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ORIGINAL RESEARCH

Emergency Medical Services

Early intranasal medication administration in out-of-hospital cardiac arrest: Two randomized simulation trials

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Meetings: Preliminary results from the lay rescuer trial were presented as a poster at the University of Michigan Undergraduate Research Opportunity Research Symposium in 2022. Final results were presented at a closed University of Michigan, Michigan Resuscitation Innovation and Science Enterprise (MRISE) 4th Annual Retreat in June 2023, at the Learning Health System (LHS) Collaboratory Seminar Series on September 27,2023, and at the Society for Academic Emergency Medicine Midwest Regional Meeting on September 14,

Abstract

Objective: Intranasal medications have been proposed as adjuncts to out-of-hospital cardiac arrest (OHCA) care. We sought to quantify the effects of intranasal medication administration (INMA) in OHCA workflows.

Methods: We conducted separate randomized OHCA simulation trials with lay rescuers (LRs) and first responders (FRs). Participants were randomized to groups performing hands-only cardiopulmonary resuscitation (CPR)/automated external defibrillator with or without INMA during the second analysis phase. Time to compression following the second shock (CPR2) was the primary outcome and compression quality (chest compression rate (CCR) and fraction (CCF)) was the secondary outcome. We fit linear regression models adjusted for CPR training in the LR group and service years in the FR group.

Results: Among LRs, INMA was associated with a significant increase in CPR2 (mean diff. 44.1 s, 95% CI: 14.9, 73.3), which persisted after adjustment (p = 0.005). We

2023. This manuscript, related data, figures, and tables have not been published previously and are not under consideration elsewhere.

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observed a significant decrease in CCR (INMA 95.1 compressions per min (cpm) vs control 104.2 cpm, mean diff. −9.1 cpm, 95% CI −16.6, −1.6) and CCF (INMA 62.4% vs control 69.8%, mean diff. −7.5%, 95% CI −12.0, −2.9). Among FRs, we found no significant CPR2 delays (mean diff. −2.1 s, 95% CI −15.9, 11.7), which persisted after adjustment (p = 0.704), or difference in quality (CCR INMA 115.5 cpm vs control 120.8 cpm, mean diff. −5.3 cpm, 95% CI −12.6, 2.0; CCF INMA 79.6% vs control 81.2% mean diff. −1.6%, 95% CI −7.4, 4.3%)

Conclusions: INMA in LR resuscitation was associated with diminished resuscitation performance. INMA by FR did not impede key times or quality.

KEYWORDS
first responder, intranasal, lay rescuer, OHCA, randomized trial, simulation

1 | INTRODUCTION

1.1 | Background

Care for out-of-hospital cardiac arrest (OHCA) in the United States emphasizes interventions following the American Heart Association's (AHA) six-link OHCA Chain of Survival.[1] Of the 294,683 nontraumatic, emergency medical services (EMS)-treated OHCAs estimated to have occurred in the United States in 2022, less than 10% survived to hospital discharge with neurologically favorable outcomes.[2]

Intranasal medication administration (INMA) during cardiopulmonary resuscitation (CPR) may present an opportunity to improve neurologic outcomes after OHCA. Neuroprotective medications that can be delivered intranasally are under clinical investigation in other neurologic disorders such as stroke and Alzheimer's disease.[3,4] During cardiac arrest, intranasal medications can be given with minimal training during CPR, which could optimize therapeutic benefit. Intranasal medications offer advantages over traditional intravenous (IV) or intraosseous (IO) routes including ease of use, reduced delays associated with the IV/IO routes, bypass of the blood–brain barrier, and negligible systemic absorption. A potential challenge in INMA during OHCA is disruption or delay in CPR or defibrillation. The AHA therefore cautions clinicians to avoid delays to chest compression and defibrillation that may be associated with existing prehospital INMA therapy, but suggests clinicians may consider INMA if delays can be avoided.[5]

1.2 | Importance

To date, no studies have examined the effects of INMA on OHCA resuscitation quality.

1.3 | Goals

In preparation for human clinical trials in cardiac arrest, we sought to test the potential impact of INMA on delays to key treatments, including chest compressions and defibrillation provided by lay rescuers and first responders while managing a simulated nontraumatic adult OHCA.

2 | METHODS

2.1 | Design

We conducted two prospective randomized simulation trials comparing resuscitation performance with and without INMA among (1) lay rescuers and (2) first responders. The Institutional Review Board at the University of Michigan Medical School approved the study (HUM00194119). All participants provided verbal and written informed consent.

2.2 | Setting

The study was conducted at the University of Michigan Medical School's Clinical Simulation Center from March to July of 2022. We used a simulation suite adapted to reflect the appearance of a generic office waiting room (Supporting Information Appendix A). The suite was equipped with audiovisual recording devices and software, a corded telephone, and a SimMan® 3G Simulator (Laerdal Medical, Stavanger, Norway) supine on the floor.

2.3 | Selection of subjects

Our recruitment approach was multimodal. For lay rescuers, we obtained a convenience sample of participants via either email solicitation or the UM Health Research participant pool, a registry connecting study candidates to research teams. For first responders, we obtained a convenience sample recruited via emails and flyers distributed to local public safety agencies and organizations (i.e., police, fire, EMS). These strategies were complemented by posts on regional first-responder social media groups and announcements at local EMS oversight meetings.

The study enrolled lay rescuers from March to June and first responders from June to July 2022. Subjects received gift card incentives for participation. Potential participants were tracked in a Research Electronic Data Capture (REDCap) database, which was used for all data collection. Study candidates were called by study staff using a standardized telephone script to ensure eligibility and scheduling. Eligibility criteria for lay rescuers included: the ability to read and write English, being at least 18 years of age, self-reported COVID-19 vaccination, capacity to walk and get up from the floor without assistance, and capacity to perform strenuous activity, determined by the self-reported ability to climb six flights of stairs or perform CPR. Eligibility for first responders required meeting the above criteria and having work experience as a first responder (i.e., police, firefighter, or emergency medical technician (EMT)). Medical professionals with advanced training such as advanced emergency medical technicians, paramedics, nurses, physician assistants, nurse practitioners, physicians, or those in training for such credentials were excluded. Given time and budget constraints, we sought to enroll 60 total participants, 30 lay rescuers, and 30 first responders. We ended the trial when we met our recruitment goals.

2.4 | Simulation-based interventions

The simulation scenario was designed by the study team, leveraging expertise in cardiac arrest management and simulation to represent the earliest stages of OHCA management and optimal INMA practice. Hands-only CPR by a single rescuer and limited access to resuscitation devices (i.e., automated external defibrillator [AED]) were selected features for ease of standardization and to allow the team to focus analysis on compression quality effects. We conducted pilot scenario testing to refine the study protocol. Pilot cases were not included in the final quantitative analysis (Figure 1).

Upon arrival, participants were briefed according to a standardized script on the objectives of the study, as well as risks and benefits, and completed the informed consent. After signing, participants completed an electronic survey using REDCap, which included demographics, the number of minutes per week spent in physical activity (weekly active minutes), past CPR or medical training, and prior OHCA experiences.

Participants in both trials were randomized to either the control (CPR/AED) or experimental group (INMA/CPR/AED) upon arrival. Allocation used computer-generated randomly permuted blocks of 2 and 4, resulting in an approximate 1:1 ratio (http://www.jerrydallal.com/random/random_block_size_r.htm). For each trial (i.e., lay rescuer, first responder) group, assignment lists were generated, and placed in blinded, externally numbered envelopes by staff uninvolved in the data collection process. Data collection facilitators were blinded to the allocation sequences but aware of the group to which the participant was randomized.

The Bottom Line

Prompt delivery of medications during out-of-hospital cardiac arrest (OHCA) poses a clinical challenge as vascular access takes time and skill. Alternate routes of medication administration, such as intraosseous and intranasal, have been proposed. The authors performed randomized simulation trials with lay rescuers and first responders during OHCA where they examined the effect of intranasal medication administration on cardiopulmonary resuscitation (CPR) metrics. They found that, in lay rescuers but not in first responders, CPR metrics worsened when intranasal medication administration was added to the simulation. Future studies will need to examine the optimal timing and approach to intranasal medication administration during OHCA before this technology is widely adopted.

For both trials, we simulated an OHCA with a protocol that involved providing chest compressions and applying an AED. All participants were equipped with a Phillips HeartStart AED Trainer 2 (Philips Medical Systems, Bothell, WA, USA). INMA group participants were equipped with a nasal spray device which consisted of a standard intranasal aerosolizer trainer with modified packaging (Supporting Information Appendix A). The scenario began when the participant was instructed to enter the room and ended at the beginning of the AED's third analysis phase. The AED was programmed to recommend shock following each analysis. Participants wore masks and nitrile gloves underneath fingerless work gloves to comply with COVID-19 protocol and to protect participants from CPR-associated blistering.

2.4.1 | Lay rescuer simulation

In the lay rescuer trial, participants were directed to determine if the patient could talk and to call 911 for additional assistance. Both control and experimental (INMA) groups received instructions from a simulated telecommunicator (author SRD) using one of two telecommunicator scripts (Supporting Information Appendix B). The control script guided the participant through hands-only CPR/AED application. The experimental script included the control instructions and additional instructions for INMA, including removing the device from packaging during the first AED analysis phase and to tilt the head back prior to INMA during the second analysis phase.[11] Scripts were

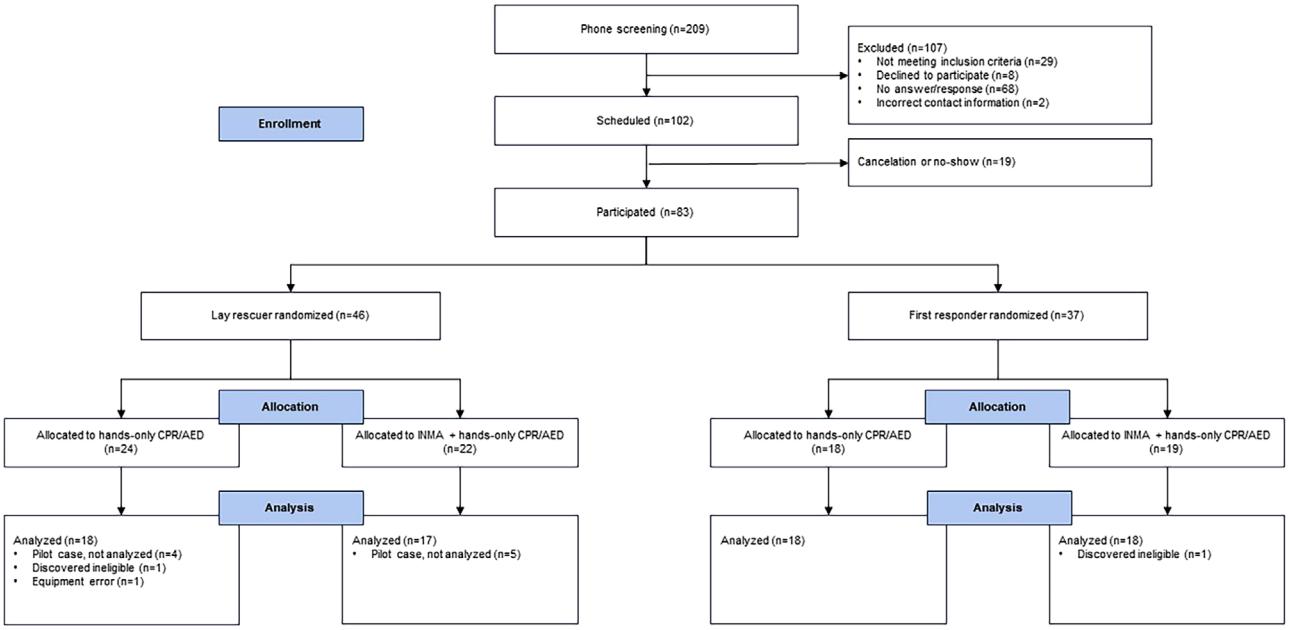

FIGURE 1 Screening and enrollment process for subjects in both the lay rescuer and first responder trials. Several cases were excluded after randomization. A total of nine pilot cases were excluded due to significant protocol changes following pilot testing. Two participants were determined to be to ineligible for the study based on preexisting exclusion criteria after they had already participated, and one participant was excluded due to mid-simulation equipment failure.

the same until the first AED analysis, when the telecommunicator instructed the subject to remove the device from the bag (Supporting Information Appendix B). To ensure standardized delivery of scripts, the telecommunicator could not watch the scenario while managing the caller and delivered the script language according to auditory cues from the participant on the phone (Supporting Information Appendix B).

2.4.2 | First responder simulation

First responders were advised to perform hands-only CPR and to apply and use the AED according to the AHA 2020 Basic Life Support (BLS) algorithm, which advises use of the AED as soon as possible.[5] Before the simulation, experimental group first responders watched a 6-min just-in-time training video depicting hands-only CPR, AED use, and proper INMA, which included tilting the head prior to administration.[6] First responder participants could examine the INMA device and ask questions before starting. The first responder experimental group was asked to perform hands-only CPR and AED application, open the intranasal medication packaging during the first AED analysis, and provide INMA during the second. First responders did not receive telecommunicator guidance.

2.5 | Data collection

Simulations were video and audio recorded and tracked using SimMan® 3G's recording software. The research team abstracted data from the recordings into REDCap. Trained data abstractors reviewed the videos for key event times (defined in Supporting Information Appendix C), abnormal pauses in chest compressions, and errors in nasal spray delivery. For participants in experimental groups, successful nasal spray delivery occurred if the subject (1) placed the device in one of the manikin's nostrils and (2) visibly depressed the device plunger to deliver the medication. One time point, time to end of scenario (end time) (Supporting Information Appendix C) was captured, but was lost in 22 cases because a software error resulted in truncated recordings. For the 22 truncated cases, we calculated the missing end time using other abstracted values. To calculate the end time, we added 128 s to the time to the second shock (Shock 2). This was the standard interval between these events preprogrammed into the AED and was constant across all cases. To calculate chest compression fraction (CCF), we tracked chest compression duration for the overall scenario and for the first cycle of CPR, measured as the interval between first analysis (Analysis 1) and second analysis (Analysis 2), with calibration-certified[1] stopwatches. The mean chest compression rate (CCR) was used from the SimMan® 3G event log. In three cases, this was not available and was calculated manually as number of compressions delivered divided by the total time delivering compression.

To ensure the accuracy of data abstraction, all reviewers received training on a standard set of metric definitions (Supporting Information Appendix C) and were asked to independently review the same four case videos: two control and two experimental. Responses were assessed for agreement to a key developed via simultaneous review

[1] International Standardization Organization/International Electrotechnical Commission Standard 17025; Traceable® Products, Webster, TX, USA.

of the cases by two senior authors (SRD and ALM). Any discordance between a staff reviewer (MLD, NKM, IGS, and JM) and the key resulted in revision and review of the metric definition, and additional training on the metric in question prior to the reviewer conducting additional video review.

2.5.1 | Outcomes

The primary outcome was the interval from the beginning of the scenario to the initial chest compression following the second shock (CPR2) because this was the first timepoint occurring in all cases following INMA. Secondary outcomes were two measures of compression quality, CCR and CCF.

2.6 | Data analysis

Analyses for first responders and lay rescuers were conducted separately. Descriptive statistics are reported as means and standard deviations (SD), medians and interquartile ranges (IQR), or percentages. Independent *t*-tests, chi-square, and Wilcoxon Rank Sum were used to determine differences between the experimental and control groups. CPR2 was analyzed using unadjusted and adjusted linear regression. We hypothesized that the resuscitation quality of those with more experience (CPR training or work related) would be less affected by integrating INMA into their workflows. Therefore, the lay rescuer and first responder model was adjusted for prior CPR training and years of public safety experience respectively.

To further examine the place where key delays occurred, we conducted a post-hoc sensitivity analysis of the primary outcome, CPR2, by limiting our analysis to delays that occurred after the scripts deviated. We also conducted a follow-up video review to examine the source of delays that may have occurred in the lay responder trial before the scripts deviated.

We calculated an overall CCF and CCFs for the first and second cycles of CPR. The denominators were the time intervals from Analysis 1 to the end time, the time from Analysis 1 to Analysis 2, and the time from Analysis 2 to the end time for the overall, first cycle and second cycle calculations, respectively. For the second cycle calculation, the numerator was calculated by subtracting the first cycle compression duration from the overall compression duration. For truncated cases, CCFs were calculated with the assumption participants continued compressions until the end time. To assess this strategy, we conducted a sensitivity analysis for only nontruncated files and compared with all participants. All analyses were performed using RStudio 4.2.2 and met model assumptions.

3 | RESULTS

3.1 | Recruitment

Our team contacted a total of 209 potential participants (includes first responders and lay rescuers) in order of expressed interest. We ultimately scheduled 102. Of these, there were 19 cancellations or no-shows prior to the study appointment and subsequent randomization. Of the 83 subjects participating in the study, 71 (35 lay rescuers and 36 first responders) were included in the final quantitative analysis (Figure 1).

3.2 | Demographics

Demographics for both trials are reported in Table 1. Among lay rescuers, median age was 54 years and 57.1% were female. A higher proportion of females were in the INMA group and mean weekly active minutes was higher in the control group. Among first responders, median age was 31.5 years, 36.1% were female, 44% were ambulance EMTs, 39% firefighter EMTs, and 8% law enforcement.

3.3 | Performance measures

The lay rescuer INMA group had longer times to all key events beginning with time to AED pad application (Figure 2A). Video review found that while three cases of delay were due in part to the presence of an additional bag containing the INMA, the remainder of the cases were due to longer times to place the AED pads. Detailed interval times and comparisons are presented in Table 2.

3.3.1 | Primary outcome

For lay rescuers, the time from the start of the scenario to initial compression following the second shock (CPR2) was 331.5 s (SD 28.0) in the control group and 375.6 s (SD 53.7) in the INMA group, a mean difference of 44.1 s (95% CI 14.9, 73.3, $p = 0.004$). This difference persisted after adjusting for previous CPR training (adjusted mean diff. 44.0 s, 95% CI 14.1, 73.8, $p = 0.005$) (Table 3). A sensitivity analysis found that the longer time to CPR2 remained statistically significant after removing the effect due to longer pad placement.

In the first responder group, we found no significant differences in time to CPR2 (mean diff. −2.1 s, 95% CI −15.9, 11.7, $p = 0.757$). This persisted after adjusting for years of public safety experience (adjusted mean diff. −2.8 s, 95% CI −17.5, 12.0, $p = 0.704$) (Table 3).

TABLE 1 Participant characteristics.

Lay rescuer characteristics	Overall (*N* = 35)	CPR/AED (*N* = 18)	INMA/CPR/AED (*N* = 17)	*p* value
Age, median [IQR]	54.0 [30.5, 65.5]	53.5 [31.0, 65.3]	54.0 [26.0, 65.0]	0.921
Gender				0.003*
Female, *n* (%)	20 (57.1%)	6 (33.3%)	14 (82.4%)	
Male, *n* (%)	15 (42.9%)	12 (66.7%)	3 (17.6%)	
BMI, mean (SD)	26.4 (5.6)	26.1 (5.6)	26.7 (5.8)	0.757
Weekly active minutes, mean (SD)	190.1 (129.0)	238.9 (143.6)	138.5 (89.2)	0.019*
CPR training				0.582
No training, *n* (%)	9 (25.7%)	4 (22.2%)	5 (29.4%)	
Training less than 2 years ago, *n* (%)	4 (11.4%)	3 (16.7%)	1 (5.9%)	
Training more than 2 years ago, *n* (%)	22 (62.9%)	11 (61.1%)	11 (64.7%)	
Present at past cardiac arrest				0.330
No	29 (82.9%)	16 (88.9%)	13 (76.5%)	
Yes	6 (17.1%)	2 (11.1%)	4 (23.5%)	
First responder characteristics	Overall (*N* = 36)	CPR/AED (*N* = 18)	INMA/CPR/AED (*N* = 18)	*p* Value
Age, median [IQR]	31.5 [21.0, 45.0]	25.0 [21.0, 40.8]	38.5 [22.5, 45.0]	0.273
Gender				0.729
Female, *n* (%)	13 (36.1%)	6 (33.3%)	7 (38.9%)	
Male, *n* (%)	23 (63.9%)	12 (66.7%)	11 (61.1%)	
BMI, mean (SD)	27.4 (6.8)	25.8 (5.2)	29.0 (7.8)	0.159
Weekly active minutes, mean (SD)	209.8 (172.7)	236.2 (156.4)	183.3 (188.3)	0.366
Primary role				0.417
Ambulance EMT, *n* (%)	16 (44.4%)	9 (50.0%)	7 (38.9%)	
Firefighter/EMT, *n* (%)	14 (38.9%)	6 (33.3%)	8 (44.4%)	
Law enforcement, *n* (%)	3 (8.3%)	1 (5.6%)	2 (11.1%)	
Other, *n* (%)	2 (5.6%)	2 (11.1%)	0 (0%)	
Missing, *n* (%)	1 (2.8%)	0 (0%)	1 (5.6%)	
Years public safety experience				0.509
<2 years, *n* (%)	18 (50.0%)	11 (61.1%)	7 (38.9%)	
2–5 years, *n* (%)	7 (19.4%)	3 (16.7%)	4 (22.2%)	
6–10 years, *n* (%)	4 (11.1%)	2 (11.1%)	2 (11.1%)	
>10 years, *n* (%)	7 (19.4%)	2 (11.1%)	5 (27.8%)	
Years of experience in primary role				0.380
<2 years, *n* (%)	19 (52.8%)	12 (66.7%)	7 (38.9%)	
2–5 years, *n* (%)	7 (19.4%)	3 (16.7%)	4 (22.2%)	
6–10 years, *n* (%)	3 (8.3%)	1 (5.6%)	2 (11.1%)	
>10 years, *n* (%)	7 (19.4%)	2 (11.1%)	5 (27.8%)	
CPR training				0.627
Training less than 2 years ago, *n* (%)	26 (72.2%)	12 (66.7%)	14 (77.8%)	
Training more than 2 years ago, *n* (%)	9 (25.0%)	5 (27.8%)	4 (22.2%)	
Missing	1 (2.8%)	1 (5.6%)	0 (0%)	
Cardiac arrest responses in past year				0.129
0	12 (33.3%)	8 (44.4%)	4 (22.2%)	
1	7 (19.4%)	4 (22.2%)	3 (16.7%)	
2–5	9 (25.0%)	3 (16.7%)	6 (33.3%)	

(Continues)

TABLE 1 (Continued)

Lay rescuer characteristics	Overall ($N = 35$)	CPR/AED ($N = 18$)	INMA/CPR/AED ($N = 17$)	*p* value
6–10	2 (5.6%)	2 (11.1%)	0 (0%)	
>10	6 (16.7%)	1 (5.6%)	5 (27.8%)	
Performed CPR in last year, *n* (%)	19 (52.8%)	8 (44.4%)	11 (61.1%)	0.317
Used naloxone in last year, n (%)	9 (25.0%)	1 (5.6%)	8 (44.4%)	0.007*
Used AED in last year, *n* (%)	15 (41.7%)	7 (38.9%)	8 (44.4%)	0.735

Comparison of participant characteristics in both the lay rescuer and first responder trials. Median values were compared using the Wilcox Ranked Sum Test. Means and proportions were compared using an independent *t*-test or chi-square test respectively. Using $\alpha = 0.05$, significant differences between groups are indicated with an asterisk (*). BMI, body mass index; CPR, cardiopulmonary resuscitation; EMT, emergency medical technician; AED, automated external defibrillator.

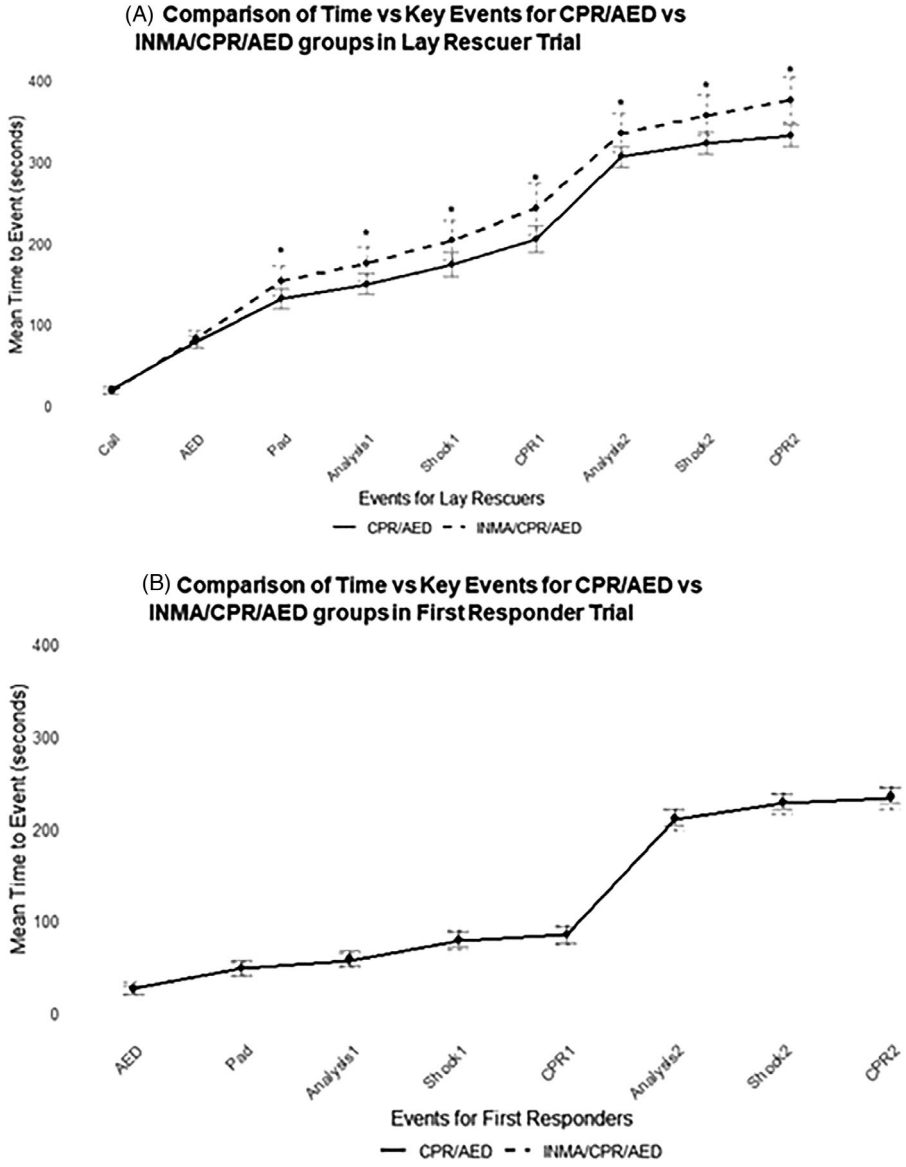

FIGURE 2 Graphs showing the timing (*y* axis) of sequential key events (*x* axis) for both the control and intervention groups in the lay rescuer (A) and first responder (B) trials. Time points with significant differences according to independent *t*-tests, using an α of 0.05 are denoted with an asterisk (*). The INMA/CPR/AED line in figure panel B directly overlaps the CPR/AED line. All times were measured from the standardized start of the scenario. Call, time to call 911; AED, time to retrieve AED; Pad, time to apply AED pads; Analysis 1, time to the first analysis; Shock 1, time to first shock; CPR1, time to initial compression following the first shock; Analysis 2, time to the second analysis; Shock 2, time to second shock; CPR2, time to initial compression following the second shock; INMA, intranasal medication administration; CPR, cardiopulmonary resuscitation; AED, automated external defibrillator.

TABLE 2 Resuscitation quality measures.

Lay rescuers Resuscitation events (seconds)	Overall ($n = 35$) Mean (SD)	CPR/AED ($n = 17$) Mean (SD)	INMA/CPR/AED ($n = 18$) Mean (SD)	Mean difference (95% CI)	*p* Value
Call	18.1 (8.2)	19.1 (9.8)	17.1 (6.1)	−2.0 (−7.7, 3.7)	0.479
AED	79.9 (16.8)	77.4 (15.5)	82.5 (18.1)	5.1 (−6.4, 16.7)	0.373
Pad	142.0 (31.7)	130.9 (23.2)	153.1 (35.8)	22.2 (1.1, 43.2)	0.040*
Analysis 1	161.1 (36.1)	149.1 (25.8)	173.9 (41.6)	24.8 (1.2, 48.5)	0.040*
Shock 1	187.8 (40.8)	173.1 (27.9)	202.5 (46.8)	29.5 (2.6, 56.4)	0.033*
CPR 1	222.5 (51.8)	204.4 (32.7)	241.6 (61.7)	37.2 (3.5, 70.9)	0.031*
Analysis 2	319.8 (40.3)	305.3 (27.2)	335.1 (46.8)	29.7 (3.6, 55.9)	0.027*
Shock 2	339.2 (42.5)	322.7 (27.4)	356.7 (49.2)	34.0 (6.8, 61.1)	0.016*
CPR 2	352.9 (47.5)	331.5 (28.0)	375.6 (53.7)	44.1 (14.9, 73.3)	0.004*
Chest compression quality metrics					
First cycle CCF (%)	55.2 (11.4)	58.3 (10.9)	51.9 (11.3)	−6.4 (−14.1, 1.2)	0.097
Second cycle CCF (%)	78.1 (6.6)	82.2 (1.8)	73.7 (7.1)	−8.4 (−12.0, −4.9)	<0.001*
Overall CCF (%)	66.2 (7.5)	69.8 (5.6)	62.4 (7.6)	−7.5 (−12.0, −2.9)	0.002*
CCR (compressions/minute)	100.0 (11.3)	104.2 (7.9)	95.1 (13.0)	−9.1 (−16.6, −1.6)	0.019*
First responders Resuscitation events (seconds)	**Overall ($n = 36$) Mean (SD)**	**CPR/AED ($n = 18$) Mean (SD)**	**INMA/CPR/AED ($n = 18$) Mean (SD)**	**Mean difference (95% CI)**	***p* Value**
AED	25.7 (11.0)	24.8 (9.1)	26.5 (12.8)	1.7 (−5.9, 9.2)	0.655
Pad	47.8 (15.4)	48.0 (16.3)	47.6 (14.8)	−0.4 (−11.0, 10.1)	0.932
Analysis 1	57.6 (15.7)	58.6 (16.3)	56.7 (15.4)	−1.9 (−12.7, 8.8)	0.716
Shock 1	78.9 (18.2)	79.2 (16.6)	78.6 (20.2)	−0.6 (−13.1, 11.9)	0.922
CPR 1	84.2 (18.8)	84.2 (17.2)	84.1 (20.8)	−0.1 (−13.1, 12.8)	0.986
Analysis 2	210.3 (19.7)	211.6 (16.5)	209.1 (22.9)	−2.6 (−16.1, 11.0)	0.704
Shock 2	227.8 (19.7)	228.7 (16.5)	226.8 (23.0)	−1.9 (−15.5, 11.6)	0.772
CPR 2	233.8 (20.1)	234.8 (16.4)	232.7 (23.6)	−2.1 (−15.9, 11.7)	0.757
Chest compression quality metrics					
First cycle CCF (%)	77.5 (10.5)	78.8 (7.4)	76.1 (13.0)	−2.64 (−9.8, 4.5)	0.459
Second cycle CCF (%)	83.5 (7.7)	83.7 (8.3)	83.2 (7.3)	−0.5 (−5.7, 4.8)	0.864
Overall CCF (%)	80.4 (8.6)	81.2 (7.3)	79.6(9.9)	−1.6 (−7.4, 4.3)	0.592
CCR (compressions/minute)	118.1 (10.9)	120.8 (11.0)	115.5 (10.5)	−5.3 (−12.6, 2.0)	0.151

Comparison of key event times and CPR quality metrics across control (CPR/AED) and experimental (INMA/CPR/AED) groups for both the lay rescuer and first responder trials. Independent *t*-tests were used to compare mean times using $\alpha = 0.05$ to assess for significance. Event times with significant differences are denoted with an asterisk (*). Call, time to call 911; AED, time to retrieve AED; Pad, time to apply AED pads; Analysis 1, time to the first analysis; Shock 1, time to first shock; CPR1, time to initial compression following the first shock; Analysis 2, time to the second analysis; Shock 2, time to second shock; CPR2, time to initial compression following the second shock; Interval 1, time from Analysis 1 to Analysis 2; Interval 2, time from Analysis 2 to end of scenario; CCF, chest compression fraction; CCR, chest compression rate; SD, standard deviation; CI, confidence interval; INMA, intranasal medication administration; CPR, cardiopulmonary resuscitation; AED, automated external defibrillator.

3.3.2 | Secondary outcomes

Among lay rescuers, there was a significant reduction in chest compression quality in the INMA group. We observed a greater detrimental effect on lay rescuer CCF during the second CPR cycle compared with the first. Among the first responders, compression quality did not differ significantly between groups, although a higher CCF during the second cycle compared with the first cycle was also observed. We found no significant CCF differences between the nontruncated dataset and the full dataset. These values are reported in Table 2. Figure 3 illustrates both individual and aggregate compression quality metrics.

3.3.3 | Intervention success

The nasal spray was administered intranasally by 15 out of 17 (88.2%) lay rescuers and 18 out of 18 (100%) first responders. Lay rescuers

TABLE 3 Effect of the addition of INMA on time to initial compression following second shock in lay rescuer and first responder trials.

Lay rescuers		
Independent variable	**Unadjusted (95% CI)**	**Adjusted (95% CI)**
Group		
CPR/AED	Reference	Reference
INMA/ CPR/AED	44.1 (14.9, 73.3)	44.0 (14.1, 73.8)
Prior CPR training		
None	Reference	Reference
Received training	−5.8 (−43.6, 32.0)	−1.7 (−35.8, 32.4)
First responders		
Independent variable	**Unadjusted (95% CI)**	**Adjusted (95% CI)**
Group		
CPR/AED	Reference	Reference
INMA/CPR/AED	−2.1 (−15.9, 11.7)	−2.8 (−17.5, 12.0)
Years of experience		
Less than 2 years	Reference	Reference
2–5 years	−4.8 (−23.5, 14.0)	−4.3 (−23.5, 15.0)
6–10 years	−6.0 (−29.3, 17.3)	−5.7 (−29.4, 18.0)
More than 10 years	4.5 (−14.3, 23.3)	5.4 (−14.2, 25.0)

INMA, intranasal medication administration; CPR, cardiopulmonary resuscitation; AED, automated external defibrillator; CI, confidence interval.

tilted the patient's head back in 12 out of 17 (70.6%) cases, while first responders did this in 10 out of 18 (55.6%) cases.

4 | LIMITATIONS

Our study has several limitations. First, the telecommunicator instruction, hands-only CPR, and personal protective equipment protocols used in this study do not represent the standard in every EMS system. CPR instructions vary based on the scripting system a telecommunicator uses,[7] and OHCA service delivery models vary considerably across American municipalities.[8–10] We tried to represent the care that might be provided by a single responder under less resourced conditions—for example a lone bystander finding someone collapsed, or, for first responders, a volunteer firefighter in a rural setting. In representing early care, we were unable to assess the INMA influence during a multirescuer response or in the presence of other clinical interventions (e.g., mechanical CPR, advanced airway). The use of a convenience sample of participants obtained from a regional participant pool limits its generalizability due to skewed demographic representation. Finally, despite randomization, there were statistically and nonstatistically significant differences between groups. Among lay rescuers, we had more females and participants were less active in the intervention group. Among first responders, participants were less experienced in the control group as evidenced by only one of them giving naloxone in the last year and a higher percentage with less than 2 years of experience. It is possible these influenced differences between groups.

5 | DISCUSSION

Results from two randomized simulation trials examining the effects of INMA on lay rescuer and first responder OHCA resuscitation quality found INMA had significant detrimental effects on the quality of lay rescuer resuscitation and no significant effects on first responder care.

Among lay rescuers administering INMA, we observed significant delays beginning with time to AED pad placement (pad time) and persisting throughout the simulation. Among lay rescuers, we observed a 22-s difference in pad time despite similar levels of previous CPR training between groups and receipt of the same telecommunicator instructions up to that point (scripts diverge at Analysis 1). The only design difference for the intervention group at that point is the INMA device clipped to the AED in a separate canvas bag (Supporting Information Appendix A), which appeared to be a factor for three lay rescuers based on video review. Video review found that the primary reason for the 22-s difference was due to the time to apply the AED pads. A sensitivity analysis confirmed a statistically significant longer time to our primary endpoint after removing the effect due to pad application. Therefore, the remaining timepoint differences may be explained by both the presence of the experimental device and the differences in instruction provided by the telecommunicator. In the lay rescuer INMA group, we also observed significant reductions in overall CCF and CCR measurements, and a significant reduction in the second cycle CCF, which suggests the instructions in the second cycle (i.e., the act of drug delivery) resulted in delay. Given the time delays and reduced compression quality observed, further implementation and usability studies are needed to determine if it is possible to streamline

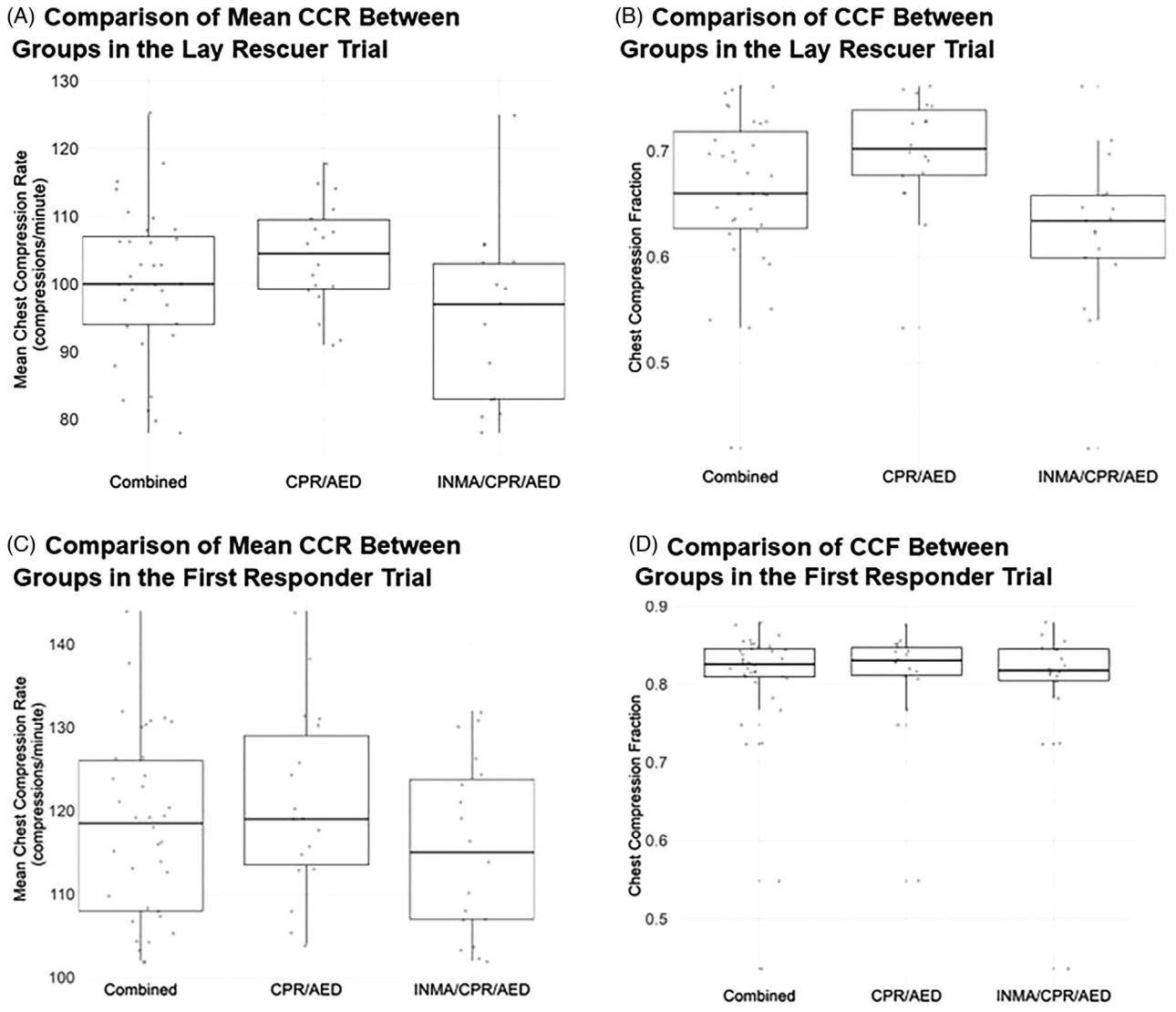

FIGURE 3 The box plots (median and IQR) above show the median and interquartile range of mean CCR and CCF for both the lay rescuer (A and B) and first responder (C and D) trials. CCR, chest compression rate; CCF, chest compression fraction; INMA, intranasal medication administration.

and improve instructions to make INMA in OHCA a feasible intervention for lay rescuers. Current use of naloxone by lay rescuers for opiate overdose suggests that the action of delivering intranasal medications in an emergency is feasible.[11–13]

In the first responder trial, the similar CPR2 time, other secondary time points, and all measures of compression quality support the notion that the earliest first responders in our prehospital systems of care can implement INMA without delaying critical interventions or reducing resuscitation quality.

When implemented without significant delays or quality detriment, such as in our first responder trial, INMA presents an opportunity to deliver resuscitation therapies earlier in the chain of survival. Intranasal insulin, insulin-like growth factor 1, salvinorin A, pyrrolidine dithiocarbamate, and exendin-4 are medications under investigation that may offer neuroprotection based on a growing body of preclinical data demonstrating neuroprotective efficacy in acute cerebral ischemia and chronic neurodegenerative diseases,[3,4,14–18] as well as limited systemic absorption and hypoglycemia.[19] Our findings suggest well-trained first responders may be able to provide intranasal therapies without undermining the quality of other critical interventions.

We found among first responders, key event intervals and compression quality measures did not significantly differ between groups with and without INMA. These results support the use of INMA by early first responders. However, INMA use by lay rescuers resulted in a longer time to the initiation of compressions following the second shock, the first event following administration of INMA, and reduced compression quality. Further studies are needed to improve usability and assess the feasibility of INMA as an intervention for lay rescuers without creating delays to CPR and defibrillation.

AUTHOR CONTRIBUTION

Stephen R. Dowker (SRD), Madison L. Downey (MLD), Brad Trumpower (BT), Debra Yake (DY), Michelle Williams (MW), Emilee Coulter-Thompson (ECT), Christine M. Brent (CMB), Graham C. Smith (GCS), David A. Berger (DAB), Robert Swor (RS), Deborah M. Rooney (DMR), Robert W. Neumar (RWN), Charles P. Friedman (CPF), James M. Cooke (JMC), and Amanda L. Missel (ALM) conceived of the study and collaboratively developed the study design. SRD, BT, RS, CPF, JMC, and ALM designed the data elements and created and maintained the database. SRD, Daniel Rizk (DR), RS, DMR, CPF, JMC, RWN, and ALM designed the analysis. SRD, DR, and ALM executed the analysis. BT, DY, MW, ECT, GCS, RS, RWN, and JMC were involved in funding acquisition. SRD, MLD, Noor K. Majhail (NKM), Isabella G. Scott (IGS), Jonah Mathisson (JM), and DY conducted the investigation and collected the data. SRD, CMB, GCS, SR, DB, DMR, CPF, JMC, and ALM reviewed the methodology. SRD, BT, MW, ECT, JMC, and ALM performed project administration. JMC provided the simulation resources. SRD, MLD, NKM, IGS, JM, JMC, and ALM cowrote the original draft. All authors provided critical review and edits in accordance with ICMJE guidelines.

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CONFLICT OF INTEREST STATEMENT

Mr. Dowker reports grant-funding from the National Institutes of Health (grant R01-HL137964), travel support from National Association of EMS Physicians (NAEMSP)/GMR Foundation, and concurrent employment as a firefighter/EMT with the Green Oak Charter Township Fire Department a licensed nontransporting Basic Life Support (BLS) agency in Michigan. Ms. Majhail and Ms. Scott report employment, during one or more phases of the study, with Emergent Health Partners, a licensed transporting Advanced Life Support (ALS) agency that serves as a regional provider of BLS/ALS medical transport and 911 dispatched emergency response in southern Michigan. Dr. Brent reports a leadership position for the Washtenaw/Livingston Medical Control Authority, she is an Air Medical Physician Association Board Member, NAEMSP Air Medical Committee Vice Chair, NAEMSP Council of EMS Fellowship Directors Vice Chair, and grant funding CMB Toyota Grant on Prehospital Medical Drones, and travel support from Air Medical Physician Association. Dr. Smith reports effort as associate medical director for the Washtenaw/Livingston Medical Control Authority, a regional EMS oversight body. Dr. Berger reports grant funding from AHRQ R01 HS025411-02BCBSM Foundation, Dr. Neumar reports the following grant support National Institutes of Health: K12HL133304, R01HL133129, R34HL130738 - Institution; Laerdal Foundation-Institution, and he is SaveMiHeart President and Board Chair, ILCOR cochair. All other authors report no relevant interests.

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DATA AVAILABILITY STATEMENT

Partial deidentified data will be made available in a data repository. Please email Dr. Missel for detailed information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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