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Efficacy of etripamil nasal spray for acute conversion of supraventricular tachycardia: A network meta-analysis

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Supraventricular tachycardia (SVT) is a major public health issue because it is common and has a considerable influence on patient health in many populations. According to epidemiological research, SVT affects around 2.25 individuals per 1000 people, with a significant female predominance of 2:1, regardless of age [1]. This syndrome, marked by an orthodromic reentry event that causes rapid heart rates, significantly raises patient morbidity, especially when effective management techniques are lacking [2]. Excluding atrial fibrillation or flutter, and multifocal atrial tachycardia, the prevalence of SVT in the general population is estimated to be 35 cases per 100,000 person-years [3]. Ultimately, the occurrence of paroxysmal supraventricular tachycardia (SVT) varies from 1 to 3 occurrences per 1000 individuals, which provides an estimated prevalence rate of 0.2%. This makes atrial fibrillation the most prevalent kind of SVT. These epidemiological findings highlight the importance of increased awareness and enhanced therapeutic strategies to reduce the impact of SVT on affected people.

In the realm of cardiovascular therapeutics, the rapid conversion of supraventricular tachycardia (SVT) to sinus rhythm has historically been a challenge, particularly in the absence of non-parenteral medication options for patients outside of healthcare settings. The development of Etripamil as a nasal spray, a short-acting calcium-channel blocker, serves as a groundbreaking intervention to bridge this significant gap. Early-phase studies have underscored its potential by demonstrating promising efficacy and safety profiles for the rapid termination of paroxysmal SVT, thus heralding a new opportunity in patient-managed care. These studies, especially the phase 2 NODE-1 trial [4], have shown that etripamil can quickly change SVT

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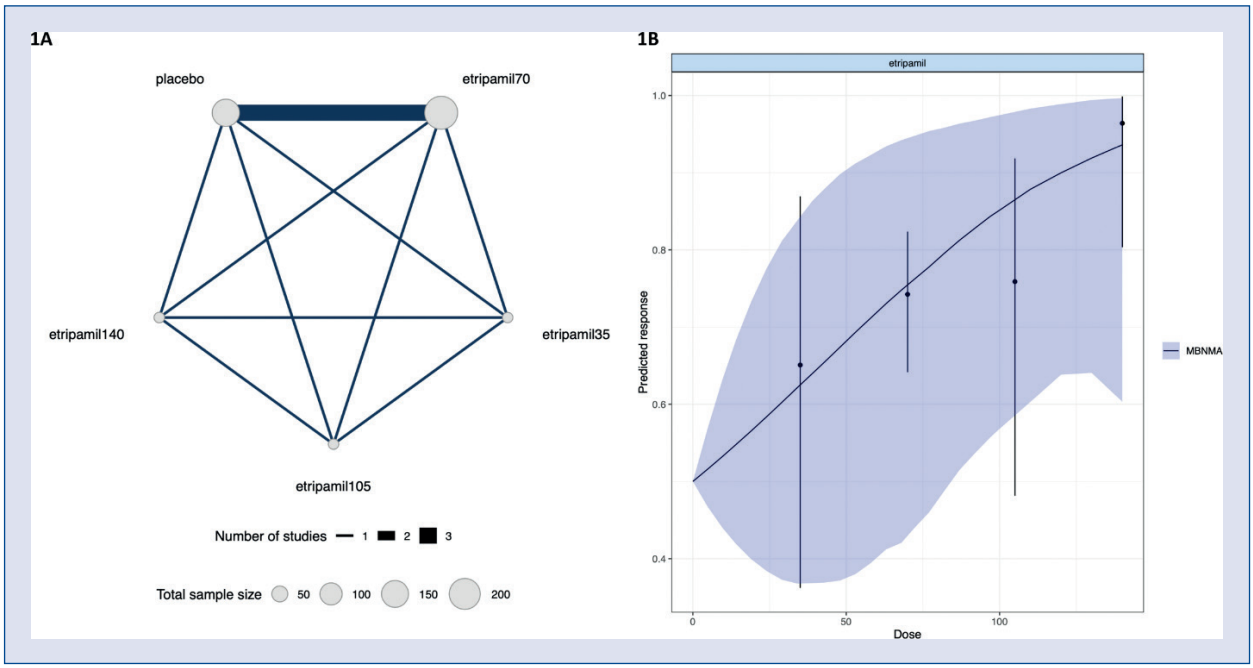

Figure 1. A. The network plot for Etripamil Nasal Spray for Acute Conversion of Supraventricular Tachycardia; **B.** Visual representation of the dose-response relationship

to sinus rhythm. Different doses have shown significant effectiveness while maintaining acceptable safety concerns. However, the determination of the most effective and safest dose for real-world application remains an area ripe for further exploration.

This research aims to conduct a comprehensive network meta-analysis (NMA) to ascertain the optimal dosing strategy for etripamil, leveraging data from multiple studies, including those previously mentioned. By employing a systematic and comparative approach, the intent was to bridge the knowledge gap surrounding the dose-efficacy relationship of etripamil, thus providing a clearer direction for its application in clinical practice.

This systematic review and NMA is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Guidelines [5] and its extension for NMA [6]. Searched databases include PubMed, Embase, Cochrane Library, and ClinicalTrials.gov up until April 2024 for randomized controlled trials (RCTs) evaluating the effects of Etripamil on either SVT. The keywords for the literature search were "etripamil" OR "MSP-2017" AND "supraventricular tachycardia" OR "SVT". The quality of the studies included were checked using the Cochrane risk of bias assessment tool (RoB-2) [7].

The NMA for treatment acceptability included 3 studies with 5 interventions and a total of 444 participants. The network plot shows that all the included interventions were well connected (Fig. 1A).

Based on the duplicate removal, title, and abstract examination processes, the present search strategy identified 86 studies, of which 74 were excluded. Nine of the remaining 12 studies were excluded because they lacked an adequate comparator or necessary data. Finally, the three studies included involved a total of 444 participants [4, 8, 9]. The included studies ranged in publication from 2018 to 2023. Node-splitting analysis of all the comparisons indicated consistency ($p > 0.05$).

Supplementary Table 1 shows the dose-ranging results comparing etripamil doses vs. the odds ratio for 15-minute acute conversion of supraventricular tachycardia. Etripamil 140 mg showed significantly higher efficacy vs. placebo, etripamil 35 mg, and 70 mg (OR 2.49, CI 1.11 to 4.36 for Etripamil 140 vs. placebo; OR 2.05, CI 0.49 to 4.17 for etripamil 140 vs. 35 mg; OR 1.48, CI 0.09 to 3.4 for etripamil 140 vs. 70 mg). Etripamil 140 mg had similar efficacy as etripamil 105 mg (OR 0.8, CI –0.09 to 2.01).

Figure 1B provides a visual representation of the dose-response relationship for etripamil, derived from a network meta-analysis (NMA), illustrating the variation in predicted response across a range of doses. The curve, marked as "MBNMA", shows an incremental increase in the effectiveness of etripamil with rising dosages.

The Surface Under the Cumulative Ranking Curve (SUCRA), a (Bayesian) summary of the rank distribution that provides the estimated proportion of treatments worse than the treatment of interest, provided results for the total effective rate of etripamil 140 mg (79.67%) > etripamil 105 mg (56.07%) > etripamil 70 mg (54.09%) > etripamil 35 mg (36.8%) > placebo (13.37%).

In conclusion, the current network meta-analysis demonstrates that the 140 mg dose of Etripamil nasal spray is a highly effective option for the rapid conversion of supraventricular tachycardia (SVT) to sinus rhythm. This finding highlights the potential of Etripamil nasal spray as a groundbreaking intervention in patient-managed care outside of healthcare settings, promising to significantly impact SVT management.

Data availability statement: The data that support the findings of this study are available on request from the corresponding author (L.S.).

Ethics statement: Not applicable.

Author contributions: Adam Macech — conceptualization, data curation, formal analysis, investigation, methodology, resources, writing original draft, writing review & editing; Nicola Luigi Bragazzi — supervision, writing review & editing; Francesco Chirico — software, supervision, writing review & editing; Basar Cander — methodology, supervision, writing review & editing; Michal Pruc — data curation, investigation, resources, writing original draft, writing review & editing; Zubaid Rafique — supervision, writing original draft, writing review & editing; William Frank Peacock — supervision, writing original draft, writing review & editing; Arash Ziapour — writing original draft, writing review & editing; Łukasz Szarpak — conceptualization, data curation, formal analysis, investigation, methodology, project administration; resources, software, validation, visualization, writing original draft, writing review & editing. Anna Salak — writing original draft, writing review & editing; Milosz J. Jaguszewski — writing original draft, writing review & editing.

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Supplementary material: Supplementary Table 1. Etripamil dose ranging league table presented as odds ratios for the acute conversion of supraventricular tachycardia in 15 minutes.

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