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Intranasal versus Intramuscular/Intravenous Naloxone for Pre-hospital Opioid Overdose: A Systematic Review and Meta-analysis

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Abstract

Context: The present systematic review and meta-analysis aims to perform an extensive search in databases to compare the efficacy of the intranasal administration of naloxone with its intramuscular/intravenous administration in the pre-hospital management of opioid overdose.

Evidence acquisition: This meta-analysis included controlled trials conducted on the efficacy of naloxone administration in the pre-hospital management of opioid overdose. A search was carried out in electronic databases on relevant articles published by the end of 2018. After data collection, analyses were performed in STATA 14.0 software and the efficacy and side-effects of the two administration routes of naloxone, i.e. intranasal and intramuscular/intravenous, were compared. An overall effect size with 95% confidence interval (95% CI) was provided for each section.

Results: Eventually, data from six studies were included in this meta-analysis. The success rate of the intranasal and intramuscular/intravenous administration of naloxone in the management of opioid overdose in pre-hospital settings was 82.54% (95% CI: 57.97 to 97.89%) and 80.39% (95% CI: 57.38 to 96.04%), respectively. There was no difference between injectable (intramuscular/intravenous) naloxone and intranasal naloxone in the pre-hospital management of opioid overdose (Odds Ratio=1.01; 95% CI: 0.42 to 2.43; P=0.98). The onset of action of intranasal naloxone, however, was slightly longer than injectable naloxone (Standardized Mean Difference=0.63; 95% CI: 0.07 to 1.19; P=0.03). Additionally, the odds of needing a rescue dose was 2.17 times higher for intranasal naloxone than intramuscular/intravenous naloxone (OR=2.17; 95% CI: 1.53 to 3.09; P<0.0001). The prevalence of major side-effects was non-significant for both intranasal (0.00%) and intramuscular/intravenous (0.05%) routes of naloxone administration and there was no difference in the prevalence of major (OR=1.18; 95% CI: 0.38 to 3.69; P=0.777) and minor (OR=0.64; 95% CI: 0.17 to 2.34; P=0.497) side-effects between the two routes.

Conclusion: The present meta-analysis demonstrated that intranasal naloxone is as effective as injectable naloxone in the pre-hospital management of opioid overdose complications. Consequently, intranasal naloxone may be an appropriate alternative to injectable naloxone.

Key words: Drug Administration Routes; Emergency Medical Services; Naloxone; Opioid-Related Disorders; Substance-Related Disorders

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Context

Opioid overdose is one of the most common causes of death and disability worldwide. Statistics suggest that the prevalence of complications of opioid overdose is increasing in various societies and the number of emergency medical service calls and hospital referrals related to this disorder has increased dramatically (1, 2). According to the existing guidelines, naloxone is prescribed for the treatment of opioid overdose. Nonetheless, the majority of these guidelines are designed for in-hospital settings, and there are still questions regarding the use of naloxone in pre-hospital settings. For instance, the optimum routes and dosage for naloxone administration in the pre-hospital management of opioid overdose

complications are still unclear. Research in this area thus continues.

In recent years, numerous clinical trials have investigated the administration of naloxone for the pre-hospital management of opioid overdose complications. As an example, Kelly et al. demonstrated that, in the first ten minutes of administration, the success rate of intravenous naloxone is more than intranasal naloxone in the management of respiratory depression symptoms of opioid overdose (3). In another study, Kerr et al. displayed that the intranasal and intramuscular administration of naloxone have the same efficacy in the management of opioid overdose complications. Nevertheless, it seems that a rescue dose is less needed in intramuscular than intranasal administration (4). These inconsistencies in studies led Cho et al. to conduct a systematic review about the subject. Their findings revealed that high-dose intranasal naloxone may have a similar efficacy to intramuscular naloxone (5). Meanwhile, limitations such as not performing a meta-analysis and not including the records of the Embase database may have resulted in a potential bias in their findings. Considering the limitations of previous studies, the present systematic review and meta-analysis aims to carry out an extensive search in databases to compare the efficacy of intranasal and intramuscular/intravenous naloxone in the pre-hospital management of opioid overdose complications.

EVIDENCE ACQUISITION

Study design

The present review intends to answer the following three questions:

1. What would be the optimum route for naloxone in pre-hospital settings to manage opioid overdose symptoms?
2. What is the optimum dose of naloxone needed for the management of opioid overdose complications in pre-hospital settings?
3. What side-effects would naloxone, administered for the management of opioid overdose complications, cause in pre-hospital settings?

To answer these questions, a comprehensive search was carried out in electronic databases for articles published by the end of 2018. The study was designed based on the Cochrane meta-analysis guidelines for clinical trials and its method is similar to the one used in the other systematic reviews conducted by the present article's authors (6-18). Panel 1 presents the PICO for the study.

Search strategy

Initially, several keywords were selected upon the advice of toxicologists and emergency medicine specialists. These words were then searched in MeSH and Emtree and the related words and synonyms found were added to the search strategy. Other related words were added by screening the titles and abstracts of any relevant articles. All keywords were related to opioid overdose and naloxone. Afterwards, a comprehensive search was carried out in Medline, Embase, Scopus, CENTRAL and Web of Science for articles published by the end of 2018. Appendix 1 presents the search strategy in Medline database. In addition to the systematic search, a manual search was also performed in Google search engine, and Google Scholar and the articles noted in the bibliography of the retrieved articles were also examined.

Eligibility criteria

Prospective clinical trials and cohorts conducted on adult patients were included in the present study. The absence of data on the route and doses of naloxone administration, being conducted in hospital settings and being a review article were taken as the exclusion criteria.

Data synthesis and quality assessment

At first, a researcher conducted a search in the noted databases using proper keyword combinations and standard tags. The search results were then added to EndNote program and duplicates were omitted. The records obtained were then handed over to two other researchers so that the results would be independently screened based on their titles and abstracts. The full texts of the selected records were adopted and eventually the relevant articles were summarized in a checklist designed based on PRISMA protocols. The data entered into the checklist consisted of the first author's name, year of publication, patients' characteristics, route of naloxone administration, dose of injection and outcomes. All these steps

Panel 1: PICO definitions of the study

PICO	Definition
Problem (P)	Opioid overdose in prehospital settings
Intervention (I)	Intranasal naloxone administration
Comparison (C)	Intramuscular/intravenous naloxone administration
Outcome (O)	Success rate, onset of action and complications

were completed independently. Any disagreement was resolved through discussion (19).

If the required data were not presented in the paper or could not be extracted from its content, a request for data was emailed to its authors. In the case of no response to the first email, a reminder was sent. If there was still no response, a second reminder was sent within a week. At last, other authors were contacted via social media such as ResearchGate and LinkedIn to obtain the data. only one of the articles included underwent this step.

The quality assessment of the studies was carried out with the aid of Cochrane's suggested guidelines. Inter-rater reliability was evaluated to assess the two researchers' agreement and any disagreement was resolved through discussions with a third researcher.

Statistical Analysis

The analyses were carried out in STATA 14.0. An analysis was conducted separately for each outcome, which consisted of the success rate of naloxone in opioid overdose symptom management, the onset of action of naloxone and its side-effects. Depending on the presence or absence of heterogeneity, either the random effects model or fixed effects model were used. In order to evaluate heterogeneity, I^2 was performed. Eventually, the studies were pooled and an overall effect size with 95% confidence interval (CI 95%) was presented. It is worth noting that the meta-analyses were conducted under the condition that the data were reported in at least three different studies. Funnel plots were used to investigate publication bias using Egger's tests (20).

RESULTS

Studies' characteristics

The systematic search conducted in this study resulted in a total of 1195 records. After omitting the duplicates, 775 records were screened; 84 of the eligible records, which were mainly cross-sectional studies or case reports, were studied in detail. Eventually, six studies were included in the study, including four clinical trials and two cohort studies. The studies contained data on 965 patients suspected of opioid overdose (4, 21-25). All of these patients had been treated with naloxone. In the control groups, the patients were treated with intravenous (21, 23-25) or intramuscular (4, 22) naloxone. In the treatment groups, intranasal naloxone was administered to the patients. The prescribed dosage for intranasal administration was 2 mg. Figure 1 demonstrates the search flowchart and study selection process. Table 1 presents the characteristics of the included studies.

Quality assessment of the studies and publication bias

The quality assessment of the records was performed based on the Cochrane guidelines. As illustrated in table 2 and figure 2-A, the risk of bias

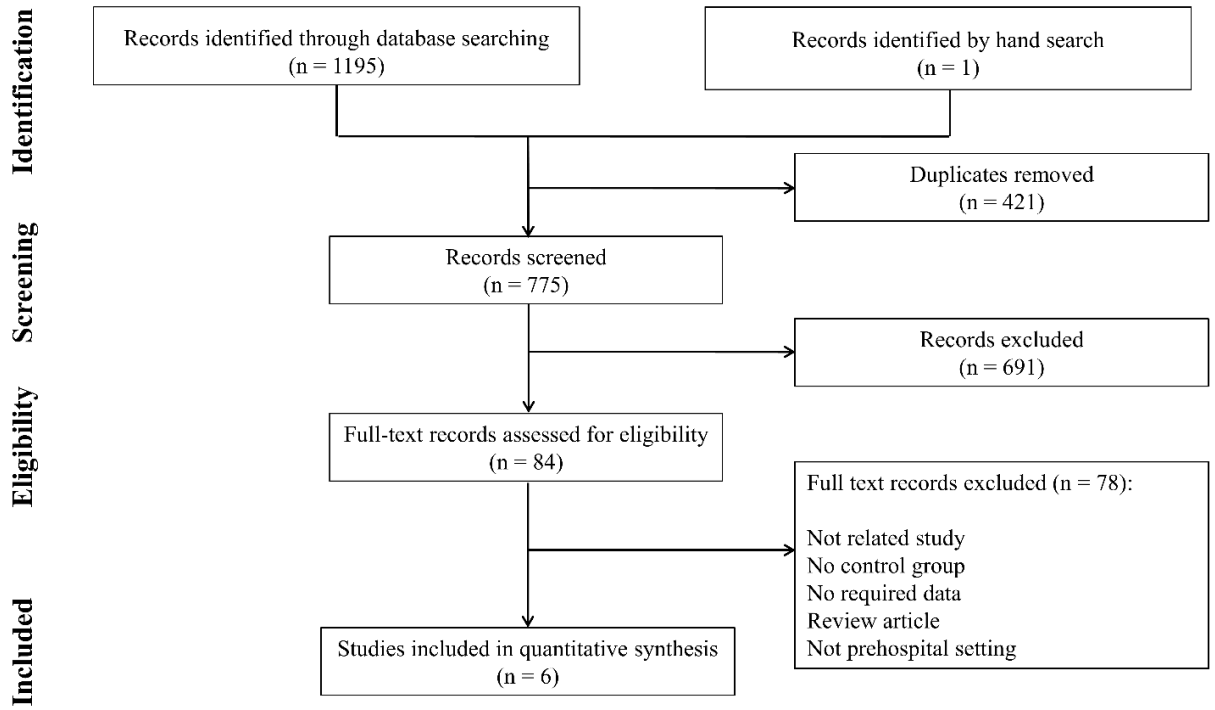

Figure 1: PRISMA flow diagram of the meta-analysis

Table 1: Characteristics of the included studies

Author; year; country	Study design	Number of patients treatment / control	Sampling method	Age	Male	Control group	IN naloxone group	Assessed outcome
Barton; 2005; USA	Non-randomized trial	43 / 9	Consecutive	>14	NR	IV, 2 mg	2 mg	Success rate; onset of action; need for rescue dose; drug-related side-effects
Kelly; 2005; Australia	RCT	84 / 71	Convenience	13 to 57	111	IM, 2 mg	2 mg	Success rate; onset of action; need for rescue dose; drug-related side-effects
Kerr; 2005; Australia	RCT	83 / 89	Convenience	13 to 57	127	IM, 2 mg	2 mg	Success rate; onset of action; need for rescue dose; drug-related side-effects
Merlin; 2010; USA	Historical cohort	38 / 55	Consecutive	27 to 54	60	IV, 1 to 2 mg	2 mg	Success rate
Robertson; 2009; USA	Historical cohort	50 / 104	Consecutive	3 to 06	98	IV, 2 mg	2 mg	Success rate; onset of action; need for rescue dose
Sabzghabaee; 2014; Iran	RCT	50 / 50	Convenience	15 to 50	76	IV, 0.4 mg	0.4 mg	Success rate; onset of action; drug-related side-effects

IM: Intramuscular; IN: Intranasal; IV: Intravenous; NR: Not reported; RCT: Randomized clinical trial

Table 2: Assessing the risk of bias in the included studies

☹: High risk of bias ☺: Low risk of bias 😐: Unclear risk of bias	Barton; 2005	Kelly; 2005	Kerr; 2005	Merlin; 2010	Robertson; 2009	Sabzghabaee; 2014
Random sequence generation	☹	☺	☺	☹	☹	☺
Allocation concealment	☹	☹	☹	☹	☹	☺
Matching the patients	☹	☺	☺	☺	☺	☺
Meeting the inclusion and exclusion criteria	☺	☺	☺	☺	☺	☺
Blinding of the patients	☹	☹	☹	☹	☹	☺
Blinding of the outcome assessment	☹	☹	☹	☹	☹	☺
Incomplete outcome data	☺	☺	☺	☺	☺	☺
Selective reporting	☺	☺	☺	☺	☺	☺
Other bias	☹	☺	☺	☹	😐	☺

in matching the patients (five articles; 83.33%), meeting the inclusion and exclusion criteria (six articles; 100%), incomplete outcome data (six articles; 100%) and selective reporting (six articles; 100%) was low in the majority of the studies. In contrast, the risk of bias was high in allocation concealment (five articles; 83.33%), blinding of the patients (five articles; 83.33%) and blinding of the outcome assessment (five articles; 83.33%) in most of the studies. No publication bias was observed in the assessment of the therapeutic success rate of intranasal naloxone compared to intramuscular/intravenous naloxone in managing opioid overdose signs and symptoms (Bias

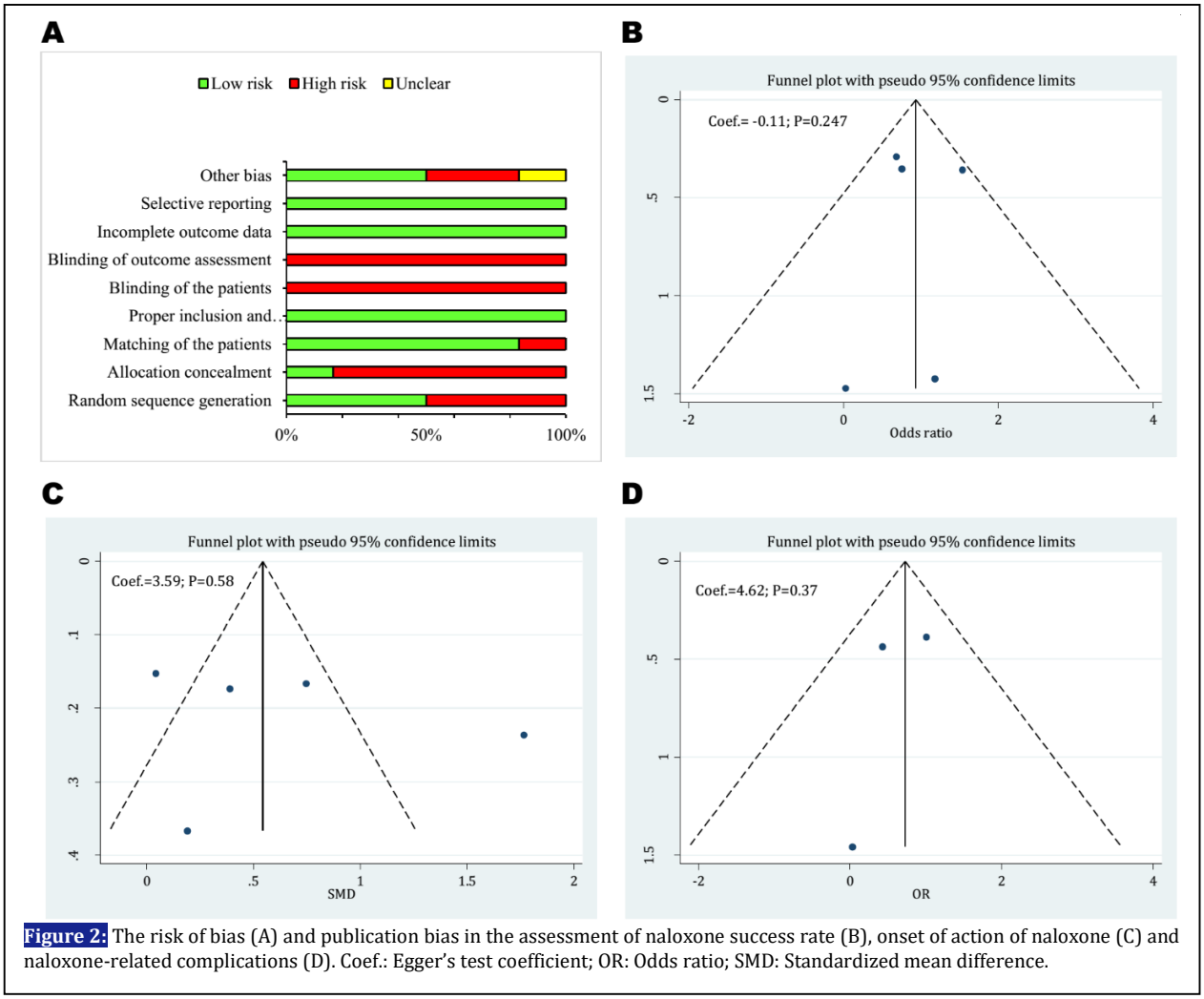

Figure 2: The risk of bias (A) and publication bias in the assessment of naloxone success rate (B), onset of action of naloxone (C) and naloxone-related complications (D). Coef.: Egger's test coefficient; OR: Odds ratio; SMD: Standardized mean difference.

Coefficient=-0.11; P=0.93). No publication bias was observed in assessing the onset of action of naloxone either (Bias Coefficient=3.59, P=0.58). Lastly, no publication bias was noted in the evaluation of the prevalence of naloxone side-effects (Bias Coefficient= 4.62; P=0.37); (Figures 2-B to 2-D).

Meta-analysis

- ***A comparison of the therapeutic success rate of naloxone in the management of opioid overdose***

All the six articles reported the therapeutic success rate of naloxone in the management of the opioid overdose, which is defined as the recovery of patients' consciousness and spontaneous respiration. The analyses indicated that intranasal naloxone controlled the complications of opioid overdose in pre-hospital settings in 82.54% (95% CI: 57.97 to 97.89%) of the cases and facilitated the return of normal respiration and consciousness. Also, the therapeutic success rate of the intravenous/intramuscular form was 80.39% (95% CI: 57.38 to 96.04%). There was no difference between intranasal naloxone and intramuscular/intravenous naloxone in the management of opioid overdose complications (OR=1.01; 95% CI: 0.42 to 2.43; P=0.98); (Figures 3-A to 3-C).

- ***Onset of action of naloxone***

Five studies attempted to evaluate the onset of action of intranasal and intramuscular/intravenous naloxone administration. The findings showed that the time required to observe a response to intranasal naloxone is slightly longer than that for intramuscular/intravenous naloxone (SMD=0.63; 95% CI: 0.07 to 1.19; P=0.03]. Nonetheless, although the observed difference is statistically significant, the SMD is weak and the finding may therefore not be clinically significant (Figure 3-D).

- ***The efficacy of naloxone in respiratory depression recovery after opioid overdose***

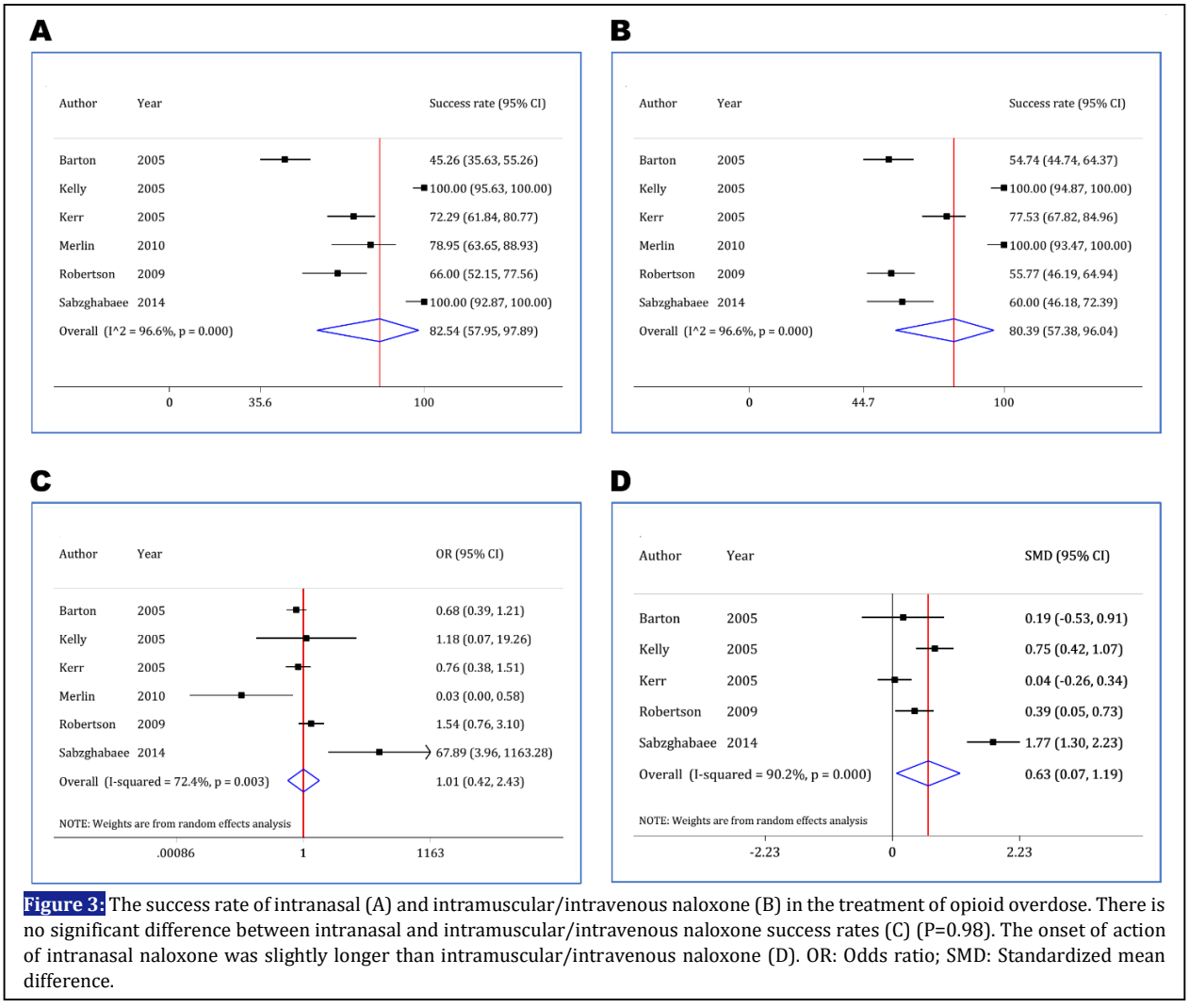

Figure 3: The success rate of intranasal (A) and intramuscular/intravenous naloxone (B) in the treatment of opioid overdose. There is no significant difference between intranasal and intramuscular/intravenous naloxone success rates (C) (P=0.98). The onset of action of intranasal naloxone was slightly longer than intramuscular/intravenous naloxone (D). OR: Odds ratio; SMD: Standardized mean difference.

Three studies evaluated the efficacy of naloxone in the management of respiratory depression caused by opioid overdose. The findings of these three studies indicate that intranasal naloxone improved respiratory depression and restored normal respiration in 93.63% (95% CI: 60.17 to 100.0%) of the patients. This rate was 96.93% (95% CI: 81.11 to 100.0%) for intramuscular/intravenous naloxone. A comparison of the success rate of naloxone in the management of respiratory depression in the two groups revealed that the efficacy of intramuscular/intravenous naloxone was slightly better compared to the intranasal route (OR=0.42; 95% CI: 0.21 to 0.85; P=0.016); (Table 3).

- ***The efficacy of naloxone in the recovery of consciousness following opioid overdose***

Three studies evaluated the efficacy of naloxone in the recovery of consciousness following opioid overdose. According to their findings, intranasal naloxone increased the level of consciousness in 83.95% (95% CI: 47.85 to 100.0%) of the cases and altered their coma and stupor to obtundation (GCS above 11). This rate was 77.10% (95% CI: 33.55 to 100.0%) for intramuscular/intravenous naloxone. The comparison of the success rate of naloxone therapy in improving the level of consciousness between the two groups showed no significant differences (OR=1.33; 95% CI: 0.02 to 87.55; P=0.894); (Table 3).

- ***The need for a rescue dose of naloxone to manage opioid overdose***

Five studies reported the need for a rescue dose of naloxone in the management of opioid overdose. Their findings indicated that, in 33.26% (95% CI: 21.60 to 46.02%) of the cases, there is a need for a rescue dose after intranasal naloxone administration. This rate was 17.74% (95% CI: 7.37 to 31.19%) in the intramuscular/intravenous group. A comparison of the two administration routes revealed that the odds of needing a rescue dose were 2.17 times higher with intranasal

Table 3: The subgroup analysis of intranasal versus intramuscular/intravenous naloxone administration in the management of opioid overdose in prehospital settings

Variable	Heterogeneity	Effect size	95% CI	P
Spontaneous respiration (success rate, %)				
Intranasal	96.6% (p<0.0001)	93.63	60.17 to 100.0	<0.0001
Intramuscular/intravenous	91.9% (p<0.0001)	96.93	81.11 to 100.0	<0.0001
Difference among the subgroups	**0.0% (p=0.760)**	**OR=0.42 95% CI: 0.21 to 0.85; p=0.016**		
Improved consciousness (success rate, %)				
Intranasal	96.0% (p<0.0001)	83.95	47.85 to 100.0	<0.0001
Intramuscular/intravenous	97.2% (p<0.0001)	77.10	33.55 to 100.0	<0.0001
Difference among the subgroups	**91.4% (p<0.0001)**	**OR=1.33 95% CI: 0.02 to 87.55; p=0.894**		
Need for rescue dose (%)				
Intranasal	82.9 (p<0.0001)	33.26	21.60 to 46.02	<0.0001
Intramuscular/intravenous	90.3% (p<0.0001)	17.74	7.37 to 31.19	<0.0001
Difference among the subgroups	**0.0% (p=0.407)**	**OR=2.17 95% CI: 1.53 to 3.09; p<0.0001**		
Major complications (%)				
Intranasal	0.0% (p>0.999)	0.00	0.00 to 0.50	<0.0001
Intramuscular/intravenous	0.0% (p=0.910)	0.05	0.00 to 0.75	<0.0001
Difference among the subgroups	**0.0% (p=0.407)**	**OR=1.18; 95% CI: 0.38 to 3.69; p=0.777**		
Minor complications (%)				
Intranasal	86.1 (p<0.0001)	7.43	1.26 to 17.43	<0.0001
Intramuscular/intravenous	94.2% (p<0.0001)	13.50	1.59 to 33.33	<0.0001
Difference among the subgroups	**71.3% (p=0.015)**	**OR=0.64; 95% CI: 0.17 to 2.34; p=0.497**		

CI: Confidence interval; OR: Odds ratio

naloxone than the intravenous/intramuscular route (OR=2.17; 95% CI: 1.53 to 3.09; P<0.0001); (Table 3).

- ***A comparison of the incidence of naloxone side-effects in intranasal versus intramuscular/intravenous administration***

The analyses revealed that intranasal naloxone administration does not cause any major complications (Prevalence=0.00%; 95% CI: 0.00 to 0.51%). In the reviewed literature, only one serious complication was reported for intramuscular/intravenous naloxone, including one case of grand mal epileptic seizure following intramuscular administration (Prevalence=0.05%; 95% CI: 0.00 to 0.75%). The prevalence of serious complications did not differ significantly between the two administration routes (OR=1.18; 95% CI: 0.38 to 3.69; P=0.777). All the side-effects of naloxone reported in the articles are considered minor. The prevalence of these side-effects was 7.43% (95% CI: 1.26 to 17.43%) in the intranasal naloxone group. The rate of these complications was 13.50% (95% CI: 1.59 to 33.33%) in the intramuscular/intravenous naloxone group. There was no difference between the intranasal naloxone groups and intramuscular/intravenous naloxone groups (OR=0.64; 95% CI: 0.17 to 2.34; P=0.497) in terms of the prevalence of these mild side-effects (Table 3).

Discussion

The present meta-analysis summarized the evidence on the efficacy of intranasal naloxone compared with intramuscular/intravenous naloxone in improving opioid overdose complications in pre-hospital settings. The findings demonstrated that intranasal naloxone is as effective as intramuscular/intravenous naloxone in the pre-hospital management of opioid overdose complications. Intranasal naloxone aids in restoring the patients' spontaneous respiration and increases their consciousness level. The administration of intranasal naloxone was also found to cause no serious side-effects and all the reported complications were mild. Nevertheless, intranasal naloxone has a somewhat longer onset of action than intramuscular/intravenous naloxone. In addition, intranasal naloxone administration requires higher rescue doses compared to the other routes of administration. Overall, it seems that intranasal naloxone can be an acceptable substitute for the intramuscular/intravenous form in the management of opioid overdose in pre-hospital settings.

Only one case of grand mal seizure was reported as a serious complication of intramuscular naloxone injection. Other side-effects were chiefly minor and consisted of nausea, vomiting, agitation, headaches and diaphoresis, which are mostly related to the withdrawal syndrome. Intranasal naloxone therefore appears to be a safe medication for use in pre-hospital settings.

The patients' response time (i.e. onset of action) was slightly prolonged with the intranasal form of naloxone. With a close inspection of the studies, however, the difference showed to be only one to two minutes. Moreover, the SMD obtained in the

meta-analysis of the records was rather weak and negligible.

This study also revealed that intranasal naloxone quickly restores normal respiration in 93.63% of the cases, while this rate was 96.3% for the intravenous form. Although this 3.3% difference is statistically significant, it can be clinically ignored.

The need for a rescue dose of naloxone for opioid overdose was up to 2.2 times higher with intranasal administration compared to intravenous administration, which could be construed as a limitation for intranasal naloxone. Nevertheless, since intravenous naloxone does not require intravenous access and its re-administration does not cause serious complications, this limitation is not major enough to prevent its use.

The review of literature showed two similar systematic reviews and meta-analyses on the effectiveness of naloxone administration in controlling opioid overdose symptoms in pre-hospital settings. Compared to the findings of the present study, a systematic review by Chou et al. in 2017 indicated that high-dose intranasal naloxone may have a similar efficacy to intramuscular naloxone (without performing a meta-analysis). This study demonstrated that the complications of high-dose intranasal naloxone are similar to those of intramuscular naloxone (5). Nonetheless, the failure to perform a meta-analysis or review Embase were major weaknesses of this article. Also, another systematic review in 2018 with a search carried out in PubMed, Ovid and Google Scholar revealed the lack of a consensus over the best route for the administration of naloxone for opioid overdose management in pre-hospital settings. The cited study was also a qualitative study of clinical trials and its findings were based on an incomplete database search (26). In contrast, the present study used an analytical approach to show that intranasal naloxone administration is as effective as injectable naloxone in the management of opioid overdose complications.

Limitations and strengths

The present study conducted an extensive search of electronic resources, contacted the authors and searched relevant webpages to obtain the maximum number of articles and also examined gray literature. The lack of publication bias is another strength of this study. The heterogeneity in the analyses was one of the study's limitations. The non-blinded observers in some of the included studies was another limitation of this study, as non-blinded observers may cause bias in the findings.

Conclusion

The present meta-analysis demonstrated that the therapeutic success rates of intramuscular/intravenous naloxone and intranasal naloxone are similar and both routes do not cause any serious complications. Therefore, intranasal naloxone may be a suitable alternative to intramuscular/intravenous naloxone in pre-hospital settings in the treatment of opioid overdose.

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None.

Authors' contribution

Study design: MY, MA, PS, AB; Conducting the search: MY; Data collection: MY, MHVM, AMN, SNRA; Analysis: MY; Interpreting the findings: MA, AB, PS; Article drafting: MY, MHVM and AMN; Critical revision of the paper: All authors.

Conflict of interest

None declared.

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Appendix 1: Medline search query

Search terms
1. "Emergency Medical Services"[mh] OR "Emergency Health Service"[tiab] OR "Emergency Care"[tiab] OR "Prehospital Medication"[tiab] OR "Prehospital Care"[tiab] OR "Prehospital"[tiab] OR "Emergency Services, Medical"[tiab] OR "Emergency Service, Medical"[tiab] OR "Medical Emergency Service"[tiab] OR "Medical Emergency Services"[tiab] OR "Service, Medical Emergency"[tiab] OR "Services, Medical Emergency"[tiab] OR "Medical Services, Emergency"[tiab] OR "Emergency Medical Service"[tiab] OR "Medical Service, Emergency"[tiab] OR "Service, Emergency Medical"[tiab] OR "Services, Emergency Medical"[tiab] OR "Prehospital Emergency Care"[tiab] OR "Emergency Care, Prehospital"[tiab] OR "Emergicenters"[tiab] OR "Emergicenter"[tiab] OR "Emergency Care"[tiab] OR "Emergency Health Services"[tiab] OR "Emergency Health Service"[tiab] OR "Health Service, Emergency"[tiab] OR "Health Services, Emergency"[tiab] OR "Service, Emergency Health"[tiab] OR "Services, Emergency Health"[tiab]
2. "Drug Overdose"[mh] OR "Substance-Related Disorders"[mh] OR "Analgesics, Opioid"[mh] OR "Opioid-Related Disorders"[mh] OR "Heroin Dependence"[mh] OR "Morphine Dependence"[mh] OR "Opium Dependence"[mh] OR "Drug Overdose"[tiab] OR "Substance-Related Disorders"[tiab] OR "Analgesics, Opioid"[tiab] OR "Opioid-Related Disorders"[tiab] OR "Heroin Dependence"[tiab] OR "Morphine Dependence"[tiab] OR "Opium Dependence"[tiab] OR "Drug Overdoses"[tiab] OR "Overdose, Drug"[tiab] OR "Overdoses, Drug"[tiab] OR "Drug Overdose"[tiab] OR "Drug Abuse"[tiab] OR "Abuse, Drug"[tiab] OR "Drug Dependence"[tiab] OR "Dependence, Drug"[tiab] OR "Drug Addiction"[tiab] OR "Addiction, Drug"[tiab] OR "Substance Use Disorders"[tiab] OR "Disorder, Substance Use"[tiab] OR "Substance Use Disorder"[tiab] OR "Drug Use Disorders"[tiab] OR "Disorder, Drug Use"[tiab] OR "Drug Use Disorder"[tiab] OR "Organic Mental Disorders, Substance-Induced"[tiab] OR "Organic Mental Disorders, Substance Induced"[tiab] OR "Substance Abuse"[tiab] OR "Abuse, Substance"[tiab] OR "Abuses, Substance"[tiab] OR "Substance Abuses"[tiab] OR "Substance Dependence"[tiab] OR "Dependence, Substance"[tiab] OR "Substance Addiction"[tiab] OR "Addiction, Substance"[tiab] OR "Prescription Drug Abuse"[tiab] OR "Abuse, Prescription Drug"[tiab] OR "Drug Abuse, Prescription"[tiab] OR "Drug Habituation"[tiab] OR "Habituation, Drug"[tiab] OR "Opioid Related Disorders"[tiab] OR "Opioid-Related Disorder"[tiab] OR "Addiction, Opioid"[tiab] OR "Opioid Addiction"[tiab] OR "Addictions, Opioid"[tiab] OR "Opioid Addictions"[tiab] OR "Opioid Dependence"[tiab] OR "Dependences, Opioid"[tiab] OR "Opioid Dependences"[tiab] OR "Dependence, Opioid"[tiab] OR "Opioid Abuse"[tiab] OR "Abuse, Opioid"[tiab] OR "Abuses, Opioid"[tiab] OR "Opioid Abuses"[tiab] OR "Narcotic Abuse"[tiab] OR "Abuse, Narcotic"[tiab] OR "Abuses, Narcotic"[tiab] OR "Narcotic Abuses"[tiab] OR "Opiate Abuse"[tiab] OR "Abuse, Opiate"[tiab] OR "Abuses, Opiate"[tiab] OR "Opiate Abuses"[tiab] OR "Opiate Dependence"[tiab] OR "Dependence, Opiate"[tiab] OR "Opiate Addiction"[tiab] OR "Addiction, Opiate"[tiab] OR "Narcotic Dependence"[tiab] OR "Dependence, Narcotic"[tiab] OR "Dependences, Narcotic"[tiab] OR "Narcotic Dependences"[tiab] OR "Narcotic Addiction"[tiab] OR "Addiction, Narcotic"[tiab] OR "Addictions, Narcotic"[tiab] OR "Narcotic Addictions"[tiab] OR "Dependence, Heroin"[tiab] OR "Heroin Addiction"[tiab] OR "Addiction, Heroin"[tiab] OR "Heroin Abuse"[tiab] OR "Abuse, Heroin"[tiab] OR "Heroin Smoking"[tiab] OR "Heroin Smokings"[tiab] OR "Smoking, Heroin"[tiab] OR "Dependence, Morphine"[tiab] OR "Morphine Addiction"[tiab] OR "Addiction, Morphine"[tiab] OR "Morphine Abuse"[tiab] OR "Abuse, Morphine"[tiab] OR "Dependence, Opium"[tiab] OR "Opium Addiction"[tiab] OR "Addiction, Opium"[tiab] OR "Opium Use"[tiab] OR "Opium Uses"[tiab] OR "Use, Opium"[tiab] OR "Uses, Opium"[tiab] OR "Opium Abuse"[tiab] OR "Abuse, Opium"[tiab] OR "Abuses, Opium"[tiab] OR "Opium Abuses"[tiab] OR "Opium Smoking"[tiab] OR "Smoking, Opium"[tiab]
3. "Narcotic Antagonists"[mh] OR "Naloxone"[mh] OR "Narcotic Antagonists"[tiab] OR "Naloxone"[tiab] OR "Antagonists, Narcotic"[tiab] OR "Opioid Receptor Antagonists"[tiab] OR "Antagonists, Opioid Receptor"[tiab] OR "Receptor Antagonists, Opioid"[tiab] OR "Opioid Antagonists"[tiab] OR "Antagonists, Opioid"[tiab] OR "Competitive Opioid Antagonists"[tiab] OR "Antagonists, Competitive Opioid"[tiab] OR "Opioid Antagonists, Competitive"[tiab] OR "Opioid Reversal Agents"[tiab] OR "Agents, Opioid Reversal"[tiab] OR "Nalone"[tiab] OR "Naloxon Curamed"[tiab] OR "Curamed, Naloxon"[tiab] OR "Naloxon-Ratiopharm"[tiab] OR "Naloxon Ratiopharm"[tiab] OR "Naloxone Abello"[tiab] OR "Abello, Naloxone"[tiab] OR "Naloxone Hydrochloride"[tiab] OR "Hydrochloride, Naloxone"[tiab] OR "Naloxone Hydrochloride Dihydride"[tiab] OR "Dihydride, Naloxone Hydrochloride"[tiab] OR "Hydrochloride Dihydride, Naloxone"[tiab] OR "Naloxone Hydrochloride, (5 beta,9 alpha,13 alpha,14 alpha)-Isomer"[tiab] OR "Naloxone, (5 beta,9 alpha,13 alpha,14 alpha)-Isomer"[tiab] OR "Narcan"[tiab] OR "Narcanti"[tiab] OR "MRZ-2593"[tiab] OR "MRZ 2593"[tiab] OR "MRZ2593"[tiab] OR "MRZ 2593-Br"[tiab] OR "MRZ 2593 Br"[tiab] OR "MRZ 2593Br"[tiab] OR "Naloxone Hydrobromide"[tiab] OR "Hydrobromide, Naloxone"[tiab]
4. #1 AND #2 AND #3