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REVIEWS

THE USE OF NALOXONE IN CARDIAC ARREST MANAGEMENT: A RAPID REVIEW

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ABSTRACT

Introduction: Naloxone is a mu-opioid receptor antagonist that is best known for reversing opioid overdose by restoring spontaneous respirations and level of consciousness. It has been postulated that naloxone may possess antiarrhythmic properties as well as the ability to reverse endogenous opioid-related myocardial depression and stimulate catecholamine release, suggesting utility in cardiac arrest. The survivability of cardiac arrest is relatively low, and the impact of opioid toxicity deaths is staggeringly high. Optimizing the medical management of patients in cardiac arrest, particularly in the context of opioid use, is a priority.

Research Question: Does naloxone improve rates of return of spontaneous circulation (ROSC) and survival to hospital discharge when administered during cardiac arrest?

Methods: Pubmed and EMBase were searched with 187 articles progressing to the screening stage. Inclusion criteria included cardiac arrest patients receiving naloxone pre-hospital or in-hospital with outcomes relating to resuscitation rates and/or survival. Exclusion criteria included traumatic cardiac arrests and pediatrics. Eleven articles were chosen following title and abstract screen, full text review, and data extraction.

Results and Discussion: Five randomized controlled trials with animals found that intra-arrest naloxone improved rates of ROSC, particularly when combined with epinephrine. Two human case reports describe patients receiving naloxone during cardiac arrest and experiencing spontaneous improvement in cardiac rhythm, neither with favourable neurological outcomes. Over the past five years, evidence includes a retrospective cohort study, two observational studies, and one case-control study. Two reported higher ROSC rates and improved survival to discharge with naloxone, while the others found no significant differences between exposure groups.

Conclusion: Currently, there is conflicting evidence on whether naloxone improves rates of ROSC and survival to hospital discharge. Although naloxone does not appear to be harmful when administered in the context of cardiac arrest, further research is needed to determine its efficacy for this indication.

INTRODUCTION

Naloxone is a mu-opioid receptor antagonist that can reverse the effects of both exogenous and endogenous opioids, restoring spontaneous respirations and level of consciousness in the context of opioid overdose (Lavonas et al., 2023). If untreated with oxygenation and a reversal agent like naloxone, opioid overdose can swiftly progress from central nervous system and respiratory depression towards apnea and cardiac arrest.

In contrast, the utility of naloxone in the context of cardiac arrest is much less understood. It has been postulated that naloxone may reverse endogenous opioid-related myocardial depression and stimulate catecholamine release, thus improving blood pressure and heart rate (Dillon et al., 2024). It has also been suggested that naloxone may have antiarrhythmic properties (Strong et al., 2024). Despite this, much is still unknown about naloxone's efficacy in cardiac arrest management, and there are no prospective studies to provide guidance for practice. It is also questioned whether naloxone has benefit in all causes of cardiac arrest, or purely opioid-induced cardiac arrests. At the time of the American Heart Association 2023 guideline update, there was not enough evidence to support routine administration of intra-arrest naloxone, and they recommend that naloxone should only be considered if the delivery of high-quality cardiopulmonary resuscitation (CPR) is not impacted (Lavonas et al., 2023). However, only 1 in 10 people are prospected to survive an out-of-hospital cardiac arrest (OHCA) in Canada (Heart and Stroke, 2024) and the benefit of epinephrine, the current first-line drug, is controversial when considering mortality (Chen, Xie et al, 2006). Furthermore, from January to March 2024, there were 1,906 opioid toxicity deaths, or 21 deaths per day on average in Canada (Government of Canada, 2024). Therefore, optimizing the medical management of patients in cardiac arrest, particularly in the context of opioid use, should be a priority.

RESEARCH QUESTION

Does naloxone improve rates of return of spontaneous circulation (ROSC) and survival to hospital discharge when administered during cardiac arrest?

METHODS

Two electronic databases, Medline and EMBase, were searched in November 2024 with results demonstrated in Figure 1. Inclusion criteria included studies involving cardiac arrest patients receiving naloxone both pre-hospital and in-hospital with outcomes related to rates of resuscitation and/or survival. Exclusion criteria included traumatic cardiac arrests, pediatrics (<18 years old), and non-English results. Medline was searched via Pubmed using search terms and Boolean operators (Naloxone OR Narcan) AND (Cardiac AND Arrest), generating 127 results, and (Naloxone OR Narcan) AND ((Cardiopulmonary AND Resuscitation) OR (CPR)), generating 92 results. EMBase was then searched using search terms and Boolean operators (naloxone:ti OR narcan:ti) AND 'cardiac arrest':ti, generating 25 results, and (naloxone:ti OR narcan:ti) AND ('cardiopulmonary resuscitation':ti OR 'cpr':ti), generating 14 results. Search results were imported to Covidence and duplicates were removed, generating 187 studies which were screened by title and abstract. 30 studies were selected for full text review, with 18 not meeting the inclusion and exclusion criteria. Data was extracted from 12 studies into an extraction form, and the results then converted into a table which underwent quality assessment. Studies varied in strength upon critical appraisal, and one study was eliminated at this stage for lacking a control group. The resulting data table was utilized for synthesis and analysis. Ultimately, 11 studies were included in the final synthesis. Data was organized by study methodology and subject type to compare similar studies.

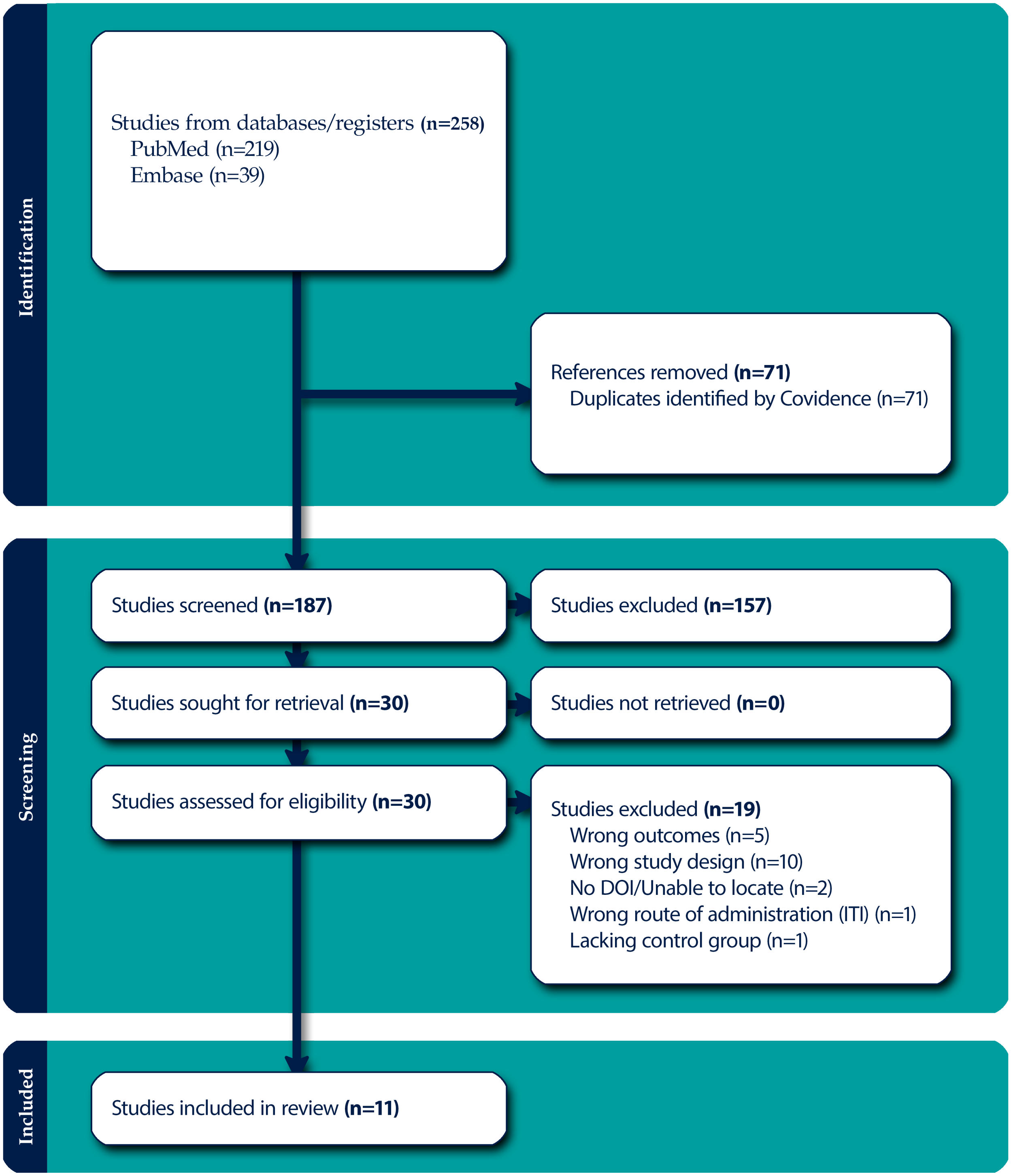

Figure 1. Search Strategy.

RESULTS

Experimental Animal Studies

Four randomized controlled trials (RCTs) from China studied the effects of naloxone in asphyxia-induced cardiac arrest with samples of 24 rats (Chen, Liu, et al., 2006; Chen, Xie et al., 2006; Wang et al., 2008; Wang et al., 2010). One additional RCT was included from the USA, which looked at 10 dogs in ventricular fibrillation (VF) (Rothstein et al., 1985).

All subjects received standard CPR, including chest compressions and ventilation, prior to the treatment being randomized and administered synchronously (Chen, Liu, et al., 2006; Chen, Xie, et al., 2006; Rothstein et al., 1985; Wang et al., 2008; Wang et al., 2010). Rothstein et al. (1985) followed up the naloxone treatment with attempted defibrillation of increasing joules. Treatment group sizes by Chen, Liu et al. (2006), Chen, Xie et al. (2006), Wang et al. (2008), and Wang et al. (2010) were eight per treatment. Rothstein et al. (1985) had smaller treatment groups of five. All groups were randomized. The relatively small sample sizes and the use of animal samples in all five studies limits generalizability to a greater human population. All four rat-based studies included a placebo control treatment group that received 1 mL normal saline, strengthening internal validity (Chen, Liu, et al., 2006; Chen, Xie, et al., 2006; Wang et al., 2008; Wang et al., 2010). Rothstein et al. (1985) did not include a placebo control group, although the dogs treated with epinephrine could act as a concurrent active treatment control group relative to the naloxone.

Chen, Liu et al. (2006) compared low dose 0.5 mg/kg IV naloxone, high dose 1 mg/kg IV naloxone, and a control group of normal saline. ROSC was observed in 12.5% of the control group, 37.5% of the low-dose naloxone group, and 87.5% of the high-dose naloxone group (Chen, Liu et al., 2006). There was a significant difference between the high-dose naloxone and control group ($p<0.05$) but the difference between the low-dose naloxone group and the other two groups was insignificant, suggesting dose-dependence (Chen, Liu et al., 2006). In another study, Chen, Xie et al. (2006) utilized 1 mg/kg IV naloxone, and compared outcomes to 0.04 mg/kg IV epinephrine and a control group. ROSC was observed in 12.5% of the control group, 87.5% of the naloxone group, and 87.5% of the epinephrine group ($p=0.01$) (Chen, Xie et al., 2006). Wang et al. (2008) compared rats receiving 0.05 mg/kg IV epinephrine, the same dose of epinephrine augmented with 1 mg/kg IV naloxone, and a saline control group. ROSC was obtained in 25% of the control group, 75% of the epinephrine group, and 87.5% of the naloxone and epinephrine group (Wang et al., 2008). The difference was statistically significant when comparing the control group to the naloxone and epinephrine group ($p<0.05$) (Wang et al., 2008). Wang et al. (2010) repeated this study with the same outcomes in terms of ROSC, but added additional metrics of interest including survival three days post-arrest. It was found that one rat from the control group (12.5% of original sample), three from the epinephrine group (37.5%), and five from the naloxone and epinephrine group (62.5%) survived (Wang et al., 2010). The difference between the naloxone and epinephrine group was statistically significant ($p<0.05$) when compared to the control group, but not to the epinephrine group (Wang et al., 2010).

Rothstein et al. (1985) treated dogs in VF with either 5 mg/kg naloxone or 1 mg epinephrine by central venous injection, followed by attempted defibrillation until ROSC was obtained. If unsuccessful after increasing the joules to the maximum energy dose, the opposite treatment was administered, and the attempted defibrillation regime was repeated (Rothstein et al., 1985). Four dogs receiving epinephrine as their first treatment converted to pulseless electrical activity (PEA) and then subsequently converted to a perfusing rhythm once naloxone was later given (Rothstein et al., 1985). For the group receiving naloxone as a first treatment, none achieved an organized rhythm after the first sequence of shocks, but four regained a perfusing rhythm once epinephrine was subsequently given and the second sequence of shocks were initiated. The difference in defibrillation outcome between the dogs receiving naloxone vs. epinephrine prior to shock was statistically significant (p=0.02), and the medications demonstrated synergism at achieving ROSC (Rothstein et al., 1985).

Human Case Reports

Two case reports from Brazil and Scotland described patients receiving naloxone during cardiac arrest who experienced a spontaneous improvement in cardiac rhythm (Martins et al., 2008; Marsden & Mora, 2008). Martins et al. (2008) describes a 55-year-old woman in persistent PEA receiving standard cardiac arrest management in a hospital setting due to an opioid-induced cardiac arrest. ROSC was obtained shortly after the administration of 2 mg IV naloxone. One week later this same patient had a Glasgow Coma Score (GCS) of 15 but had developed paraparesis and anterior spinal artery syndrome. Martins et al. (2008) also conducted a brief review of literature to accompany this case study, utilizing three reviewers and a standardized extraction form to reduce bias. The reviewers suggested that naloxone may have utility in opioid and hypoxia-related cardiac arrest (Martins et al., 2008). Marsden and Mora (1996) reported on a prehospital patient who experienced an opioid-induced cardiac arrest. Normal cardiac arrest management protocol was followed with the addition of two doses of 0.4 mg IV naloxone by paramedics to a total of 0.8 mg. This patient converted from asystole to PEA following the first dose, then to a perfusing sinus tachycardia following the second dose. Once in hospital, this patient seized and was declared brain dead with cerebral anoxia 24 hours later (Marsden & Mora, 1996). Even though improved cardiac rhythms and subsequent ROSC was observed after naloxone administration, it is not possible to conclude that ROSC was exclusively due to the naloxone and no other confounding variables. The poor outcomes of both patients require further consideration (Martins et al., 2008; Marsden & Mora, 2008).

Retrospective Human Studies

Research regarding naloxone use in cardiac arrest is currently growing, with new literature including one retrospective cohort study from the USA (Dillon et al., 2024), two retrospective observational studies from the USA (Quinn et al., 2024; Strong et al., 2024), and one retrospective case-control study from China (Lv et al., 2019). Dillon et al. (2024) extracted data from the Cardiac Arrest Registry to Enhance Survival of 8195 adults treated by five emergency medical services (EMS) agencies for OHCA in Northern California from 2015 to 2023. 7030 patients received usual care, while 1165 were treated with adjuvant naloxone. Strong et al. (2024) extracted data from 1807 medical records obtained from the Portland Cardiac Arrest Epidemiologic Registry from January 2018 to December 2021, 57 of which received naloxone prior to vascular access and 1750 who did not. Quinn et al. (2024) extracted 769 medical records of OHCA patients at a single urban hospital-based EMS system in New Jersey from January 2017 to June 2022. 175 cardiac arrest patients received naloxone, whereas 594 received usual care. Lv et al. (2019) extracted medical records of adults receiving in-hospital CPR in specific acute care units from January 2011 to December 2016 in China, with 59 patients having received naloxone, and 285 having received usual care.

Dillon et al. (2024) and Strong et al. (2024) both found that naloxone significantly improved patient outcomes when compared to the unexposed group. Dillon et al. (2024) considered any patient receiving intra-arrest naloxone, whereas Strong et al. (2024) looked specifically at intramuscular (IM) or intranasal (IN) naloxone administered to adults in cardiac arrest with non-shockable rhythms prior to vascular access. However, within the unexposed group, patients were included who later received intravenous (IV) or intraosseous (IO) naloxone, potentially confounding the results (Strong et al., 2024). According to Dillon et al. (2024), among patients receiving naloxone intra-arrest, 34.5% sustained ROSC for >20 minutes at the end of EMS care and 15.9% survived to hospital discharge. This is contrasted with the unexposed group, where 22.9% sustained ROSC and 9.7% survived to discharge, and the difference between exposed and unexposed groups was found to be statistically significant ($p<0.001$). The number needed to treat with naloxone was nine for ROSC, and 26 for survival to discharge (Dillon et al., 2024). Strong et al. (2024) found that among those who received naloxone prior to vascular access, 42.1% obtained ROSC, which was not statistically significant compared to 31.6% from the unexposed group. However, there was a statistically significant difference in patients who had ROSC upon arrival to the ED, which was 35.1% of patients who received early naloxone compared to 21.6% of those who did not ($p=0.022$) (Strong et al., 2024). Similarly, there was a statistically significant difference between the 14% of patients who survived to discharge in the group who received naloxone prior to vascular access compared to 3.3% for those who did not ($p<0.001$), following a similar trend to the findings by Dillon et al. (2024) (Strong et al., 2024). Following adjusted 1:1 propensity score matching, there was still a significant difference between the survival to discharge of these two matched groups (Strong et al., 2024). A logistic regression model was used to demonstrate that naloxone was more beneficial in patients with presumed opioid-related OHCA (Dillon et al., 2024). When respiratory and substance-use etiologies were controlled for in the early naloxone administration group, adjusted odds were higher for all outcomes for both PEA and asystole (Strong et al., 2024). This study by Dillon et al. (2024) utilized a robust sample size and propensity score-based models and analyses to adjust for potential bias. Despite this, the study lacked data regarding the timing of naloxone administration, route of naloxone, and whether bystander naloxone was administered, which could influence the interpretation and practical application of the results (Dillon et al., 2024). Additionally, younger, healthier patients are more likely to survive cardiac arrest, and younger patients with fewer comorbidities were more likely to receive naloxone by paramedics which introduces a selection bias, potentially confounding results further (Dillon et al., 2024). Strong et al. (2024) acknowledged these sources of potential for bias and performed multivariable logistic regressions to adjust for characteristics like age, sex, and initial rhythm. Further, when controlling for heart rhythms, early naloxone was also shown to improve adjusted odds of survival for patients in PEA, and ROSC at emergency department arrival for patients in asystole (Strong et al., 2024).

Quinn et al. (2024) authored a retrospective observational study with contrasting results to Strong et al. (2024) and Dillon et al. (2024). In the study by Quinn et al. (2024), confounding variables like age, initial cardiac rhythm, and chronic comorbidities were controlled for using a matched cohort analysis. 2.0 mg was the most common dose of naloxone used. Using a logistic regression model, it was found that there was no statistical significance between both matched and unmatched groups for all outcomes including ROSC and survival to discharge (Quinn et al., 2024). Within the in-hospital setting, Lv et al. (2019) found that naloxone use was not associated with a statistically significant increase in recovery of sinus rhythm, although the sample size used was the smallest when compared to the other three retrospective studies.

DISCUSSION

Whether naloxone has utility in cardiac arrest management is a recently evolving area of research. It appears naloxone is not harmful when given intra-arrest, and there is some data that suggests it may be helpful, but more research is ultimately needed. Animal studies generally found treatment with intra-arrest naloxone improved rates of ROSC, particularly when combined with epinephrine (Chen, Liu, et al., 2006; Chen, Xie, et al., 2006; Rothstein et al., 1985; Wang et al., 2008; Wang et al., 2010). Wang et al. (2010) also found that rats who received a combination of epinephrine and naloxone demonstrated better survivability at the 3-day mark, and this metric has important implications as it may indicate better long-term outcomes. It was also found by Chen, Liu et al. (2006) that the response to naloxone is dose-dependent, with 1 mg/kg IV being more efficacious than 0.05 mg/kg. This is notable for future studies, as the dose of naloxone may need to be optimized to see the intended effect. Despite all studies having statistically significant findings in support of naloxone use, small-sample animal experiments have limited generalizability to a human population. These studies serve as an initial first step when considering whether naloxone has utility beyond the current standard indication.

Two case studies highlight two patients who had a spontaneous improvement in cardiac rhythm and ROSC shortly after administration of naloxone in suspected opioid-overdose related cardiac arrests. One patient suffered significant neurological deficits following her resuscitation, and the other experienced seizures and an anoxic brain injury. Although these cases are thought-provoking, being uncontrolled, non-comparative, retrospective, and having only a sample size of one, there are limited conclusions that can be drawn from them.

In the last five years, new research has looked retrospectively at the effect of naloxone on cardiac arrest outcomes with mixed results. Two studies with robust data sets demonstrated higher rates of ROSC at the end of EMS care and improved survival to discharge when cardiac arrest patients were given naloxone, with Strong et al. (2024) looking specifically at early naloxone administration for non-shockable rhythms prior to vascular access and Dillon et al. (2024) considering any timeline of intra-arrest naloxone administration. Strong et al. (2024) chose early administration of IM/IN naloxone as the target of their study, and the exposed and unexposed groups were not limited by naloxone being administered after IV/IO access. This creates the possibility of both groups ultimately receiving naloxone at different time points. In contrast to the favorable findings by Strong et al. (2024) and Dillon et al. (2024), Quinn et al. (2024) and Lv et al. (2019) both found that there was no significant difference in outcomes between patients who received or didn't receive naloxone intra-arrest prehospitally and in-hospital, respectively.

There is ample potential for confounding variables when studying the administration of intra-arrest naloxone retrospectively. There is the question of how clinical gestalt leads healthcare providers to administer naloxone in cardiac arrest patients, as this decision-making process could further introduce bias in these retrospective studies. With substance-users being younger on average, this leads to naloxone administration to a younger population with less comorbidities, confirmed by Dillon et al. (2024), Strong et al. (2024), and Quinn et al. (2024). This could skew outcomes, as younger cardiac arrest patients generally have better outcomes, but this was controlled for by Strong et al. (2024) and Quinn et al. (2024) by comparing matched groups, and both studies yielded contrasting results. Quinn et al. (2024) acknowledged that it is possible naloxone was being administered to patients with longer cardiac arrests without ROSC, with the thought process of 'try it all by the end.' Quinn et al. (2024) only gathered data from one EMS system, and if this is common practice within that system, this thought process could certainly introduce a confounding variable and contribute to the lack of improvement observed in patient outcomes with naloxone administration. Attempts to control confounders improves validity, however retrospective observational studies are bias-prone and not useful to ascertain causality. Despite this, they present insightful preliminary data that can direct future studies. Dillon et al. (2024) and Strong et al. (2024) suggested that naloxone may be more efficacious in presumed opioid-related OHCA, highlighting the need for future research to consider the mechanism of cardiac arrest. Despite this, Strong et al. (2024) did demonstrate that naloxone may cause mild improvement in some outcomes for patients specifically in asystole.

Ultimately, whether naloxone has utility in cardiac arrest management can only be confirmed by robust randomized controlled trials spanning large areas with multiple EMS systems. Several retrospective observational studies have recently provided provocative data regarding this intervention, however determining whether an overall practice change is warranted necessitates further evidence. A placebo would need to be implemented, along with a naloxone treatment group, and EMS providers would need to be blinded to which treatment they are administering. An area with a higher concentration of substance use would be useful to include, as this may help to compare which populations may benefit most from naloxone in the context of cardiac arrest management.

LIMITATIONS

Although rapid reviews allow for quick synthesis of data, which can be useful in instances such as this when there is new and evolving data on a topic, limitations do exist. Having one reviewer may introduce an unavoidable risk of bias in article selection and interpretation. This rapid review also only included two search databases, which may result in some relevant articles being missed.

CONCLUSION

Currently, there is conflicting evidence on whether naloxone improves rates of ROSC and survival to hospital discharge. Cardiac arrest management can be a task-saturating undertaking, and adding additional treatments without sufficient evidence may take away from evidence-driven interventions, such as high-quality CPR, airway management, and ventilation. Despite this, the question of whether naloxone has utility in improving resuscitation rates and survivability is important to answer, as only 1 in 10 people survive an OHCA in Canada (Heart and Stroke, 2024). A randomized controlled trial involving a wide area of EMS systems and hospitals may be the next step to address this question. Therefore, although naloxone does not appear to be harmful in the context of cardiac arrest, further research is needed to determine whether it is truly efficacious.

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