ISUB

ARTÍCULO DE REVISIÓN

REVISTA DE INVESTIGACIÓN EN SALUD. UNIVERSIDAD DE BOYACÁ
2023;10 (1): 112-128. doi: https://doi.org/10.24267/23897325.890

Usefulness of Midodrine for the Control of Recurrent Vasovagal Syncope: Does the Evidence Recommend it?

Yelson Alejandro Picón Jaimes[1], Diana María Toro Gómez[2], Manuela Castillo Restrepo[3], Luis Fernando Sánchez Estrada[4], Diego Fernando Cárdenas Bravo[5], Diana Marcela Acosta Agámez[6], María Alejandra Gómez Galán[7], Teosmar Jhonswaldo Chamorro Azuaje[8], María del Carmen Salcedo Pacheco[9]

Abstract

Introduction: Vasovagal syncope is the main cause of transient loss of consciousness, being an increasingly frequent reason for consultation in pediatrics and adult medicine. Midodrine, a peripherally acting alpha-receptor agonist, is mainly used in the management of orthostatic hypotension. However, it has also been evaluated in vasovagal syncope, with promising results. **Objective**: To analyze the most recent evidence on the usefulness of midodrine for the control and prevention of vasovagal syncope. **Materials and Methods**: A literature search was performed using search terms such as "Vasovagal Syncope" and "Midodrine," as well as synonyms, which were combined with Boolean operators, in 5 databases until October 2022. Original studies, systematic reviews and meta-analyses, published in both English and Spanish, were included. **Results**: Randomized controlled trials and systematic reviews and meta-analyses differ slightly between results, but these demonstrate an overall protective effect. The most recent and complete evidence shows that using this agent significantly reduces the probability of positivity when performing the tilt table test and prevents the occurrence of syncopal episodes. **Conclusions**: Although current evidence on the efficacy of midodrine with respect to the prevention and control of vasovagal syncope is limited, a significant protective effect is observed, reducing the risk of suffering syncopal episode by approximately up to 50 %. **Keywords:** midodrine; vasovagal syncope; syncope; adrenergic agents; evidence-based medicine.

Corresponding author: Yelson Alejandro Picón Jaimes. Email: colmedsurg.center@gmail.com

[1] Universidad Internacional de Valencia (Valencia, Spain). [2] Universidad del Valle (Cali, Colombia). [3] Universidad CES (Medellín, Colombia). [4] Universidad de Pamplona (Pamplona, Colombia). [5] Universidad Nacional de Colombia (Bogotá, Colombia). [6] Corporación Universitaria Rafael Núñez (Cartagena, Colombia). [7] Universidad Pedagógica y Tecnológica de Colombia (Tunja, Colombia). [8] Universidad de Carabobo (Valencia, Venezuela). [9] Universidad Libre (Barranquilla, Colombia).

How to cite this article:

Picón Jaimes YA, Toro Gómez DM, Castillo Restrepo M, Sánchez Estrada LF, Cárdenas Bravo DF, Acosta Agámez DM, Gómez Galán MA, Chamorro Azuaje TJ, Salcedo Pacheco MdelC. Utilidad de la midodrina para controlar el síncope vasovagal: ¿la recomienda la evidencia? Rev Investig Salud Univ Boyacá. 2023;10(1): 112-128. https://doi.org/10.24267/23897325.890

Date received: 25/10/2022 **Date accepted:** 19/12/2022

Utilidad de la midodrina para controlar el síncope vasovagal: ¿la recomienda la evidencia?

Resumen

Introducción: El síncope vasovagal es la principal causa de pérdida transitoria de la conciencia, y es un motivo de consulta cada vez más frecuente en pediatría y medicina del adulto. La midodrina es un agonista de los receptores alfa, de acción periférica, empleada principalmente en el manejo de la hipotensión ortostática; sin embargo, también se ha evaluado en el síncope vasovagal, con resultados prometedores.

Objetivo: Analizar la evidencia más reciente sobre la utilidad de la midodrina para el control y la prevención del síncope vasovagal.

Materiales y métodos: Se realizó una búsqueda bibliográfica utilizando términos de búsqueda como *Vasovagal Syncope y Midodrine*, así como sinónimos, que se combinaron con operadores booleanos, en cinco bases de datos, hasta octubre del 2022. Se incluyeron estudios originales, revisiones sistemáticas y metanálisis, publicados tanto en inglés como en español.

Resultados: Ensayos controlados aleatorizados y revisiones sistemáticas y metanálisis difieren ligeramente entre resultados, pero estos demuestran un efecto global protector. La evidencia más reciente y completa indica que utilizar este agente reduce significativamente la positividad al realizar la prueba de la mesa inclinada y que previene la aparición de episodios sincopales.

Conclusiones: Aunque la evidencia actual sobre la eficacia de la midodrina respecto a la prevención y control del síncope vasovagal es limitada, se observa un efecto protector significativo, porque disminuye el riesgo de sufrir un episodio sincopal, aproximadamente hasta en un 50%.

Palabras clave: midodrina; síncope vasovagal; síncope; adrenérgicos; medicina basada en la evidencia.

Utilidade da midodrina no controle da síncope vasovagal: as evidencias a recomendam?

Resumo

Introdução: a síncope vasovagal é a principal causa de perda transitória de consciência e é um motivo cada vez mais comum de consulta em pediatria e medicina de adultos. A midodrina é um agonista do receptor alfa de ação periférica usado principalmente no tratamento da hipotensão ortostática; no entanto, ela também foi avaliada na síncope vasovagal, com resultados promissores.

Objetivo: Revisar as evidências mais recentes sobre a utilidade da midodrina para o controle e a prevenção da síncope vasovagal.

Materiais e métodos: Foi realizada uma pesquisa na literatura usando termos de pesquisa como Vasovagal, Syncope e Medodrine, bem como sinônimos, que foram combinados com operadores booleanos, em cinco bancos de dados, até outubro de 2022. Foram incluídos estudos originais, revisões sistemáticas e metanálises, publicados em inglês e espanhol.

Resultados: Os ensaios clínicos randomizados, as revisões sistemáticas e as metanálises diferem ligeiramente entre os resultados, mas demonstram um efeito protetor geral. As evidências mais recentes e abrangentes indicam que o uso desse agente reduz significativamente a positividade no teste de inclinação da mesa e evita a ocorrência de episódios de síncope.

Conclusões: Embora as evidências atuais sobre a eficácia da midodrina em relação à prevenção e ao controle da síncope vasovagal sejam limitadas, observa-se um efeito protetor significativo, pois ela diminui o risco de sofrer um episódio sincopal em aproximadamente 50%.

Palavras-chave: midodrina; síncope vasovagal; síncope; adrenérgicos; medicina baseada em evidências.

INTRODUCTION

Vasovagal syncope (VVS) is the leading cause of transient loss of consciousness and is an increasingly common reason for consultation in pediatrics and adult medicine (1,2). It has been described as more frequent in women (3) during adolescence (4). Although its course is usually benign, it can persist throughout life, making its precise diagnosis at late ages difficult when established cardiovascular or cerebrovascular diseases may simulate the same clinical picture (5). Despite not being associated with mortality, VVS inherently affects the patient's quality of life and functional capacity and entails excessive costs due to the entire arsenal of diagnostic tools that must be used to reach the final diagnosis (6).

It is necessary to differentiate VVS from other syncope types, such as cardiovascular or postural (5). Cardiovascular syncope may be due to arrhythmias or structural disease, and postural syncope is caused by primary or secondary autonomic failure, hypovolemia, or drugs. VVS is part of the neurally mediated syncope (reflex syncope) group, which includes situational syncope secondary to carotid sinus involvement and other atypical forms (5). Even though the pathophysiology of VVS is not precisely known, according to what has been reported, it could be classified as neurocardiogenic syncope (7,8).

The relevance of clinically studying, investigating, preventing, and controlling this condition lies in its adverse impact on the affected individual. Atici et al. (9), Ng et al. (10), and Alhuzaimi et al. (11) evaluated the relationship between clinical manifestations, psychological conditions, and quality of life of patients with VVS. They showed that the total number of syncopal episodes is positively and significantly associated with higher levels of distress, anxiety, depression, other somatization types, and low quality of life, especially in recurrent syncope (Figure 1) (9-11).

Although the usefulness of specific conservative and invasive therapies has been assessed, they do not have the same result in all patients (perhaps due to the difficulty of accurately defining the syncope type), which can cause frustration and intensify suffering (Table 1) (5,6). Midodrine is an alpha receptor agonist with peripheral action, mainly used to manage orthostatic hypotension (12). However, it has also been evaluated in VVS with promising results. In 2022, a systematic review and meta-analysis of randomized controlled trials assessed the effectiveness of this drug in preventing recurrent VVS, obtaining significant positive results ($p < 0.001$) (13).

Figure 1. Summary of direct or indirect complications of vasovagal syncope (1,5-7).

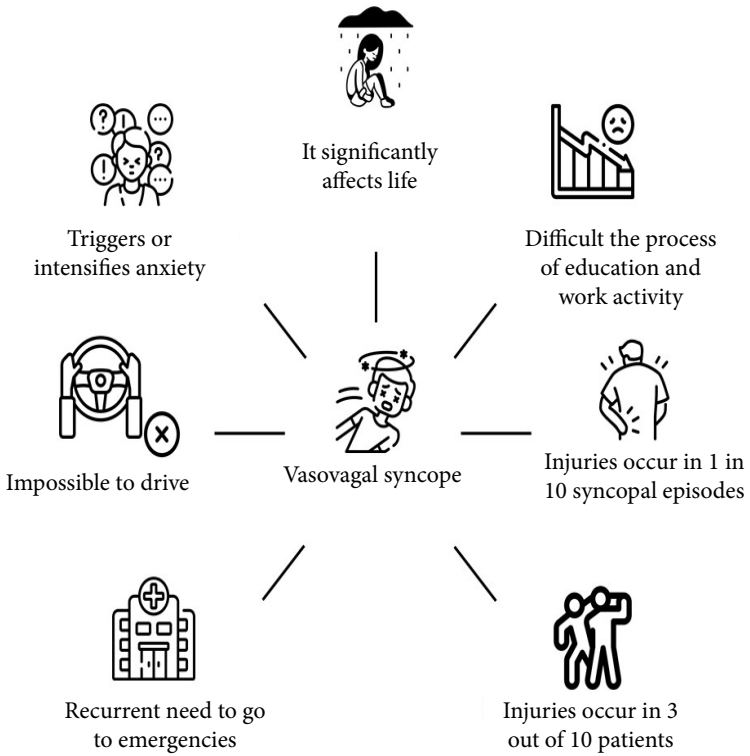

Table 1. Summary of the therapeutic options available to manage vasovagal syncope (1,5-7)

Conservative	Pharmacological	Invasive
Describe the diagnosis and mechanism that precipitates the disease	Fludrocortisone	Use of permanent pacemaker
Reassure about the favorable prognosis in terms of mortality	Midodrine	Cardioneuroablation
Explain the possibility of recurrence	Serotonin reuptake inhibitors	
Avoid possible triggers		
Increase water and salt intake (if not contraindicated)		
Practice yoga		
Practice physical activity|		

Considering the novelty and magnitude of VVS in clinical medicine and that in the Spanish-speaking literature, no reviews have synthesized evidence on the potential of this molecule and VVS, this review aims to analyze the most recent findings on the usefulness of midodrine to control and prevent VVS.

MATERIALS AND METHODS

This narrative review involved a bibliographic search using terms such as Vasovagal Syncope and Midodrine, as well as synonyms, which were combined with the Boolean operators AND and OR in search engines and databases such as Pubmed, ScienceDirect, Embase, EBSCO, and Medline, until October 2022. We defined that any article evaluating the usefulness of midodrine to control VVS would be included, even though priority was given to original studies, systematic reviews, and meta-analyses. Articles related to basic concepts about the pathophysiology of the disease were also included. They had to be available in full text. Articles published in languages other than Spanish and English would not be included. Considering the topic's limited nature and the wide variety of publications, articles published between 2000 and 2022 were included. A total of 82 potentially relevant articles were identified, with a review of their title and abstract, of which 43 were finally included after discrimination according to the inclusion and non-inclusion criteria. The estimates and calculations found were expressed in their original measurements, whether frequencies, percentages, confidence intervals *(CI)*, mean difference *(MD)*, relative risk *(RR)*, odds ratio *(OR)*, incidence rate *(IR)*, or hazard ratio *(HR)*.

RESULTS AND DISCUSSION

Pathophysiological aspects of vasovagal syncope

Little is known about the pathogenesis and pathophysiology of VVS (14). Some authors extrapolate hypotheses and mechanisms from other syncope types to those of neurocardiogenic origin (14-16). One must know the two neuromediatory pathways to understand this reflex: afferent and efferent. The former is triggered by an indistinguishable factor, which can be pain, anguish, or excitement, among others, which, accompanied by central hypotension of multifactorial origin, exacerbates an exaggerated positive chronotropic response and activates ventricular mechanoreceptors ascending to the central nervous system (15,16). At this point (efferent pathway), a parasympathetic response through the vagus nerve to the sinus and atrioventricular nodes causes an adverse chronotropic reaction and decreases heart rate. However, under some circumstances, this parasympathetic stimulus can become so profound that it causes asystole for

a few seconds while decreasing sympathetic activity (given by a dysfunction of the baroreflex or failure in the neuroendocrine response) and the vascular tone of small vessels. With this, there is a significant reduction in preload, ventricular volume, and venous return (15 -18). Cardiac output and mean arterial pressure drop, affecting the autoregulation of cerebral blood flow and triggering loss of consciousness. This process happens abruptly and transiently, preventing an effective hemodynamic and neuroendocrine response. Thus, four phases of syncope have been described: 1) early stabilization, 2) circulatory instability or presyncope), 3) terminal hypotension and syncope, and 4) recovery (19-21).

It has been proposed that the same dysfunction of the baroreflex initially causes central hypotension, as an effective neuroendocrine response to a stressor cannot be regulated (15). Since epinephrine is a potent vasoconstrictor released in these circumstances, it should theoretically help maintain hemodynamics (22). Nonetheless, because of a failure in the baroreflex, there is no control of the elevated concentrations of this hormone, producing vasodilation of the skeletal muscles and precipitating hypotension (phases 2-3), also due to the loss of control of the cardiovagal reflex (22-25). In children, adolescents, and young adults, phases 1 and 2 are slightly longer due to the sustained pattern of tachycardia and vasoconstriction (26). In older adults, the chronotropic and vascular response is poorer—perhaps due to aging and vascular oxidation—(27), and thus the presyncope phase is shortened.

Recent evidence has suggested *low blood pressure* phenotype as a predisposition to VVS (28,29) after analyzing data on the behavior of systolic and diastolic pressures of a group of individuals with VVS vs. a control group. Diastolic pressure was higher in the VVS group. Still, systolic pressure was lower (28), explaining why, in theory, these patients have a lower pulse pressure and, therefore, lower venous return and a reduced stroke volume. It has been indicated that this may occur for several reasons, including 1) low general circulatory volume, 2) failure in volume redistribution, 3) low blood pressure set point, or 4) alteration of neuroendocrine regulation (15-17). Another concept, *hypotensive susceptibility*, has been mentioned since the publication of the 2018 European Society of Cardiology Guidelines on Syncope (30). Still, it has only been related to the idiopathic mechanism of the abrupt decrease in blood pressure in the face of strong emotional events (29,30).

The role of specific neurohormones, such as catecholamines, vasopressin, endothelin-1, adrenomedullin, brain natriuretic peptide and atrial natriuretic peptide, galanin, pancreatic polypeptide, endogenous opioids, angiotensin II, serotonin,

among others, has also been discussed due to its potential link with the neurohumoral response in specific phases of VVS (17). Nevertheless, very little is still known. At this point, it can be stated that the pathophysiology of VVS is very broad and involves aspects of various systems; hence, it is complex to identify a particular alteration capable of explaining the neurocardiogenic alteration's dimension in the vasovagal reflex regulation. Despite this gap in knowledge of VVS, pharmacological therapies aimed at inhibiting or stimulating some of the phases have been proposed to prevent or control VVS, and promising results have been obtained, such as the case of midodrine. Being an alpha-adrenergic agonist, it causes vasoconstriction (regulating vessel tone) and increases peripheral vascular resistance, maintaining cardiac output and adequate cerebral perfusion pressure (cerebral autoregulation).

Evidence on the use of midodrine in the prevention and control of vasovagal syncope

In 2006, Qingyou et al. (31) carried out one of the first randomized controlled trials to evaluate the potential of midodrine in preventing VVS in children, even though it had a limited sample ($n = 26$) and a follow-up of six months. However, they found a dominant trend compared to conventional therapy ($p < 0.05$) and during the tilt table test (75 % vs. 20 %; $p < 0.05$) (31).

In 2011, Romme et al. (32) conducted the STAND trial to evaluate midodrine for recurrent VVS resistant to pharmacological therapy in 23 patients who received three-month treatment. They sought to see changes in recurrent presyncope and syncope episodes, quality of life, and adverse effects. There were no significant differences between both groups regarding the recurrence of presyncopal and syncopal episodes ($p > 0.99$ and $p = 0.22$, respectively) (32). Even when calculating the median number of presyncope and syncope episodes in the three-month treatment, these did not differ notably (0 vs. 1 and 6 vs. 8). The occurrence of adverse effects was similar in both groups (48 % vs. 57 %; $p = 0.75$), and quality of life did not improve significantly (32). So, up to this point, there was no evidence to support the use of midodrine, given the results obtained by these two trials.

Almost a decade later, Sheldon et al. (33) published the results of another multicenter trial, whose objective was to study the effectiveness of this agent in preventing VVS in 133 individuals, with a 12-month follow-up. Compared with the placebo group, those who received midodrine had fewer syncopal episodes (42 % vs. 67 %; $RR = 0.69$; 95 % CI: 0.49-0.97; $p = 0.035$). They found that the number needed to treat for prevention in a patient is 5.3. However, a longer time window was identified regarding the manifestation of the next syncopal episode (HR: 0.59; 95 %

CI: 0.37-0.96; $p = 0.035$). Adverse effects were similar in both groups. The authors then concluded that midodrine can reduce the recurrence of syncopal episodes in VVS (33).

Accordingly, Bagrul et al. (34) conducted a retrospective study reviewing the response of 24 patients to midodrine (dose of 5 mg/day) regarding the number of syncopal episodes. Compared to the number of episodes before treatment (5.75 ± 2.67), there was a significant reduction (0.42 ± 0.89) without recurrence in 17 patients (34). Thus, the trend was similar to that found in the trial by Sheldon et al. (33); however, the study's retrospective nature and the small sample are a limitation.

In 2022, Lei et al. (13) made a systematic review and meta-analysis of randomized controlled trials and found seven studies with 315 patients in which midodrine was evaluated for preventing VVS. The average age of these patients was 33 years (young adults), and approximately 70% were women. A significant reduction was noted in the probability of positivity when performing the tilt table test (*RR*: 0.37; 95% *CI*: 0.23-0.59; $p < 0.001$) and prevention in the appearance of syncopal episodes (*RR*: 0.51; 95% *CI*: 0.33-0.79; $p = 0.003$). Of note is that the overall heterogeneity of the trials was 54%. Only when analyzing two trials that reported heterogeneity of 0% there was an overall reduction in the risk of events of 29% (*RR*: 0.71; 95% *CI*: 0.53-0.95; $p = 0.02$). Thus, this meta-analysis (which would be the most complete to date) concluded that midodrine effectively prevents VVS (13).

Other results worth discussing are those achieved by Jorge et al. (35), who systematized and meta-analyzed evidence on the probability of injury during a syncopal episode. The authors included 23 studies with a total of 3,593 individuals. The tilt table test was positive in 60% of cases, and more than half of the studies reported patients with comorbidities (mainly high blood pressure). The average number of injuries found was 33.5% (95% *CI*: 27.3-40.5%), and this was correlated only with age ($p < 0.05$). In young patients, an average injury rate of 25.7% was observed vs. 43.4% in adults ≥ 50 ($p = 0.002$). Only nine studies revealed major injuries (13.9%; 95% *CI*: 9.5-19.8%). While VVS is described as a benign condition, it is necessary to consider the risks of direct morbidity and mortality for the kinematics of the trauma suffered during loss of consciousness, which may vary depending on work activity and daily life. Therefore, the current evidence, although limited, allows us to conclude that the potential of midodrine is favorable for preventing and controlling VVS, with an excellent risk-benefit balance concerning adverse effects (Table 2).

Table 2. Summary of the characteristics of the included studies on the usefulness of midodrine for the control of vasovagal syncope (13,31-34,45)

Authors	Aim	Study design	Sample size and outcome evaluated	Results
Qingyou et al. (31)	To determine whether midodrine could prevent vasovagal syncope in pediatric patients	Randomized controlled trial	Twenty-six participants were randomized into two groups (midodrine plus conventional therapy vs. conventional therapy only). They underwent a head-up tilt test and followed up for six months to measure syncopal episodes	Subjecting the participants to the test was more effective in the intervention group (75 % vs. 20 %; $p < 0.001$). Besides, the intervention group had lower syncopal episodes ($p < 0.001$)
Romme et al. (32)	To evaluate the effectiveness of midodrine in patients with recurrent vasovagal syncope resistant to pharmacological treatment	Randomized controlled trial	Twenty-three patients with at least three recurrent syncopal episodes or one severe one were randomized for three months. Recurrence, adverse effects, and quality of life were evaluated.	No significant differences were found between both groups regarding recurrence, adverse effects ($p = 0.75$), and quality of life.
Sheldon et al. (33)	To determine the effectiveness of midodrine in preventing vasovagal syncope under usual clinical conditions	Double-blind randomized controlled trial	One hundred thirty-three participants were assigned 1:1 to a midodrine vs. placebo group and followed for 12 months. The proportion of patients who had an episode at least once during follow-up was evaluated	Compared with the placebo group, midodrine reduced syncopal episodes during the follow-up period (42 % vs. 61 %). Similarly, there was a prolongation of time between episodes ($p < 0.035$)
Bagrul et al. (34)	To investigate the response to midodrine treatment in patients with refractory vasovagal syncope	Retrospective observational study	Twenty-four patients with a diagnosis of recurrent vasovagal syncope resistant to treatment. The frequency of syncopal episodes was evaluated	Before treatment, the average number of episodes was 5.75. After treatment, it was 0.42, but it only occurred in four of seven patients and only in the first three months of treatment
Lei et al. (13)	To evaluate the efficacy of midodrine in preventing syncopal episodes in patients with recurrent vasovagal syncope	Systematic review and meta-analysis of randomized controlled trials	Seven studies were included with a total of 315 patients, where the benefit of using midodrine vs. placebo or traditional treatment was assessed	It was identified that midodrine substantially reduces positivity in the head tilt test (*RR*: 0.37; $p < 0.001$). An estimated *RR* of 0.51 was found to prevent vasovagal syncope ($p = 0.003$)

Currently, the COMFORTS study (36) is underway, a randomized controlled trial that seeks both to include 1,375 patients with VVS and to evaluate the potential of midodrine and fludrocortisone on the prevention of the first syncopal episode after the start of treatment, with follow-up at 3, 6, 9 and 12 months. As secondary outcomes, it also intends to assess VVS recurrence, quality of life, and the time window between syncopal episodes.

Future perspectives

The literature review found no observational or experimental studies designed and conducted in Latin America. Lozada-Martínez et al. (37) highlighted the need for studies to understand the pathophysiological dynamics of unknown diseases, and genetic and epigenetic ecology are suspected of playing a fundamental role; that is, obtaining primary data according to sociodemographic, clinical, and test characteristics will serve as a basis for understanding the behavior of specific outcomes or unwanted effects.

At this point, it is very complex to extrapolate study results in populations that differ significantly in their genotype, phenotype, and epigenetics. Among the objectives of global health is contributing to the resolution of understudied conditions in which there is a proven considerable impact on the quality of life and functional capacity of the affected person and their environment (38). Therefore, VVS should be a line of research of interest in basic, translational, clinical, and outcome sciences in Latin America and the Caribbean, where evidence is very scarce, even knowing that many syncope phenotypes have been described as of today.

It would be interesting to study if there is a different pathological pattern that can exacerbate or control the appearance of episodes in patients with post-COVID-19 neurological or cardiovascular syndrome, in whom there is evidence of chronicity of neurological or cardiac injury and appearance of sequelae, by altering neurally mediated reactions (39-42). In 2022, the results of an international multicenter prospective study were shared, enabling the creation of the Canadian syncope risk score (43), which included 2,283 individuals with an average age of 68. This showed an area under the curve of 0.83 (95% *CI*: 0.80-0.87), which is still under discussion and validation by the academic community.

Additionally, there are novel lines of research based on translational research, which aim, through the identification of polymorphisms, to categorize the existence of phenotypes resistant or responsive to specific therapies, which would help to describe new pathophysiological mechanisms and to design new therapeutic targets (44-50). It can be stated that it is a current issue about which not much is known and on which the sociodemographic, clinical, and genotype characterization of the affected population depends greatly. Thus, tools continue to be built that allow syncope to be comprehensively addressed and the disease burden it produces to be controlled. However, there is still much to study and prove.

As limitations, we highlight that this is a narrative review, which does not include any statistical method to verify the effect measures found in the

results of the studies analyzed, so the scope of this study was reduced only to the description of the main findings in the articles. Likewise, only articles in English and Spanish were included, and gray literature was not included.

CONCLUSIONS

Although the current evidence on the effectiveness of midodrine concerning the prevention and control of VVS is limited, a significant protective effect is observed because it reduces the risk of suffering a syncopal episode by approximately 50%. However, we must also consider the indirect benefits of preventing a syncopal episode, such as the risk of trauma, functional capacity, health costs for recurrent care, and quality of life.

CONFLICTS OF INTEREST

The authors report no conflicts of interest.

REFERENCES

1. Hatoum T, Raj S, Sheldon RS. Current approach to the treatment of vasovagal syncope in adults. Intern Emerg Med. 2022;18:23-30. https://doi.org/10.1007/s11739-022-03102-w

2. Tao C, Cui Y, Zhang C, Liu X, Zhang Q, Liu P, et al. Clinical efficacy of empirical therapy in children with vasovagal syncope. Children (Basel). 2022;9(7):1065. https://doi.org/10.3390/children9071065

3. Sheldon RS, Sheldon AG, Connolly SJ, Morillo CA, Klingenheben T, Krahn AD, et al. Age of first faint in patients with vasovagal syncope. J Cardiovasc Electrophysiol. 2006;17(1):49-54. https://doi.org/10.1111/j.1540-8167.2005.00267.x

4. Deveau AP, Sheldon R, Maxey C, Ritchie D, Doucette S, Parkash R. Sex Differences in vasovagal syncope: a post hoc analysis of the prevention of syncope trials (POST) I and II. Can J Cardiol. 2020;36(1):79-83. https://doi.org/10.1016/j.cjca.2019.10.008

5. Aydin MA, Salukhe TV, Wilke I, Willems S. Management and therapy of vasovagal syncope: a review. World J Cardiol. 2010;2(10):308-15. https://doi.org/10.4330/wjc.v2.i10.308

6. Vaddadi G, Corcoran SJ, Esler M. Management strategies for recurrent vasovagal syncope. Intern Med J. 2010;40(8):554-60. https://doi.org/10.1111/j.1445-5994.2010.02295.x

7. Raj SR, Coffin ST. Medical therapy and physical maneuvers in the treatment of the vasovagal syncope and orthostatic hypotension. Prog Cardiovasc Dis. 2013;55(4):425-33. https://doi.org/10.1016/j.pcad.2012.11.004

8. Malave B, Vrooman B. Vasovagal reactions during interventional pain management procedures-a review of pathophysiology, incidence, risk factors, prevention, and management. Med Sci (Basel). 2022;10(3):39. https://doi.org/10.3390/medsci10030039

9. Atici A, Asoglu R, Demirkiran A, Serbest NG, Emektas B, Sarikaya R, et al. The relationship between clinical characteristics and psychological status and quality of life in patients with vasovagal syncope. North Clin Istanb. 2020;7(3):237-45. https://doi.org/10.14744/nci.2020.93753

10. Ng J, Sheldon RS, Ritchie D, Raj V, Raj SR. Reduced quality of life and greater psychological distress in vasovagal syncope patients compared to healthy individuals. Pacing Clin Electrophysiol. 2019;42(2):180-8. https://doi.org/10.1111/pace.13559

11. Alhuzaimi A, Aljohar A, Alhadi AN, Aljenedil A, Hersi AS. Psychiatric traits in patients with vasovagal and unexplained syncope. Int J Gen Med. 2018;11:99-104. https://doi.org/10.2147/IJGM.S157335

12. Carretero Colomer M. Midodrina. Offarm [internet]. 2008;27(4):112-3. Disponible en: https://www.elsevier.es/es-revista-offarm-4-articulo-midodrina-13120074

13. Lei LY, Raj SR, Sheldon RS. Midodrine for the prevention of vasovagal syncope: a systematic review and meta-analysis. EP Europace. 2022;24(7):1171-8. https://doi.org/10.1093/europace/euab323

14. Jeanmonod R, Sahni D, Silberman M. Vasovagal episode. En: StatPearls [internet]. Treasure Island (FL): StatPearls Publishing; 2022 [citado 2022 jul 18]. Disponible en: https://www.ncbi.nlm.nih.gov/books/NBK470277/

15. Jardine DL, Wieling W, Brignole M, Lenders JWM, Sutton R, Stewart J. The pathophysiology of the vasovagal response. Heart Rhythm. 2018;15(6):921-9. https://doi.org/10.1016/j.hrthm.2017.12.013

16. Gert van Dijk J, van Rossum IA, Thijs RD. The pathophysiology of vasovagal syncope: novel insights. Autonomic Neurosci. 2021;236:102899. https://doi.org/10.1016/j.autneu.2021.102899

17. Benditt DG, Gert van Dijk J, Krishnappa D, Adkisson WO, Sakaguchi S. Neurohormones in the pathophysiology of vasovagal syncope in adults. Front Cardiovasc Med. 2020;7:76. https://doi.org/10.3389/fcvm.2020.00076

18. Stewart JM, Medow MS, Sutton R, Visintainer P, Jardine DL, Wieling W. Mechanisms of vaso-

vagal syncope in the young: reduced systemic vascular resistance versus reduced cardiac output. J Am Heart Assoc. 2017;6(1):e004417. https://doi.org/10.1161/JAHA.116.004417

19. Wieling W, Jardine DL, de Lange FJ, Brignole M, Nielsen HB, Stewart J, et al. Cardiac output and vasodilation in the vasovagal response: an analysis of the classic papers. Heart Rhythm. 2016;13(3):798-805. https://doi.org/10.1016/j.hrthm.2015.11.023

20. Malamud-Kessler C, Bruno E, Chiquete E, Sentíes-Madrid H, Campos-Sánchez M. Pathophysiology of neurally-mediated syncope. Neurología (English Edition). 2016;31(9):620-7. https://doi.org/10.1016/j.nrleng.2014.04.015

21. Hainsworth R. Pathophysiology of syncope. Clin Autonom Res. 2004;14(S-1):I/18-I/24. https://doi.org/10.1007/s10286-004-1004-2

22. Gelman S, Mushin PS. Catecholamine-induced changes in the splanchnic circulation affecting systemic hemodynamics. Anesthesiology. 2004;100:434-9. https://doi.org/10.1097/00000542-200402000-00036

23. Zhang R, Behbehani K, Crandall C, Zuckerman J, Levine B. Dynamic regulation of heart rate during acute hypotension: new insight into baroreflex function. Am J Physiol Heart Circ Physiol. 2000;280:H407-9. https://doi.org/10.1152/ajpheart.2001.280.1.H407

24. Ocon A, Medow M, Taneja I, Stewart J. Respiration drives phase synchronization between blood pressure and RR interval following loss of cardiovagal baroreflex during vasovagal syncope. Am J Physiol Heart Circ Physiol. 2010;300:H527-40. https://doi.org/10.1152/ajpheart.00257.2010

25. Iwase S, Mano T, Kamiya A, Niimi Y, Qi Fu, Suzumura A. Syncopal attack alters the burst properties of muscle sympathetic nerve activity in humans. Auton Neurosci. 2002;95:141-5. https://doi.org/10.1016/s1566-0702(01)00362-9

26. de Jong-de Vos van Steenwijk CCE, Wieling W, Harms MPM, Wesseling KH. Variability of nearfainting responses in healthy 6-16-year-old subjects. Clin Sci (Lond). 1997;93:205-11. https://doi.org/10.1042/cs0930205

27. Fu Q, Verheyden B, Wieling W, Levine BD. Cardiac output and sympathetic vasoconstrictor responses during upright tilt to presyncope in healthy humans. J Physiol. 2012;590:1839-48. https://doi.org/10.1113/jphysiol.2011.224998

28. Brignole M, Rivasi G, Sutton R, Kenny RA, Morillo CA, Sheldon R, et al. Low-blood pressure phenotype underpins the tendency to reflex syncope. J Hypertens. 2021;39(7):1319-25. https://doi.org/10.1097/HJH.0000000000002800

29. Sutton R, Brignole M. Twenty-eight years of research permit reinterpretation of tilt-testing: hypotensive susceptibility rather than diagnosis. Eur Heart J. 2014;35(33):2211-2. https://doi.org/10.1093/eurheartj/ehu255

30. Brignole M, Moya A, de Lange FJ, Deharo JC, Elliott PM, Fanciulli A, et al. 2018 ESC Guidelines for the diagnosis and management of syncope. Eur Heart J. 2018;39(21):1883-1948. https://doi.org/10.1093/eurheartj/ehy037

31. Qingyou Z, Junbao D, Chaoshu T. The efficacy of midodrine hydrochloride in the treatment of children with vasovagal syncope. J Pediatr. 2006;149(6):777-80. https://doi.org/10.1016/j.jpeds.2006.07.031

32. Romme JJ, van Dijk N, Go-Schön IK, Reitsma JB, Wieling W. Effectiveness of midodrine treatment in patients with recurrent vasovagal syncope not responding to non-pharmacological treatment (STAND-trial). Europace. 2011;13(11):1639-47. https://doi.org/10.1093/europace/eur200

33. Sheldon R, Faris P, Tang A, Ayala-Paredes F, Guzman J, Marquez M, et al. Midodrine for the prevention of vasovagal syncope: a randomized clinical trial. Ann Intern Med. 2021;174(10):1349-1356. https://doi.org/10.7326/M20-5415

34. Bagrul D, Ece I, Yılmaz A, Atik F, Kavurt AV. Midodrine treatment in children with recurrent vasovagal syncope. Cardiol Young. 2021;31(5):817-21. https://doi.org/10.1017/S1047951120004746

35. Jorge JG, Raj SR, Teixeira PS, Teixeira JAC, Sheldon RS. Likelihood of injury due to vasovagal syncope: a systematic review and meta-analysis. Europace. 2021;23(7):1092-99. https://doi.org/10.1093/europace/euab041

36. Aminorroaya A, Tavolinejad H, Sadeghian S, Jalali A, Alaeddini F, Emkanjoo Z, et al. Comparison of outcomes with midodrine and fludrocortisone for objective recurrence in treating syncope (COMFORTS trial): rationale and design for a multi-center randomized controlled trial. Am Heart J. 2021;237:5-12. https://doi.org/10.1016/j.ahj.2021.03.002

37. Lozada-Martínez ID, Suarez-Causado A, Solana-Tinoco JB. Ethnicity, genetic variants, risk factors and cholelithiasis: the need for eco-epidemiological studies and genomic

analysis in Latin American surgery. Int J Surg. 2022;99:106589. https://doi.org/10.1016/j.ijsu.2022.106589

38. Mass-Hernández LM, Acevedo-Aguilar LM, Lozada-Martínez ID, Osorio-Agudelo LS, Maya-Betancourth JGEM, Paz-Echeverry OA, et al. Undergraduate research in medicine: a summary of the evidence on problems, solutions and outcomes. Ann Med Surg (Lond). 2022;74:103280. https://doi.org/10.1016/j.amsu.2022.103280

39. Lozada-Martínez ID, Díaz-Castillo OJ, Pearson-Arrieta AC, Galeano-Buelvas A, Moscote-Salazar LR. Post-COVID 19 neurological syndrome: a new risk factor that modifies the prognosis of patients with dementia. Alzheimers Dement. 2022;18(3):542-3. https://doi.org/10.1002/alz.12459

40. Rodríguez-Hernández YA, Villamizar-Gómez FJ, Mantilla-Pardo JC, Robledo-Arias JS, Rahman S, Lozada-Martínez ID, et al. Post-COVID 19 neurological syndrome: the need to define a cut-off score between the acute and post-COVID 19 phases. Ann Med Surg (Lond). 2021;71:102983. https://doi.org/10.1016/j.amsu.2021.102983

41. Lozada-Martínez ID, Pava-Barrios GA, Yoli-Garrido A, Leal-Buitrago A, Rodríguez-Medina N. Post-COVID-19 cardiovascular syndrome: what does the evidence tell us? J Pract Cardiovasc Sci. 2022;8:65-7. https://doi.org/10.4103/jpcs.jpcs_69_21

42. Lozada-Martínez ID, Torres-Llinás DM, Moscote-Salazar LR. Myocardial lesion in patients with COVID-19: not all is in the lung. J Taibah Univ Med Sci. 2021;16(2):303-4. https://doi.org/10.1016/j.jtumed.2021.01.006

43. Zimmermann T, du Fay de Lavallaz J, Nestelberger T, Gualandro DM, Lopez-Ayala P, Badertscher P, et al. International validation of the canadian syncope risk score: a cohort study. Ann Intern Med. 2022;175(6):783-94. https://doi.org/10.7326/M21-2313

44. Xia G, Jin JF, Ye Y, Wang XD, Hu B, Pu JL. The effects of ALDH2 Glu487Lys polymorphism on vasovagal syncope patients undergoing head-up tilt test supplemented with sublingual nitroglycerin. BMC Cardiovasc Disord. 2022;22(1):451. https://doi.org/10.1186/s12872-022-02901-5

45. Wang Y, Wang Y, He B, Tao C, Han Z, Liu P, et al. Plasma human growth cytokines in children with vasovagal syncope. Front Cardiovasc Med. 2022;9:1030618. https://doi.org/10.3389/fcvm.2022.1030618

46. Li L, Zhao H, Ma X, Jiao F, Lin J. Calcitonin gene-related peptide predicts therapeutic response to midodrine hydrochloride in children with vasovagal syncope. Front Neurosci. 2022;16:1026539. https://doi.org/10.3389/fnins.2022.1026539

47. Raj SR, Sheldon RS. Vasovagal syncope: treat the patient, and not just the disease. Auton Neurosci. 2022;243:103035. https://doi.org/10.1016/j.autneu.2022.103035

48. Titov B, Matveeva N, Kulakova O, Baulina N, Bazyleva E, Kheymets G, et al. Vasovagal syncope is associated with variants in genes involved in neurohumoral signaling pathways. genes (Basel). 2022;13(9):1653. https://doi.org/10.3390/genes13091653

49. Wang C, Chen L, Sun C, Zhang Y, Cao C, Ma Y, et al. Prevention of blood donation-related vasovagal response by applied muscle tension: a meta-analysis. J Int Med Res. 2022;50(9):3000605221121958. https://doi.org/10.1177/03000605221121958

50. Lazurova Z, Mitro P, Popovnakova M. The role of adenosine and its degradation enzymes - adenosinedeaminase and adenosinekinase in pathogenesis of vasovagal syncope. Eur J Intern Med. 2022;105:77-81. https://doi.org/10.1016/j.ejim.2022.08.037