic acid. 3. Increase in blood level of epinephrine and norepinephrine. All outcomes were measured during 15 minutes.
Notes	Department of Anesthesiology at first affiliated hospital of China Medical University in Senyang (China). No comment of when the study was conducted. Case fatality unspecified.

Risk of bias

Lu 1995 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Montastruc 1985

Methods	A placebo-controlled, randomized, double-blind trial of single dose of naloxone in patients with hypovolemic, cardiogenic, septic, or spinal shock to evaluate the hemodynamic effects.
Participants	30 patients (16 men and 14 women from 8 to 87 years; mean age: 51 +/- 4.9 years) suffering from hypovolemic (17 cases), cardiogenic (9 cases), septic (3 cases) and spinal shock (1 case) with SBP < 85 mmHg. Usual treatment of shock for every patient: blood products and plasma substitutes in hypovolemic, septic, and spinal shock; and catecholamines (dopamine and/or dobutamine) in cardiogenic shock.
Interventions	Naloxone group (n=15): bolus of 0.8 mg of naloxone in 2 ml. Control group (n=15): bolus of an equivalent volume of normal saline.
Outcomes	Primary outcome • Change in SBP and HR 5 minutes after the end of the perfusion of naloxone or placebo.
Notes	Department of Anesthesiology and Intensive Care Medicine at Purpan Hospital in Toulouse (France). No comment on when the study was conducted. Case fatality unspecified.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	D - Not used

Roberts 1988

Methods	A controlled, randomized, double-blind trial of a longer continuous intravenous infusion of naloxone in patients with septic shock to evaluate the hemodynamic effects.
Participants	Criteria for inclusion (n=16): 1. proven bacterial or fungal infection; 2. hypotension (BP<60 mmHg) despite adequate fluid resuscitation (PWP>12 mmHg); 3. vasopressor or inotrope dependence (BP < 60 mmHg with trial of drug withdrawal); 4. written informed consent. Exclusion criteria: 1. recent or ongoing myocardial infarction; 2. active bleeding; 3. requirement for opioid analgesia; 4. severe head injury with high intracranial pressure or coma; 5. congestive heart failure or CI<2.2 l/min/m^2.
Interventions	Bolus of 30 µg/kg of naloxone followed by continuous infusion of 30 µg/kg/hr for 8 to 16 hrs.

Roberts 1988 *(Continued)*

	Control: bolus of an equivalent volume of normal saline.
Outcomes	Primary outcome 1. Decrease in vasopressor requirement, as recorded up to 16 hours after baseline. 2. Case fatality: number of deaths at 14 days.
Notes	Medical and surgical intensive care units at the Health Sciences Center in Winnipeg, Manitoba. No comment on when the study was conducted.

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Safani 1989

Methods	A controlled, randomized trial of naloxone infusion in early hyperdynamic septic shock.
Participants	Criteria for inclusion (n=22): 1. sustained SBP <90 mmHg of 45 min duration; 2. clinical evidence of infection including febrile episodes (rectal temperature >101 °F) and leukocytosis with bandemia >10% and/or positives documented cultures (oxygen extraction value used to differentiate septic and cardiogenic shock); 3. over 18 years of age; 4. signed consent form. Excluded: 1. known history of hypersensitivity to naloxone; 2. pregnancy; 3. corticoadrenal axis depression (other than steroid induced); 4. cardiogenic shock; 5. patients requiring narcotic analgesics; 6. opiate addicts.
Interventions	Naloxone group: bolus of 30 µg/kg of naloxone over 3 to 5 min followed by continuous infusion of 60 µg/kg/hr for 1 h. If hemodynamic improvement was observed within the first hour, the infusion was continued at the same rate for an additional 4 to 24 h. Control group: infusion of dextrose 5% in water. If deterioration of hemodynamic status was observed, the infusion of naloxone or dextrose 5% in water was resumed immediately.
Outcomes	Primary outcome Increase in MAP >15%, as recorded up to 24 hours after the end of the perfusion of naloxone or dextrose 5%.
Notes	Division of Respiratory and Critical Care Medicine at Memorial Medical Center of Long Beach, CA. No comment on when the study was conducted. Case fatality unspecified.

Risk of bias

Safani 1989 *(Continued)*

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

BP: blood pressure
MAP: mean arterial pressure
SBP: systolic blood pressure
PWP: pulmonary wedge pressure
CI: cardiac index
SVR: systemic vascular resistance
CVP: central venous pressure
HR: heart rate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Allolio 1986	Not a randomised controlled trial.
Allolio 1987	Ten cases, 10 controls. Inappropriate control group (patients were not in shock). No randomization.
Bone 1982	No control (case series of 10 patients).
Bonnet 1985	No control (case series of 7 patients).
Canady 1989	No control (case series of 5 patients).
Desmonts 1978	Fourteen cases, 11 controls. Cases and control were not in shock. No randomization.
Duarte 1992	No control (case series of 5 patients).
Estilo 1982	Six cases, 6 controls. Cases and controls were not in shock. No randomization.
Gerad 1983	No control (case series of 5 patients).
Groeger 1983	No control (case series of 10 patients).
Hackshaw 1990	No control (case series of 13 patients).
Hughes 1983	No control (case series of 8 patients).
ILCOR 2006	Not a randomized controlled trial.
Lightfoot 2000	Repeated measures design in 8 healthy male subjects. No randomization.
Martinon 1982	No control (case series of 6 patients).
Oldroyd 1995	Ten patients with heart failure were randomized to study the effects of naloxone or placebo on cardiopulmonary exercise performance (outcome measure not considered in this systematic review).
Peters 1981	No control (case series of 13 patients).
Putterman 1986	No control (case series of 10 patients).

Study	Reason for exclusion
Rock 1985	No control (case series of 12 patients).
Tarelkina 1989	No control (case series of 12 patients).
VelizPintos 1985	No control (case series of 15 patients).

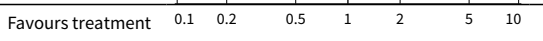
DATA AND ANALYSES

Comparison 1. Naloxone versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death rate	3	59	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.59 [0.21, 1.67]
2 Reduction in dose of vasoactive drug	1	22	Odds Ratio (M-H, Fixed, 95% CI)	0.12 [0.01, 1.29]

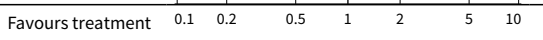
Analysis 1.1. Comparison 1 Naloxone versus control, Outcome 1 Death rate.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
DeMaria 1985	6/10	8/13		39.08%	0.94[0.18,4.91]
Roberts 1988	0/8	4/6		20.92%	0.05[0.01,0.46]
Safani 1989	6/11	5/11		40%	1.41[0.28,7.24]
Total (95% CI)	**29**	**30**		**100%**	**0.59[0.21,1.67]**
Total events: 12 (Treatment), 17 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.14, df=2(P=0.05); I^2=67.42%					
Test for overall effect: Z=0.99(P=0.32)					



Analysis 1.2. Comparison 1 Naloxone versus control, Outcome 2 Reduction in dose of vasoactive drug.

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% CI	Weight	Odds Ratio M-H, Fixed, 95% CI
Roberts 1988	6/11	10/11		100%	0.12[0.01,1.29]
Total (95% CI)	**11**	**11**		**100%**	**0.12[0.01,1.29]**
Total events: 6 (Treatment), 10 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.75(P=0.08)					

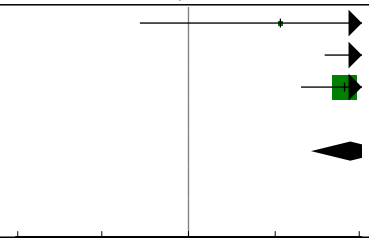


Comparison 2. After treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mean Arterial Blood Pressure (MAP)	3	66	Mean Difference (IV, Fixed, 95% CI)	9.33 [7.07, 11.59]
2 Systolic Blood Pressure (SBP)	2	36	Mean Difference (IV, Fixed, 95% CI)	0.74 [-4.10, 5.58]
3 Heart Rate (HR)	3	57	Mean Difference (IV, Fixed, 95% CI)	-2.23 [-5.77, 1.30]

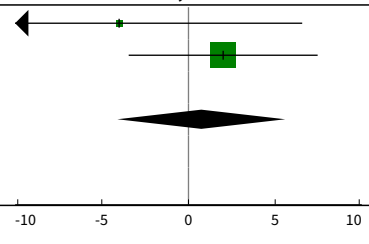
Analysis 2.1. Comparison 2 After treatment, Outcome 1 Mean Arterial Blood Pressure (MAP).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
DeMaria 1985	10	99.1 (9.1)	13	93.8 (10.7)		7.8%	5.3[-2.8,13.4]
Lu 1995	12	81.6 (9.8)	9	66.8 (6.3)		10.71%	14.77[7.85,21.69]
Safani 1989	11	74 (3)	11	65 (3)		81.49%	9[6.49,11.51]
Total ***	**33**		**33**			**100%**	**9.33[7.07,11.59]**
Heterogeneity: Tau^2=0; Chi^2=3.39, df=2(P=0.18); I^2=41.07%							
Test for overall effect: Z=8.08(P<0.0001)							



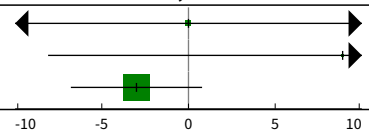
Analysis 2.2. Comparison 2 After treatment, Outcome 2 Systolic Blood Pressure (SBP).

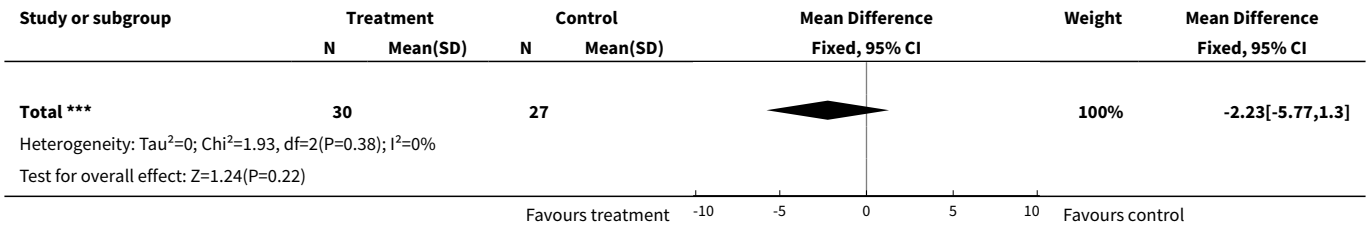
Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hughes 1984	7	95 (10.8)	7	99 (9.3)		21.03%	-4[-14.56,6.56]
Safani 1989	11	102 (7)	11	100 (6)		78.97%	2[-3.45,7.45]
Total ***	**18**		**18**			**100%**	**0.74[-4.1,5.58]**
Heterogeneity: Tau^2=0; Chi^2=0.98, df=1(P=0.32); I^2=0%							
Test for overall effect: Z=0.3(P=0.77)							



Analysis 2.3. Comparison 2 After treatment, Outcome 3 Heart Rate (HR).

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Hughes 1984	7	106 (6.9)	7	106 (15)		8.36%	0[-12.23,12.23]
Lu 1995	12	110 (20.2)	9	101.1 (19.2)		4.33%	8.89[-8.1,25.88]
Safani 1989	11	112 (4)	11	115 (5)		87.31%	-3[-6.78,0.78]





APPENDICES

Appendix 1. Search strategy

Cochrane Injuries Group Specialised Register (searched 5 December 2008)
(intensive or critical or emergency or shock* or sepsis) and (naloxon* or narcan* or maloxone or nalone* or narcon or narvcam)

CENTRAL (*The Cochrane Library* 2008, Issue 4)
#1MeSH descriptor Shock explode all trees
#2MeSH descriptor Shock, Cardiogenic explode all trees
#3MeSH descriptor Shock, Hemorrhagic explode all trees
#4MeSH descriptor Shock, Septic explode all trees
#5MeSH descriptor Shock, Traumatic explode all trees
#6MeSH descriptor Emergency Medicine explode all trees
#7MeSH descriptor Emergency Treatment explode all trees
#8MeSH descriptor Intensive Care explode all trees
#9MeSH descriptor Critical Illness explode all trees
#10MeSH descriptor Electric Injuries explode all trees
#11(intensive or critical or emergency or shock* or sepsis):ab,ti
#12(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11)
#13MeSH descriptor Naloxone explode all trees
#14(naloxon* or narcan* or maloxone or nalone* or narcon or narvcam)
#15(#13 OR #14)
#16(#12 AND #15)

MEDLINE (Ovid SP) (1950 to week 3 November 2008)
1.exp SHOCK/
2.exp Cardiogenic Shock/
3.exp Hemorrhagic Shock/
4.exp Septic Shock/
5.exp Traumatic Shock/
6.exp Emergency Medicine/
7.exp Emergency Treatment/
8.exp Intensive Care/
9.exp Critical Illness/
10.(intensive or critical or emergency or shock* or sepsis).ab,ti.
11.exp Electric Injuries/
12.or/1-11
13.exp Naloxone/
14.(naloxon* or narcan* or maloxone or nalone* or narcon or narvcam).ab,ti.
15.13 or 14
16.12 and 15
17.randomi?ed.ab,ti.
18.randomized controlled trial.pt.
19.controlled clinical trial.pt.
20.placebo.ab.
21.clinical trials as topic.sh.
22.randomly.ab.
23.trial.ti.

24.or/17-23
25.exp animals/
26.exp humans/
27.25 not (25 and 26)
28.24 not 27
29.28 and 16

EMBASE (Ovid SP) (1980 to November (week 49) 2008)
1.exp SHOCK/
2.exp Cardiogenic Shock/
3.exp Hemorrhagic Shock/
4.exp Septic Shock/
5.exp Traumatic Shock/
6.exp Burn Shock/
7.exp ELECTRIC SHOCK/
8.(intensive or critical or emergency or shock* or sepsis).ab,ti.
9.exp Emergency Medicine/
10.exp Emergency Treatment/
11.exp Intensive Care/
12.exp Critical Illness/
13.or/1-12
14.(naloxon* or narcan* or maloxone or nalone* or narcon or narvcam).ab,ti.
15.exp NALOXONE/
16.exp NALOXONE BENZOYLHYDRAZONE/
17.14 or 15 or 16
18.13 and 17
19.exp Randomized Controlled Trial/
20.exp controlled clinical trial/
21.randomi?ed.ab.
22.placebo.ab.
23.exp Clinical Trial/
24.randomly.ab.
25.trial.ti.
26.19 or 20 or 21 or 22 or 23 or 24 or 25
27.exp animal/ not (exp human/ and exp animal/)
28.26 not 27
29.28 and 18

ISI Web of Science: Science Citation Index Expanded (SCI-EXPANDED) (1970 to December 2008)
ISI Web of Science: Conference Proceedings Citation Index- Science (CPCI-S) (1990 to December 2008)
#1Topic=(intensive or critical or emergency or shock* or sepsis) AND Topic=(naloxon* or narcan* or maloxone or nalone* or narcon or narvcam)
#2Topic=(random OR placebo OR randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random) AND Title=(trial* or group* or study or studies or placebo or controlled)
#3Title=(random OR placebo OR randomised OR randomized OR randomly OR random order OR random sequence OR random allocation OR randomly allocated OR at random) AND Topic=(trial* or group* or study or studies or placebo or controlled)
#4#1 and #2
#5#1 and #3
#6#4 or #5

PubMed (searched 5 December 2008; added to PubMed in the last 180 days)
Search (intensive or critical or emergency or shock* or sepsis) AND (naloxon* or narcan* or maloxone or nalone* or narcon or narvcam)

WHAT'S NEW

Date	Event	Description
20 April 2009	New search has been performed	The search was updated to 5 December 2008. No new trials were identified. The conclusions remain the same.

HISTORY

Protocol first published: Issue 4, 2003
Review first published: Issue 4, 2003

Date	Event	Description
11 September 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Jacques Lacroix wrote the prococol of the review and wrote to authors of randomized clinical trials to check whether the data had been correctly extracted.
Catherine Ann Farrell, France Gauvin and Anne-Marie Guerguerian selected the studies.
Jacques Lacroix, Véronique Poirier, and Chantal Roy extracted the data of the retained studies and assessed their quality.
Jacques Lacroix, Benoit Boeuf, and Véronique Poirier did the meta-analysis and wrote the final report of the systematic review.
Chantal Roy helped to organize the systematic review and to edit the paper in RevMan.

DECLARATIONS OF INTEREST

None known

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Canadian Institutes of Health Research, Canada.
- Agence d'Évaluation des technologies et des modes d'intervention en santé, Canada.

INDEX TERMS

Medical Subject Headings (MeSH)

Naloxone [*therapeutic use]; Narcotic Antagonists [*therapeutic use]; Randomized Controlled Trials as Topic; Shock [*drug therapy]

MeSH check words

Adult; Child; Humans; Infant, Newborn