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ORIGINAL

Mortality in mechanical ventilation in prone position in patients with acute respiratory distress syndrome

Mortalidad en ventilación mecánica en posición prono en pacientes con síndrome de distres respiratorio aguda

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ABSTRACT

Introduction: prone ventilation has been shown to improve oxygenation and lung mechanics in patients with acute respiratory distress syndrome, but I consider it necessary to delve deeper into the relationship between the prone position and mortality. Objectives: To evaluate whether the prone position decreases the risk of mortality in adult patients with acute respiratory distress syndrome vs. supine ventilation, in a global and segmented manner, as well as to know the main adverse effects related to it.
Method: a meta-analysis of randomized controlled clinical trials comparing patients in the prone vs. supine position was performed with a search in Pubmed, Embase, Cochrane Library and LILACS, and mortality, hospital stay, days of mechanical ventilation and adverse effects were evaluated.
Results: seven randomized controlled clinical trials were included in the analysis. The prone position showed a non-significant tendency to decrease mortality when analyzed globally. When stratified by subgroups, a significant decrease in the risk of mortality was found in patients: 1) ventilated with low tidal volume, 2) prolonged prone position, and 3) established before 48 hours of disease progression in severe hypoxemia. The adverse effects related to prone position were the development of pressure ulcers and orotracheal tube obstruction.
Conclusion: prone position ventilation is a safe strategy and reduces mortality in patients with severe oxygenation impairment. It should be established early, for prolonged periods, and associated with a protective ventilation strategy.

Keywords: Respiratory Distress Syndrome; Adult; Prone Position; Meta-Analysis.

RESUMEN

Introducción: la ventilación en posición prona ha demostrado mejorar la oxigenación y la mecánica pulmonar en pacientes con síndrome de dificultad respiratoria aguda pero considero necesario profundizar sobre la relación entre la posición prono y la mortalidad.
Objetivos: evaluar si la posición en prono disminuye el riesgo de mortalidad en pacientes adultos con síndrome de distres respiratorio agudo vs. ventilación en posición supina, de manera global y segmentada así como también conocer los principales efectos adversos relacionados con la misma.
Método: se realizó un metaanálisis de ensayos clínicos controlados aleatorizados que compararon pacientes en posición prona vs. Supina con búsqueda en Pubmed, Embase, Cochrane Library y LILACS.y se evaluó la mortalidad, estancia hospitalaria, días de ventilación mecánica y efectos adversos.
Resultados: siete ensayos clínicos controlados aleatorizados fueron incluidos en el análisis. La posición prono mostró una tendencia no significativa a disminuir la mortalidad al analizarlo de manera global. Al estratificar

por subgrupos se encontró una disminución significativa en el riesgo de mortalidad en pacientes: 1) ventilados con volumen corriente bajo, 2) pronación prolongada y 3) instauración antes de 48h de evolución de la enfermedad en hipoxemia severa. Los efectos adversos relacionados con la pronación fueron el desarrollo de úlceras por presión y la obstrucción del tubo orotraqueal.
Conclusión: la ventilación en posición prono es una estrategia segura y disminuye la mortalidad en los pacientes con compromiso severo de la oxigenación, debe ser instaurada tempranamente, durante periodos prolongados y asociada a una estrategia de ventilación protectora.

Palabras clave: Síndrome de Dificultad Respiratoria del Adulto; Posición Prona; Metaanálisis.

INTRODUCTION

Sodium-glucose cotransporter 2 (SGLT2) inhibitors have become innovative in treating type 2 diabetes. Not only do they directly impact blood glucose control, but they have also been shown to reduce long-term complications related to the disease. These drugs block glucose reabsorption in the renal tubules, resulting in decreased plasma glucose levels and additional calorie loss that promotes weight loss. This mechanism of action represents a novel strategy compared to traditional treatments that focus primarily on insulin and its metabolism.[1]

The effect of SGLT2 inhibitors on reducing cardiovascular risk has been particularly noteworthy. Research has revealed that these drugs can significantly reduce the incidence of events such as heart attacks, strokes, and cardiovascular mortality, especially in patients with a history of cardiovascular disease. This is crucial, given that patients with type 2 diabetes have a significantly higher risk of cardiovascular events.[2]

SGLT2 inhibitors have also marked a significant advance in managing renal complications in patients with type 2 diabetes. Clinical studies have shown that, in addition to improving kidney function through direct protective mechanisms, these drugs reduce the progression to end-stage kidney disease, a development of great relevance in nephrology.[3,4]

In addition to these benefits, SGLT2 inhibitors have positively influenced overall mortality. Extensive clinical studies, such as EMPA-REG OUTCOME and DAPA-HF, have shown that their use is associated with a decrease in both total and cardiovascular mortality, representing a significant advance in terms of survival and quality of life for patients with type 2 diabetes.[5,6]

However, although SGLT2 inhibitors are generally well tolerated, they also present certain risks. A higher incidence of urinary tract and genital infections has been documented, as well as an increase in cases of diabetic ketoacidosis, especially in situations of metabolic stress or when the dosage is not adequate. In addition, some studies have reported an increased risk of lower limb amputations, which has sparked debate about their use in patients at high risk of peripheral vascular complications.[7,8]

In summary, SGLT2 inhibitors represent a class of drugs with great potential in treating type 2 diabetes, providing benefits beyond simple glucose control. Although current evidence supports their use in several clinical settings, further research is essential to refine their application and optimally manage the associated risks. As more data are collected and clinical experience expands, it will be possible to refine guidelines and recommendations on their safest and most effective use.[9,10,11]

General objective

To analyze the therapeutic impact of sodium-glucose cotransporter 2 (SGLT2) inhibitors in the treatment of type 2 diabetes, considering their benefits in glycemic control, cardiovascular and renal protection, as well as their potential risks, in order to assess their role in the comprehensive management of this disease.

What is the clinical impact of sodium-glucose cotransporter type 2 (SGLT2) inhibitors in the comprehensive treatment of type 2 diabetes, considering their cardiovascular, renal, and mortality benefits and the risks associated with their use?

METHOD

Study design

This study was conducted as a systematic review and meta-analysis of randomized controlled trials (RCTs) to evaluate the efficacy of SGLT2 inhibitors in patients with type 2 diabetes. The studies were reviewed and analyzed manually to ensure a rigorous and comprehensive process.

Study Search

A comprehensive search was conducted in the PubMed and Cochrane databases. The search strategy focused on randomized controlled trials published since 2009, using search terms such as “SGLT2 inhibitors,” “type 2 diabetes,” and “cardiovascular risk.” Studies published in English, Spanish, and Portuguese were included.

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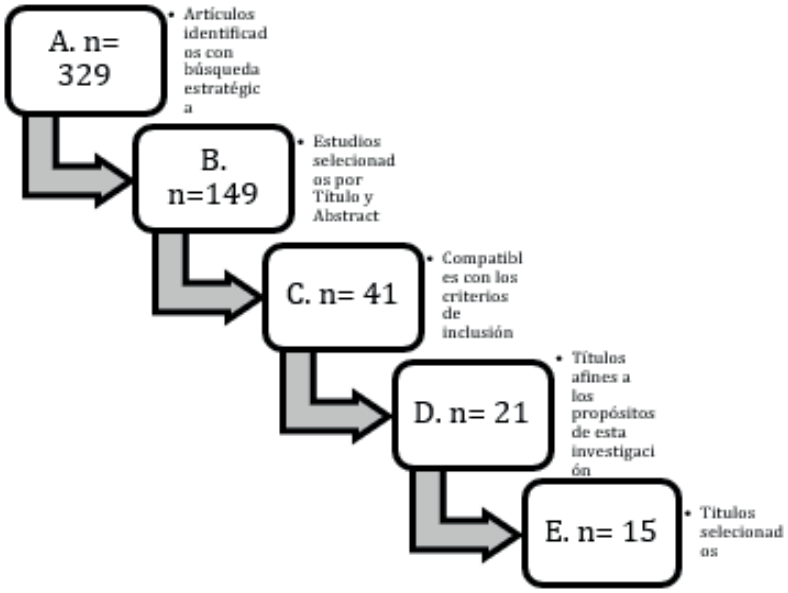

Figure 1. Process for identifying included studies

Inclusion Criteria

- Randomized controlled trials (RCTs), systematic reviews, meta-analyses, and clinical studies.
- Studies that included adults (≥18 years) diagnosed with type 2 diabetes.
- Research that evaluated the use of SGLT2 inhibitors.
- Studies that used standardized methods to measure glycemic and cardiovascular outcomes.
- Publications in peer-reviewed journals from 2009 to 2024, with no language restrictions.

Exclusion Criteria

- Non-randomized or uncontrolled studies.
- Research conducted in animals or pediatric populations.
- Studies that did not report standardized measures of glycemic and cardiovascular outcomes.

Study Variables

- Glycated hemoglobin (HbA1c): Quantitative variable, measured as a percentage (%).
- Major adverse cardiovascular events (MACE): Qualitative variable (presence/absence), number of events reported.
- Renal function (e.g., glomerular filtration rate): Quantitative variable, measured in mL/min/1,73 m^2.
- Blood Pressure: Quantitative variable, measured in millimeters of mercury (mmHg).
- Body Weight: Quantitative variable, measured in kilograms (kg).
- Adverse Events: Qualitative variable (presence/absence), number of events per patient.

Quality Assessment and Data Analysis

An initial manual review of titles and abstracts was conducted to exclude irrelevant studies. This was followed by a detailed evaluation of the full texts of the selected studies based on predefined criteria. The information was collected and organized using a data extraction form. The results were analyzed using descriptive statistics to estimate the efficacy and safety of SGLT2 inhibitors in the treatment of type 2 diabetes and cardiovascular risk reduction.

RESULTS

A comprehensive search of various databases Participant Characteristics

A total of 950 432 people participated in the included studies, all diagnosed with type 2 diabetes and various cardiovascular risk profiles. The mean age of the participants ranged from 50 to 70 years. In most studies, approximately 40 % to 65 % of individuals had established atherosclerotic cardiovascular disease. In addition, some studies also included individuals with cardiovascular risk factors but without established disease, as observed in one study where 59,4 % of participants had these factors without prior cardiovascular disease.[12,13]

Reduction in HbA1c

Regarding glycemic control, the reduction in HbA1c levels varied among the studies reviewed. In one of the trials, a 0,74 % decrease was observed compared to the placebo group.[14,15] On the other hand, a meta-analysis showed that patients treated with SGLT2 inhibitors experienced an average reduction of 0,91 %.[16,7,18] Another study found a reduction of 0,79 %, highlighting that patients with higher baseline HbA1c levels achieved a greater decrease during treatment. Overall, studies showed a lower HbA1c in the 0,42 % to 1,2 % range, with a more minor impact in those without prior cardiovascular disease.[19]

Cardiovascular Risk

Decreased cardiovascular risk was a consistent finding in most studies. In a clinical trial, a 23 % reduction in the combination of events such as cardiovascular death or hospitalization for heart failure was reported.[20] A meta-analysis indicated that the reduction in cardiovascular risk was also 23 %, with a more pronounced effect in patients who already had cardiovascular disease.[21] Another study revealed that cardiovascular mortality decreased by 38 % in patients treated with empagliflozin, while another meta-analysis reported a 26 % decrease in cardiovascular mortality in high-risk individuals.[22,23]

Blood pressure (SBP/DBP)

The studies reviewed also showed moderate effects on blood pressure. One trial reported a decrease of 4,2 mmHg in systolic blood pressure (SBP) and 1,8 mmHg in diastolic blood pressure (DBP) (Fitchett, 2017). Similarly, another meta-analysis reported an average decrease of 4,5 mmHg in SBP (Palmer, 2021). A reduction of 4,0 mmHg in SBP was observed in a third study, although some studies reported no significant changes in DBP.

Body weight

Weight reduction was a consistent finding in studies evaluating this parameter. One trial showed that patients treated with SGLT2 inhibitors experienced an average reduction of 2,63 kg at 24 weeks of follow-up.[25] In another study, weight loss was 2,2 kg,[26] while a meta-analysis indicated an average reduction of 2,6 kg.[20] In several studies, weight loss ranged from 1,6 kg to 3,0 kg, most of the reduction observed in the first months of treatment.

Adverse Events

Genitourinary infections and diabetic ketoacidosis were the most common adverse events reported. One study showed that genital infections increased by 2 % compared to placebo.[27] On the other hand, a meta-analysis identified an increased risk of diabetic ketoacidosis in some observational studies.[28] Apart from these events, studies concluded that SGLT2 inhibitors were generally well tolerated, with no other significant adverse effects reported.

Renal Results

Renal outcomes showed that disease progression slowed in several of the studies reviewed. In one clinical trial, a 35 % reduction in hospitalization for heart failure and a notable improvement in renal function were reported.[29] A meta-analysis showed a 45 % reduction in progression to end-stage renal disease,[30] while another study reported a 40 % decrease in the risk of developing end-stage renal failure.[11] Overall, SGLT2 inhibitors provided significant renal protection in patients with type 2 diabetes and cardiovascular risk.

DISCUSSION

This systematic review confirms the value of SGLT2 inhibitors in treating type 2 diabetes, especially in cardiovascular risk reduction and renal protection. Previous studies have reported these effects, and our review reinforces that evidence without claiming to present revolutionary findings. Our findings are consistent with the existing literature. For example, the EMPA-REG OUTCOME study had already shown a significant 38 % reduction in cardiovascular mortality with the use of empagliflozin, which we also observed in several reviewed studies, with reductions ranging from 23 % to 38 %, depending on the risk profile of the patients.[15,19,20] The benefits appear to be more pronounced in patients with prior cardiovascular disease, a pattern consistent with previous studies.

Regarding renal benefits, the results are also consistent with studies such as the CANVAS Program, which demonstrated a 40 % reduction in the risk of progression to end-stage renal disease.[25] Other studies reviewed in our research also reported reductions in kidney disease progression and improvements in kidney function.[4,7]

Although the results are promising, it is important to note some limitations. Heterogeneity between studies may have affected the results, as patient characteristics, follow-up duration, and methods used to measure key variables vary considerably. For example, the reduction in HbA1c ranged from 0,42 % to 1,2 %, suggesting that effects may depend on factors such as baseline glucose levels and patient demographics.[10,11] Also, some studies

did not report complete data on diastolic blood pressure, limiting the analysis of effects on blood pressure overall.[13,20,21]

Another methodological limitation was the lack of long-term follow-up in some studies to evaluate adverse effects consistently. Although most studies concluded that SGLT2 inhibitors were well tolerated, certain adverse events, such as genitourinary infections, were reported more frequently in some cases.[29,30] This suggests that more research is needed to better understand the long-term safety of these drugs.

CONCLUSIONS

Although these findings are not revolutionary, this review supports what is already known about SGLT2 inhibitors, highlighting their usefulness in glycemic control and their positive impact on reducing cardiovascular and renal risk. The main point is that patients with high cardiovascular risk-benefit most from these treatments. However, it remains to be determined whether patients with lower risk or in earlier stages of diabetes obtain the same benefits.

Despite the encouraging results, there are still areas that need further study. For example, it would be helpful to investigate the impact of SGLT2 inhibitors in patients without cardiovascular or renal complications at the start of treatment. Although current studies have focused primarily on high-risk populations, it remains to be seen whether these benefits extend to other groups.

It would also be important to study the mechanisms behind these drugs' cardiovascular and renal effects. Although the benefits of reducing cardiovascular events and renal progression are clear, the exact processes underlying these effects are not fully understood. A better understanding of these mechanisms could help optimize their use.

Finally, it would be helpful to investigate ways to mitigate adverse effects, such as genitourinary infections and diabetic ketoacidosis, to improve the tolerability of these drugs in the broader population.

BIBLIOGRAPHICAL REFERENCES

1. Esteban A, Ferguson N, Meade M, Frutos-Vivar F, Apezteguia C, Brochard L, et al. Evolution of mechanical ventilation in response to clinical research. Am J Respir Crit Care Med. 2008;177(2):170–7. doi:10.1164/rccm.200706-893OC.

2. Rubenfeld GD, Caldwell E, Peabody E, Weaver J, Martin DP, Neff M, et al. Incidence and outcomes of acute lung injury. N Engl J Med. 2005;353(16):1685–93. doi:10.1056/NEJMoa050333.

3. Villar J, Blanco J, Añón JM, Santos-Bouza A, Blanch L, Ambrós A, et al. The ALIEN study: Incidence and outcome of acute respiratory distress syndrome in the era of lung protective ventilation. Intensive Care Med. 2011;37(12):1932–41. doi:10.1007/s00134-011-2380-4.

4. Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E, Fan E, et al. Acute respiratory distress syndrome: The Berlin definition. JAMA. 2012;307(23):2526–33. doi:10.1001/jama.2012.5669.

5. Phua J, Badia JR, Adhikari NKJ, Friedrich JO, Fowler RA, Singh JM, et al. Has mortality from acute respiratory distress syndrome decreased over time?: A systematic review. Am J Respir Crit Care Med. 2009;179(3):220–7. doi:10.1164/rccm.200805-722OC.

6. ARDS Network. Ventilation with lower tidal volumes as compared with traditional tidal volumes for acute lung injury and the acute respiratory distress syndrome. N Engl J Med. 2000;342(18):1301–8. doi:10.1056/NEJM200005043421801.

7. Li G, Malinchoc M, Cartin-Ceba R, Venkata C, Kor D, Peters SG, et al. Eight-year trend of acute respiratory distress syndrome: A population-based study in Olmsted County, Minnesota. Am J Respir Crit Care Med. 2011;183(1):59–66. doi:10.1164/rccm.201003-0436OC.

8. Douglas WW, Rehder K, Beynen FM, Sessler AD, Marsh HM. Improved oxygenation in patients with acute respiratory failure: The prone position. Am Rev Respir Dis. 1977;115(4):559–66. doi:10.1164/arrd.1977.115.4.559.

9. Sud S, Friedrich JO, Taccone P, Polli F, Adhikari NKJ, Latini R, et al. Prone ventilation reduces mortality in patients with acute respiratory failure and severe hypoxemia: Systematic review and meta-analysis. Intensive Care Med. 2010;36(4):585–99. doi:10.1007/s00134-009-1748-1.

10. Gattinoni L, Tognoni G, Pesenti A, Taccone P, Mascheroni D, Labarta V, et al. Effect of prone positioning on the survival of patients with acute respiratory failure. N Engl J Med. 2001;345(8):568–73. doi:10.1056/

NEJMoa010043.

11. Fernandez R, Trenchs X, Klamburg J, Castedo J, Serrano JM, Besso G, et al. Prone positioning in acute respiratory distress syndrome: A multicenter randomized clinical trial. Intensive Care Med. 2008;34(8):1487–91. doi:10.1007/s00134-008-1119-3.

12. Mancebo J, Fernández R, Blanch L, Rialp G, Gordo F, Ferrer M, et al. A multicenter trial of prolonged prone ventilation in severe acute respiratory distress syndrome. Am J Respir Crit Care Med. 2006;173(11):1233–9. doi:10.1164/rccm.200503-353OC.

13. Guerin C, Gaillard S, Lemasson S, Ayzac L, Girard R, Beuret P, et al. Effects of systematic prone positioning in hypoxemic acute respiratory failure: A randomized controlled trial. JAMA. 2004;292(19):2379–87. doi:10.1001/jama.292.19.2379.

14. Taccone P, Pesenti A, Latini R, Polli F, Vagginelli F, Mietto C, et al. Prone positioning in patients with moderate and severe acute respiratory distress syndrome: A randomized controlled trial. JAMA. 2009;302(18):1977–84. doi:10.1001/jama.2009.1614.

15. Voggenreiter G, Aufmkolk M, Stiletto RJ, Baacke MG, Waydhas C, Ose C, et al. Prone positioning improves oxygenation in post-traumatic lung injury—a prospective randomized trial. J Trauma. 2005;59(2):333–41. PMID:16131996.

16. Guérin C, Reignier J, Richard J, Beuret P, Gacouin A, Boulain T, et al. Prone positioning in severe acute respiratory distress syndrome. N Engl J Med. 2013;368(23):2159–68. doi:10.1056/NEJMoa1214103.

17. Tiruvoipati R, Bangash M, Manktelow B, Peek GJ. Efficacy of prone ventilation in adult patients with acute respiratory failure: A meta-analysis. J Crit Care. 2008;23(1):101–10. doi:10.1016/j.jcrc.2007.09.003.

18. Sud S, Sud M, Friedrich JO, Adhikari NKJ. Effect of mechanical ventilation in the prone position on clinical outcomes in patients with acute hypoxemic respiratory failure: A systematic review and meta-analysis. CMAJ. 2008;178(9):1153–61. doi:10.1503/cmaj.071802.

19. Abroug F, Ouanes-Besbes L, Dachraoui F, Ouanes I, Brochard L. An updated study-level meta-analysis of randomised controlled trials on proning in ARDS and acute lung injury. Crit Care. 2011;15(1):R6. doi:10.1186/cc9403.

20. Gattinoni L, Carlesso E, Taccone P, Polli F, Guérin C, Mancebo J. Prone positioning improves survival in severe ARDS: A pathophysiologic review and individual patient meta-analysis. Minerva Anestesiol. 2010;76(6):448–54. PMID:20523273.

21. Abroug F, Ouanes-Besbes L, Elatrous S, Brochard L. The effect of prone positioning in acute respiratory distress syndrome or acute lung injury: A meta-analysis. Areas of uncertainty and recommendations for research. Intensive Care Med. 2008;34(6):1002–11. doi:10.1007/s00134-008-1062-3.

22. Alsaghir A, Martin C. Effect of prone positioning in patients with acute respiratory distress syndrome: A meta-analysis. Crit Care Med. 2008;36(2):603–9. doi:10.1097/01.CCM.0000299739.98236.05.

23. Kopterides P, Siempos I, Armaganidis A. Prone positioning in hypoxemic respiratory failure: Meta-analysis of randomized controlled trials. J Crit Care. 2009;24(1):89–100. doi:10.1016/j.jcrc.2007.12.014.

24. Bernard G, Artigas A, Brigham K, Carlet J, Falke K, Hudson L, et al. The American-European Consensus Conference on ARDS. Definitions, mechanisms, relevant outcomes, and clinical trial coordination. Am J Respir Crit Care Med. 1994;149(3 Pt 1):818–24. doi:10.1164/ajrccm.149.3.7509706.

25. Gattinoni L, Caironi P, Cressoni M, Chiumello D, Ranieri VM, Quintel M, et al. Lung recruitment in patients with the acute respiratory distress syndrome. N Engl J Med. 2006;354(17):1775–86. doi:10.1056/NEJMoa052052.

26. Fessler HE, Talmor DS. Should prone positioning be routinely used for lung protection during mechanical ventilation? Respir Care. 2010;55(1):88–99. PMID:20040130.

27. Pipeling MR, Fan E. Therapies for refractory hypoxemia in acute respiratory distress syndrome. JAMA. 2010;304(22):2521–7. doi:10.1001/jama.2010.1752.

28. Barbas C, Matos G, Amato M, Carvalho C. Goal-oriented respiratory management for critically ill patients with acute respiratory distress syndrome. Crit Care Res Pract. 2012;2012:952168. doi:10.1155/2012/952168.

29. Gattinoni L, Protti A. Ventilation in the prone position: For some but not for all? CMAJ. 2008;178(9):1174-6. doi:10.1503/cmaj.080359.

30. Cornejo RA, Diaz JC, Tobar EA, Bruhn AR, Ramos CA, Gonzalez RA, et al. Effects of prone positioning on lung protection in patients with acute respiratory distress syndrome. Am J Respir Crit Care Med. 2013;188(4):440-8. doi:10.1164/rccm.201207-1279OC.

FINANCING

None.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORSHIP CONTRIBUTION

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