Efficacy of nonvenous medications for acute convulsive seizures

A network meta-analysis

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ABSTRACT

Objective: This is a network meta-analysis of nonvenous drugs used in randomized controlled trials (RCTs) for treatment of acute convulsive seizures and convulsive status epilepticus.

Methods: Literature was searched according to Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines for RCTs examining treatment of acute convulsive seizures or status epilepticus with at least one of the study arms being a nonvenous medication. After demographic and outcome data extraction, a Bayesian network meta-analysis was performed and efficacy results were summarized using treatment effects and their credible intervals (CrI). We also calculated the probability of each route-drug combination being the most clinically effective for a given outcome, and provided their Bayesian hierarchical ranking.

Results: This meta-analysis of 16 studies found that intramuscular midazolam (IM-MDZ) is superior to other nonvenous medications regarding time to seizure termination after administration (2.145 minutes, 95% CrI 1.308–3.489), time to seizure cessation after arrival in the hospital (3.841 minutes, 95% CrI 2.697–5.416), and time to initiate treatment (0.779 minutes, 95% CrI 0.495–1.221). Additionally, intranasal midazolam (IN-MDZ) was adjudged most efficacious for seizure cessation within 10 minutes of administration (90.4% of participants, 95% CrI 79.4%–96.9%), and persistent seizure cessation for ≥ 1 hour (78.5% of participants, 95% CrI 59.5%–92.1%). Paucity of RCTs produced evidence gaps resulting in small networks, routes/drugs included in some networks but not others, and some trials not being connected to any network.

Conclusions: Despite the evidence gaps, IM-MDZ and IN-MDZ exhibit the best efficacy data for the nonvenous treatment of acute convulsive seizures or status epilepticus. *Neurology*® 2015;85:1859–1868

GLOSSARY

BC = buccal; **CI** = confidence interval; **CrI** = credible intervals; **DZP** = diazepam; **IM** = intramuscular; **IN** = intranasal; **LOR** = lorazepam; **MDZ** = midazolam; **OR** = odds ratio; **PLD** = paraldehyde; **PR** = rectal; **RAMPART** = Rapid Anticonvulsant Medication Prior to Arrival Trial; **RCT** = randomized controlled trial; **SL** = sublingual; **WER** = weighted event rate; **WES** = weighted effect size; **WMD** = weighted posterior median difference.

IV administration of benzodiazepines including lorazepam (LOR) and diazepam (DZP) is considered the first-line treatment for control of acute convulsive seizures and status epilepticus.^{1,2} However, in many health care environments, establishing adequate venous access may be challenging, particularly in a convulsing patient. This difficulty may be augmented by lack of supplies, nonavailability of trained personnel at the point of care including out-of-hospital settings, collapsed peripheral veins, or malnutrition-related subcutaneous edema. Hence, nonvenous routes for administration of antiseizure medications to control acute convulsive seizures and convulsive status epilepticus have been explored, including sublingual (SL), rectal (PR), intranasal (IN), buccal (BC), and intramuscular (IM) routes. The present study is a systematic review of various nonvenous routes and drugs used in randomized controlled trials (RCTs) for treatment of acute convulsive seizures and convulsive status epilepticus along with a network meta-analysis (mixed or multiple treatment comparisons) of the data.³

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METHODS Literature search and data extraction. Structured search was conducted for RCTs of treatment of acute convulsive seizures or convulsive status epilepticus where at least one of the study arms was a nonvenous medication (table e-1 on the *Neurology*[®] Web site at Neurology.org). All abstracts were screened by one of the authors (R.A.) and RCTs where the interventions seemed relevant were retained. Two authors (R.A. and H.K.) independently applied inclusion and exclusion criteria with disagreements being resolved by consensus. For eligible studies, one author (H.K.) extracted the data using a predesigned spreadsheet. Demographic and study methodology details were extracted for descriptive purposes. For each study arm, the number of participants, measured outcomes, and reported means (continuous variables) or proportions (dichotomous variables) were documented. Search results and study selection has been documented in a Preferred Reporting Items for Systematic reviews and Meta-Analyses diagram⁴ (figure e-1).

Outcome measures. The dichotomous outcome measures included the proportion of participants with the following efficacy endpoints measured from the time of drug administration: seizure cessation within 10 minutes, seizure cessation within 5 minutes, and persistent seizure cessation for at least 1 hour. We included studies with only clinical and both clinical and EEG ascertainment of seizure termination for these outcomes. Since nonvenous routes find most utility in the out-of-hospital or resource-poor settings, clinical assessment of seizure activity was a representative endpoint. Further, the duration of continued seizure cessation after drug administration was reported differently by studies, with a minimum period of 1 hour. We have interpolated the reported proportions as representing participants who were seizure-free for at least 1 hour after receiving the study medication. Continuous outcomes included time from drug administration to termination of seizures, time to cessation of seizures after arrival to the health care facility, and time taken to initiate treatment. The time to initiate treatment has been reported differently in various studies, with respect to the initial timepoint ($t = 0$), and includes time to delivery of the drug after randomization, opening of the envelope, arrival in the hospital, time to prepare and administer the drug,⁵ or time from arrival of the nurse to medication administration.⁶ The paucity of and variable definitions used for adverse events data in the RCTs makes it impossible to rigorously address differential tolerability and safety of nonvenous medications.

Data synthesis and statistical methods. Due to a variety of medications and routes used in different combinations with lack of sufficient studies for every possible pairwise comparison, a network meta-analysis was considered an appropriate methodology to synthesize the available data, and to provide an unbiased effect estimate taking into account both direct and indirect comparisons.^{3,7} We performed network meta-analyses within a Bayesian framework and summarized the treatment effects and their credible intervals (CrI). For pairwise comparisons, effect size was captured with a posterior median odds ratio (OR), which is derived from the distribution resulting from use of an assumed prior, mathematical model, and observed data. This Bayesian posterior distribution is non-normal and the appropriate measure is a median. Further, for pairwise comparisons with at least 4 available studies, we illustrated the relative strength of treatment effects using a Forest plot, and explored heterogeneity with I^2 and τ^2 statistics. We also looked at publication bias using a funnel plot. The studies with missing data or disconnected from the respective outcome network were excluded from the meta-analysis. Instead, we have directly described the treatment effects from these studies.

We assumed a binomial distribution for dichotomous outcomes with use of logit-link function in the models, and log-normal distribution for continuous time-to-event outcomes. We calculated the probability of each route–drug combination being the most clinically effective for a given outcome, the second best, and so on, and provided their relative Bayesian hierarchical ranking using the methods described in Evidence Synthesis Technical Support Documents (Decision Support Unit, UK National Institute for Health and Clinical Excellence).⁸ For fixed effects model, the common relative treatment effects were assumed for all studies. For random effects model, we assumed trial-specific relative treatment effects to come from a normal distribution with a common random effects variance for all treatment comparisons. We selected the best model based on the deviance information criteria, which provided measures of model fit.⁹ The consistency between direct and indirect evidence was performed using node splitting methods.¹⁰ To estimate the absolute treatment effects, we modeled the treatment effects of the baseline treatment independently using a fixed-effect model.⁸ The posterior distributions of the absolute treatment effect of other treatments were obtained by synthesizing the posterior samples from both the baseline treatment model and the relative treatment effects model. The analyses were performed using Just Another Gibbs Sampler (JAGS 3.2.0), which simulates Bayesian hierarchical models using Markov chain Monte Carlo method.¹¹ Noninformative priors were used for all model parameters: uniform distribution for random effects variance and normal distributions with a zero mean and very large variance for all other parameters.

RESULTS Characteristics of the included studies.

Twenty studies, published between 1997 and 2012, were eligible for the qualitative synthesis (figure e-1).^{5,6,12–29} Study participants ranged from newborns to 102 years of age, medications included LOR, DZP, midazolam (MDZ), and paraldehyde (PLD), and most studies were single-center (15/20). Four studies were excluded due to the following: not connected to the networks for any of the outcomes ($n = 2$)^{16,22} (figure 1), did not specify the number of participants allocated to each arm ($n = 1$),²¹ and did not report any of the meta-analysis outcomes ($n = 1$).¹³ Thus, 16 open-label studies were included in the quantitative synthesis, and 15/16 comprised only pediatric (≤ 18 years) participants. The methods used for randomization were either suboptimal (5/16) or not reported (2/16) in some studies (table e-2).

Seizure cessation within 10 minutes of drug administration.

Eleven studies reported this outcome with 1 being disconnected from the network (figure 1A.a).^{16,22} The route–medication combinations reported by these studies included SL-LOR, IN-LOR, BC-MDZ, IN-MDZ, PR-DZP, IV-LOR, IM-PLD, and IV-DZP (table e-3). Out of the nonvenous route–drug combinations, IN-MDZ was the best (weighted event rate [WER] 90.4%) followed by BC-MDZ (80.7%) and PR-DZP (69.9%). On pairwise comparisons, IN-MDZ was superior to PR-DZP (OR 4.420, 95% CrI 1.687–13.201). Also, BC-MDZ was superior to PR-DZP (OR 1.822, 95%

Figure 1 Bayesian network representations for individual outcomes

The size of the bubble represents the total number of participants randomized to receive a particular route-drug combination. The number by the side of a line joining 2 bubbles indicates the number of trials for that particular comparison (A.a: seizure cessation within 10 minutes of drug administration, A.b: seizure cessation within 5 minutes of drug administration, A.c: persistent seizure cessation for at least 1 hour after drug administration, B.a: time from drug administration to termination of seizure [minutes], B.b: time to cessation of seizures after arrival in hospital [minutes], B.c: time to initiate treatment [minutes]) (reference numbers in square brackets). BC = buccal; DZP = diazepam; IM = intramuscular; IN = intranasal; LOR = lorazepam; MDZ = midazolam; PR = rectal; SL = sublingual.

CrI 1.308–2.53), whereas SL-LOR was inferior to all other medications (table 1). Studies for IM-MDZ and IV-LOR were disconnected from the network, rendering this outcome uninformative for these medications. Although IN-LOR was disconnected from the network, the proportion of patients meeting the above endpoint was 78.8% (pooled event rate).

Since 4 studies compared BC-MDZ with PR-MDZ for this outcome, we performed a nested

head-to-head meta-analysis. BC-MDZ was superior to PR-DZP (random effects OR 1.78, 95% confidence interval [CI] 1.12–2.82) with trivial heterogeneity in the evidence ($I^2 = 38.9\%$, figure 2). The funnel plot did not reveal any significant impact on the conclusion about relative treatment effect, even when a “pseudostudy” was added using trim-and-fill method to adjust for funnel plot asymmetry³⁰ (figure 2).

Table 1 Relative treatment effects of pairwise comparisons expressed as posterior median odds ratio (95% credible interval), and relative ranking based on probability of being most clinically effective for dichotomous outcomes

Outcome 1A: Seizure cessation within 10 minutes of drug administration: Relative treatment effect of pairwise comparisons expressed as posterior median odds ratio (95% credible interval)

Treatment	PR-DZP	BC-MDZ	IN-MDZ	IV-DZP
BC-MDZ	1.822 (1.308, 2.53) ^a	x	x	x
IN-MDZ	4.420 (1.687, 13.201) ^a	2.441 (0.883, 7.519)	x	x
IV-DZP	7.674 (0.812, 89.264)	4.201 (0.43, 49.835)	1.684 (0.231, 15.841)	x
SL-LOR	0.332 (0.217, 0.507) ^a	0.182 (0.106, 0.31) ^a	0.075 (0.023, 0.213) ^a	0.043 (0.004, 0.43) ^a

Event rate with 95% credible intervals, rank, and probability of being the best (with respect to PR-DZP)

Treatment	Event rate (95% credible interval)	Rank	p (Best)
IV-DZP	0.915 (0.651, 0.995)	1	0.696
IN-MDZ	0.904 (0.794, 0.969)	2	0.287
BC-MDZ	0.807 (0.745, 0.859)	3	0.017
PR-DZP	0.699 (0.663, 0.734)	4	0
SL-LOR	0.436 (0.327, 0.550)	5	0

Outcome 1B: Seizure cessation within 5 minutes of drug administration: Relative treatment effect of pairwise comparisons expressed as posterior median odds ratio (95% credible interval)

Treatment	IV-DZP	BC-MDZ
BC-MDZ	0.385 (0.092, 1.293)	x
IM-MDZ	0.564 (0.068, 3.051)	1.441 (0.131, 13.353)

Event rate with 95% credible intervals, rank, and probability of being the best (with respect to IV-DZP)

Treatment	Event rate (95% credible interval)	Rank	p (Best)
IV-DZP	0.934 (0.874, 0.975)	1	0.692
IM-MDZ	0.853 (0.480, 0.984)	2	0.253
BC-MDZ	0.826 (0.535, 0.965)	3	0.055

Outcome 1C: Persistent seizure cessation for at least 1 hour after drug administration: Relative treatment effect of pairwise comparisons expressed as posterior median odds ratio (95% credible interval)

Treatment	PR-DZP	BC-MDZ
BC-MDZ	2.286 (1.602, 3.249) ^a	x
IN-MDZ	3.203 (1.24, 9.531) ^a	1.404 (0.51, 4.389)

Event rate with 95% credible intervals, rank, and probability of being the best (with respect to PR-DZP)

Treatment	Event rate (95% credible interval)	Rank	p (Best)
IN-MDZ	0.785 (0.595, 0.921)	1	0.74
BC-MDZ	0.732 (0.647, 0.805)	2	0.26
PR-DZP	0.547 (0.496, 0.598)	3	0

Abbreviations: BC = buccal; DZP = diazepam; IM = intramuscular; IN = intranasal; LOR = lorazepam; MDZ = midazolam; PR = rectal; SL = sublingual.

^a Effect estimate toward one side of the line of no effect.

Seizure cessation within 5 minutes of drug administration.

This outcome was reported by only 3 studies, 1 being disconnected from the network (figure 1A.b).¹² The route–drug combinations analyzed were SL-LOR, BC-MDZ, IM-MDZ, PR-DZP, and IV-DZP (table e-3). For the nonvenous medications, IM-MDZ had a higher WER of 85.3% compared to BC-MDZ (82.6%), though none of the pairwise comparisons was statistically significant (table 1).

Persistent seizure cessation for at least 1 hour after drug administration.

Five studies reported this outcome, 2 being disconnected from the network (figure 1A.c).^{16,22} The route–drug combinations analyzed were IN-LOR, BC-MDZ, IN-MDZ, IM-MDZ, IV-LOR, PR-DZP, and IV-DZP (table e-3). Among the nonvenous route–drug combinations, IN-MDZ had the highest WER of 78.5% followed by BC-MDZ (73.2%). In pairwise comparisons, IN-MDZ was significantly

better than PR-DZP (OR 3.203, 95% CrI 1.24–9.531) but not BC-MDZ (OR 1.404, 95% CrI 0.51–4.389, table 1). BC-MDZ was superior to PR-DZP (OR 2.286, 95% CrI 1.602–3.249). Though comparative analysis was not possible for IM-MDZ and IN-LOR, the pooled event rates were found to be 69.2% and 61.9%, respectively, for these medications.

Time from drug administration to termination of seizure. A majority of studies reported this outcome ($n = 14$). However, 2 studies were disconnected from the network (figure 1B.a),^{16,22} 3 others had missing data points,^{15,21,23} and 1 study had censored observations at 10 minutes.²⁰ The route–drug combinations analyzed were IN-MDZ, BC-MDZ, IN-LOR, IM-MDZ, IV-DZP, PR-DZP, IV-LOR, and IM-PLD (table e-3). Among the nonvenous medications, IM-MDZ was most effective, with a weighted effect size (WES) of 2.145 minutes, followed respectively by IN-MDZ (2.436 minutes), PR-DZP (3.832 minutes), and BC-MDZ (4.292 minutes). In pairwise comparisons, IM-MDZ was superior to PR-DZP (weighted posterior median

difference [WMD] -1.678 minutes, 95% CrI -2.983 to -0.178) and BC-MDZ (WMD -2.132 minutes, 95% CrI -3.638 to -0.550), but not to IN-MDZ and IV-DZP (table 2). Also, both PR-DZP (WMD 1.391 minutes, 95% CrI 0.645–2.365) and BC-MDZ (WMD 1.855 minutes, 95% CrI 0.914–3.092) were inferior to IN-MDZ (table 2). Although the 2 studies including IN-LOR were disconnected from the network, the (variance-weighted) mean time to seizure termination for IN-LOR was 6.80 minutes.

Time to termination of seizure after arrival at the health care facility. Four studies reported this outcome, all of which were included in the network, though 1 study had missing data (figure 1B.b).²¹ The route–drug combinations analyzed included IN-MDZ, IM-MDZ, and IV-DZP (table e-3). IM-MDZ was the best nonvenous medication (WES 3.841 minutes), and was superior to both IV-DZP (WMD -2.076 minutes, 95% CrI -3.199 to -0.597) and IN-MDZ (WMD -1.886 minutes, 95% CrI -3.696 to -0.048) on pairwise comparisons (table 2).

Figure 2 Forest plot and funnel diagrams for BC-MDZ and PR-DZP head-to-head comparison

Forest plot (A) for conventional head-to-head comparison between buccal (BC) midazolam (MDZ) and rectal (PR) diazepam (DZP) for seizure cessation within 10 minutes of drug administration shows minimal heterogeneity and similar relative effect compared to network meta-analysis. Funnel plots without (B) and with (C) a pseudostudy (open circle, created using trim-and-fill method to adjust for funnel plot asymmetry) shows no relevant influence on relative treatment effect of the publication bias. CI = confidence interval; OR = odds ratio.

Table 2 Relative treatment effects of pairwise comparisons expressed as posterior median difference (95% credible interval), and relative ranking based on probability of being most clinically effective for continuous outcomes

Outcome 2A: Time from drug administration to termination of seizure (minutes): Relative treatment effect of pairwise comparisons expressed as posterior median difference (95% credible interval)

Treatment	IN-MDZ	IV-DZP	PR-DZP	BC-MDZ
IV-DZP	−0.763 (−1.020, −0.479) ^a	x	x	x
PR-DZP	1.391 (0.645, 2.365) ^a	2.154 (1.345, 3.175) ^a	x	x
BC-MDZ	1.855 (0.914, 3.092) ^a	2.618 (1.619, 3.902) ^a	0.460 (−0.013, 1.038)	x
IM-MDZ	−0.292 (−1.118, 1.025)	0.472 (−0.320, 1.729)	−1.678 (−2.983, −0.178) ^a	−2.132 (−3.638, −0.550) ^a

Treatment effect with 95% credible intervals, rank, and probability of being the best (with respect to IN-MDZ)

Treatment	Effect size (95% credible interval)	Rank	p (best)
IV-DZP	1.670 (1.402, 1.996)	1	0.850
IM-MDZ	2.145 (1.308, 3.489)	2	0.150
IN-MDZ	2.436 (2.247, 2.640)	3	0.000
PR-DZP	3.832 (3.035, 4.849)	4	0.000
BC-MDZ	4.292 (3.306, 5.575)	5	0.000

Outcome 2B: Time to cessation of seizures after arrival in hospital (minutes): Relative treatment effect of pairwise comparisons expressed as posterior median difference (95% credible interval)

Treatment	IV-DZP	IN-MDZ
IN-MDZ	−0.191 (−1.321, 1.203)	x
IM-MDZ	−2.076 (−3.199, −0.597) ^a	−1.886 (−3.696, −0.048) ^a

Treatment effect with 95% credible intervals, rank, and probability of being the best (with respect to IV-DZP)

Treatment	Effect size (95% credible interval)	Rank	p (Best)
IM-MDZ	3.841 (2.697, 5.416)	1	0.9772
IN-MDZ	5.726 (4.475, 7.344)	2	0.0207
IV-DZP	5.923 (5.281, 6.645)	3	0.0021

Outcome 2C: Time to initiate treatment (minutes): Relative treatment effect of pairwise comparisons expressed as posterior median difference (95% credible interval)

Treatment	IN-MDZ	IV-DZP	PR-DZP	BC-MDZ
IV-DZP	0.797 (0.378, 1.327) ^a	x	x	x
PR-DZP	0.044 (−0.095, 0.202)	−0.753 (−1.285, −0.318) ^a	x	x
BC-MDZ	−0.212 (−0.434, 0.067)	−1.007 (−1.315, −0.768) ^a	−0.256 (−0.522, 0.043)	x
IM-MDZ	−0.415 (−0.699, 0.027)	−1.199 (−1.654, −0.793) ^a	−0.459 (−0.780, −0.005) ^a	−0.200 (−0.494, 0.176)

Treatment effect with 95% credible intervals, rank, and probability of being the best (with respect to IN-MDZ)

Treatment	Effect size (95% credible interval)	Rank	p (Best)
IM-MDZ	0.779 (0.495, 1.221)	1	0.8674
BC-MDZ	0.982 (0.755, 1.269)	2	0.1209
IN-MDZ	1.194 (1.136, 1.255)	3	0.0073
PR-DZP	1.239 (1.088, 1.409)	4	0.0040
IV-DZP	1.992 (1.565, 2.536)	5	0.0000

Abbreviations: BC = buccal; DZP = diazepam; IM = intramuscular; IN = intranasal; MDZ = midazolam; PR = rectal; SL = sublingual.

^aEffect estimate toward one side of the line of no effect.

Time taken to initiate treatment. Seven studies reported this outcome, with only 1 being disconnected (figure 1B.c).²² The route–drug combinations analyzed were IN-MDZ, BC-MDZ, IN-LOR, IM-MDZ, PR-DZP,

IV-DZP, and IM-PLD (table e-3). The best nonvenous medication was IM-MDZ (WES 0.779 minutes), followed by BC-MDZ (0.982 minutes), IN-MDZ (1.194 minutes), and PR-DZP (1.239 minutes). On

pairwise comparisons, IM-MDZ was significantly superior (allowed faster administration) compared to IV-DZP (WMD -1.199 minutes, 95% CrI -1.654 to -0.793) and PR-DZP (WMD -0.459 minutes, 95% CrI -0.780 to -0.005), but not to IN-MDZ and BC-MDZ (table 2). Additionally, both PR-DZP (WMD -0.753 minutes, 95% CrI -1.285 to -0.318) and BC-MDZ (WMD -1.007 minutes, 95% CrI -1.315 to -0.768) were superior to IV-DZP (table 2).

DISCUSSION This network meta-analysis showed that IM-MDZ is the most efficacious nonvenous medication regarding rapidity of administration and action for treatment of acute convulsive seizures and convulsive status epilepticus. IM-MDZ was the fastest nonvenous medication to terminate seizures after administration (WES 2.145 minutes, 95% CrI 1.308–3.489), and can be administered most rapidly among nonvenous drugs (WES 0.779 minutes, 95% CrI 0.495–1.221). Also, IM-MDZ was fastest to terminate seizures when measured from arrival to the health care facility (WES 3.841 minutes, 95% CrI 2.697–5.416, table 2).

IN-MDZ was the most efficacious nonvenous medication for seizure cessation within 10 minutes of drug administration, and persistent seizure cessation for at least 1 hour (table 3). More than 90% (WER 90.4%, 95% CrI 79.4%–96.9%) of patients attained seizure termination within 10 minutes of administration of IN-MDZ and nearly 80% (WER 78.5%, 95% CrI 59.5%–92.1%) sustained seizure remission for at least 1 hour (table 1). Of the 7 studies including IN-MDZ, none reported using atomizers: 3 studies used syringes (not reported whether atomizers were attached),^{21,26,28} 1 used nasal dropper,⁵ and the others did not mention their method of administration.^{14,17,27} Hence, these results for IN-MDZ should be interpreted carefully, since there is some evidence for altered absorption kinetics when an atomizer is used for nasal delivery.³¹

The Bayesian hierarchical analysis also showed BC-MDZ to be second most efficacious nonvenous medication for some of these outcomes (table 3). Notably, whereas the time to initiate treatment was not significantly different for IM-MDZ, BC-MDZ, and IN-MDZ, these drugs differed regarding time to seizure termination such that IM-MDZ and IN-MDZ were not statistically different, but both were superior to BC-MDZ in pairwise comparisons (table 2). These are important clinical considerations when prescribing a rescue medication for out-of-hospital use.

Guidelines for management of acute convulsive seizures or convulsive status epilepticus recommend IV-LOR as the first drug.^{32–34} The safety and efficacy

of IV-LOR has been demonstrated in multiple settings.^{1,16,35} In the Veterans Affairs study,¹ IV-LOR successfully stopped all clinical and electrical seizure activity within 20 minutes of administration with no recurrence for 60 minutes in 67% of patients ($n = 100$) with overt status epilepticus.¹ Recently, among children aged 3 months to 18 years, IV-LOR (97/133, 72.9%) was not found to be superior to IV-DZP (101/140, 72.1%) for cessation of convulsive status epilepticus for 10 minutes without recurrence within 30 minutes (absolute difference 0.8%, 95% CI -11.4% to 9.8%).²

While these IV medications are suitable for well-equipped emergency rooms adept at rapid vascular access and well-trained emergency response teams, there is a lack of standard recommendations regarding nonvenous route–drug combinations.^{36,37}

In the United States, PR-DZP is perhaps the most commonly prescribed nonvenous medication for use as a caregiver-administered rescue treatment of acute convulsive seizures. However, our analyses showed that it achieves seizure cessation within 10 minutes in only $\sim 70\%$ of patients, with sustained seizure cessation for ≥ 1 hour in only $\sim 55\%$ of patients, being inferior to IN-MDZ and BC-MDZ (table 1). PR-DZP was also inferior to other nonvenous medications regarding time for seizure termination and time to initiate treatment (table 2). In the community, particularly in adolescents, rectal medication may be socially embarrassing and potentially stigmatizing.

The safety and efficacy of IM-MDZ is also attested by Class I evidence from the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) study.¹³ After prehospital treatment of status epilepticus by paramedics, seizures were absent without the rescue medication on arrival to the emergency department in 329/448 (73.4%) of subjects in the IM-MDZ group compared to 282/445 (63.4%) in the IV-LOR group (absolute difference 10%, 95% CI 4.0–16.1, $p < 0.001$). While the median time to administration was significantly shorter for IM-MDZ compared to IV-LOR (1.2 vs 4.8 minutes), the termination of seizures took longer with the former (3.3 vs 1.6 minutes).¹³ For IM-MDZ, these outcomes are similar to the pooled estimates obtained in the present study (0.8 and 2.2 minutes, respectively, table 2). Adverse event rates were similar in both groups. These results together with our meta-analyses argue strongly to consider IM-MDZ as the nonvenous drug of choice for treatment of acute convulsive seizures and convulsive status epilepticus, with IN-MDZ as an alternative where IM injection is not feasible.

The limitations of this study result from evidence gaps including paucity of high-quality RCTs, variability in study populations and drug dosages, and

Table 3 Clinical efficacy ranking of nonvenous medications for given outcomes by the Bayesian network meta-analysis

Efficacy outcome	Efficacy ranking of nonvenous medications				Insufficient information to include in ranking
	1st	2nd	3rd	4th	
Seizure cessation within 10 minutes of drug administration	IN-MDZ	BC-MDZ	PR-DZP	SL-LOR	IM-MDZ, IN-LOR, IM-PLD
Seizure cessation within 5 minutes of drug administration	IM-MDZ	BC-MDZ	None	None	IN-MDZ, PR-DZP, SL-LOR
Persistent seizure cessation for at least 1 hour after drug administration	IN-MDZ	BC-MDZ	PR-DZP	None	IM-DZP, IN-LOR, SL-LOR
Time from drug administration to termination of seizure (minutes)	IM-MDZ	IN-MDZ	PR-DZP	BC-MDZ	IN-LOR, SL-LOR, IM-PLD
Time to cessation of seizures after arrival in hospital (minutes)	IM-MDZ	IN-MDZ	None	None	PR-DZP, SL-LOR, BC-MDZ
Time to initiate treatment (minutes)	IM-MDZ	BC-MDZ	IN-MDZ	PR-DZP	IN-LOR, SL-LOR, IM-PLD

Abbreviations: BC = buccal; DZP = diazepam; IM = intramuscular; IN = intranasal; LOR = lorazepam; MDZ = midazolam; PLD = paraldehyde; PR = rectal; SL = sublingual.

IV DZP and LOR were not included in the ranking.

small networks with variably disconnected studies. The meta-analysis can accommodate but cannot reconcile the scant source data. Also, all studies included in the quantitative synthesis were open-label. Certain nonvenous routes used in acute care settings, like intraosseous, are not represented due to lack of RCTs. Hence, this meta-analysis' conclusions will have the same or slightly higher level of evidence than these source RCTs. Further, in network analysis, indirect comparisons may be biased if the factors that differ across trials are effect modifiers of the response. Some studies were limited to convulsive status epilepticus while others also included relatively brief seizures. Individual studies excluded patients with prior administration of benzodiazepines,^{12,17} any antiseizure medications,^{14,16,26} signs of upper respiratory infection,¹⁴ prior IV access,^{18,28} or certain etiologies of acute symptomatic seizures.¹⁹ Although the doses of PR-DZP (0.3–0.5 mg/kg) and BC-MDZ (0.2–0.5 mg/kg, fixed 10 mg) varied across studies,^{6,19,20} the doses of IM-MDZ (0.2 mg/kg) and IN-MDZ (0.2 mg/kg) were fairly consistent.^{19,20,23,29} Also, studies have measured the time to initiate treatment differently in terms of initial reference timepoint, which can potentially bias the results. For example, the outcome can be overestimated if measured from the time of arrival in the hospital compared to if measured from time of randomization. Finally, these results only incorporated efficacy and not safety of the analyzed medications, due to variability in defining and reporting adverse events across studies. Hence, the present results should be used in conjunction with factors specific to the individual patient and the health care system.

In many health care environments, nonvenous treatment of acute convulsive seizures is highly desirable. This meta-analysis together with the RAMPART

study¹³ should encourage health care providers to consider IM-MDZ as an acceptable first choice nonvenous medication, when the IM route is feasible. IM administration may be most appropriate when used by paramedics in the field or in the hospital before IV access is established. Future availability of inexpensive, easy-to-use autoinjectors may facilitate IM administration even by nonmedical personnel in out-of-hospital settings. When the IM route is not feasible, IN-MDZ is an easily administered alternative, particularly for out-of-hospital use by nonmedical personnel. Wider use of atomizers may further improve and promote IN administration. Nonvenous formulations for treatment of seizure emergencies currently being developed are further expected to provide effective and user-friendly alternatives.³⁸

Among the various route–drug combinations used in RCTs, IM-MDZ was the most efficacious nonvenous medication for time to seizure termination after administration, and time to initiate treatment. IN-MDZ was the most efficacious nonvenous medication regarding seizure cessation within 10 minutes of administration and sustained seizure cessation for at least 1 hour. The results of this study support a practice change towards wider use of IM-MDZ and IN-MDZ in appropriate settings.

AUTHOR CONTRIBUTIONS

R.A.: concept, design, literature search, data analysis, and drafting the manuscript. H.K.: literature search, data extraction. Z.Z.: data analysis. B.H.: data analysis, critical review of the manuscript. P.S.H.: data analysis, critical review of the manuscript. T.A.G.: data analysis, critical review of the manuscript. All authors approve the final version.

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