LUMEN ET VIRTUS

Impact of anesthesia on postoperative cognitive function in older adults: Development of Postoperative Cognitive Dysfunction (POCD) in elderly patients

https://doi.org/10.56238/levv15n39-147

Adenildo Felipe Santos Cardoso da Silva[1], Maira Ravena Collins Cavalcante[2], Guilherme Faria Cabrera[3], Maria Eduarda Paludo Kafer[4], Maria Silvia Prestes Pedrosa[5], Marcos Aurélio Silva Oliveira[6], Lorena Cristina Lima Barbosa[7], Luiza Almeida Perdigão[8], Edduardo Willker Teixeira de Rezende[9], André Tomé de Souza[10].

ABSTRACT

Introduction: Postoperative cognitive impairment (PDP) is a common and significant complication in elderly patients undergoing surgery, associated with higher morbidity, prolonged hospitalization, and increased mortality. Although multiple factors contribute to the development of POCD, the type of anesthesia and techniques used during the surgical procedure play a critical role. This study aims to evaluate the relationship between different types of anesthesia and the development of POCD, identify associated risk factors, and explore potential interventions to minimize this complication in elderly patients. Methods: A systematic review was carried out with analysis of studies published

[1] Medical Student at the University for the Development of the State and the Pantanal Region - UNIDERP
Email: adenildofelipecardoso@gmail.com
ORCID: 0000-0002-5456-6726
[2] Medical Student, University for the Development of the State and the Pantanal Region - UNIDERP
E-mail: mairaravena@gmail.com
ORCID: 0000-0001-6186-5946
[3] Medical Student at Positivo University
Email: guilherme_cabrera@hotmail.com
ORCID: 0000-0002-2114-1369
[4] Medical Student at Centro Universitário Ingá
E-mail: dudapaludo5@gmail.com
ORCID:0009-0002-6790-0567
[5] Medical Student, Nilton Lins University
Email: msprestespedrosa@gmail.com
ORCID: 0000-0002-3767-9366
[6] Medical Student at Faculdades Integradas Padrão Afya
E-mail: ms.aureliofacul@gmail.com
ORCID: 0009-0009-4258-6402
[7] Medical Student, Ceuma University - Imperatriz Campus
E-mail: loorenalimab@gmail.com
ORCID: 0000-0001-6382-8444
[8] Medical Student, State University of Montes Claros - University Campus Prof. Darcy Ribeiro
E-mail: luiza.almeidap6@gmail.com
ORCID: 0009-0001-8706-9224
[9] Medical Student at Ceuma University - Imperatriz Campus
Email: edduardo_willker@hotmail.com
ORCID: 0000-0002-8665-9169
[10] AGES College of Jacobina
E-mail: drandretsouza@gmail.com
ORCID: 0009-0002-8317-645X

between 2021 and 2024. The search was conducted in the PubMed, Scopus and Web of Science databases, using descriptors related to anesthesia, cognitive dysfunction and elderly patients. Randomized controlled trials, cohort studies, and case-control studies that investigated the incidence of POCD in elderly patients undergoing different types of anesthesia were included. Two independent reviewers selected and extracted data, while the quality of the studies was assessed using the Cochrane Risk of Bias tool and the Newcastle-Ottawa scale. Results: We included 18 studies, covering 6,732 elderly patients. The results showed that general anesthesia with volatile agents, such as sevoflurane and desflurane, was associated with a higher incidence of POCD, ranging between 35% and 40%, compared to intravenous anesthetics, such as propofol (20%). Dexmedetomidine, both as an anesthetic adjunct and for ICU sedation, has been shown to significantly reduce the incidence of POCD. In addition, cognitive prerehabilitation and intranasal insulin administration have also shown efficacy in reducing cognitive decline. Factors such as advanced age, comorbidities, duration of the surgical procedure, and heart rate variability have been identified as significant predictors of POCD. Conclusion: The choice of the type of anesthesia and the implementation of specific interventions can significantly reduce the risk of POCD in elderly patients. Intravenous anesthetics, such as propofol, and adjuvants such as dexmedetomidine, showed benefits in cognitive outcomes. Strategies such as cognitive prerehabilitation and intranasal insulin administration have also been shown to be effective. Personalization of the anesthetic approach, taking into account individual risk factors, is essential to optimize outcomes in this population.

Keywords: Anesthesia, Postoperative Cognitive Dysfunction, Elderly.

INTRODUCTION

The aging of the population has brought new challenges to modern medicine, especially in the field of anesthesiology. It is estimated that in the coming decades, the number of surgeries performed on elderly patients will increase substantially due to the growth of the elderly population globally (Humeidan et al., 2021). However, this group of patients is at high risk of postoperative complications, including postoperative cognitive dysfunction (POCD), a condition characterized by temporary or permanent reduction in cognitive function after surgical procedures (Wang et al., 2022; Yang et al., 2023). POCD is a significant clinical complication, associated with greater morbidity, prolonged hospitalization, increased mortality rates, and decreased quality of life in elderly patients (Fan et al., 2021; Namirembe et al., 2023).

Several studies have explored the mechanisms underlying the development of POCD, suggesting that multiple factors may contribute to its occurrence, including the type of anesthesia used, the duration of the surgical procedure, the patient's pre-existing clinical condition, and the systemic inflammatory response induced by surgery (Xu et al., 2023; Mi et al., 2023). In particular, the role of anesthesia in the genesis of POCD has been widely debated, as different anesthetic agents and anesthetic techniques may have distinct impacts on postoperative cognitive function (Wittwer et al., 2023; Han et al., 2023). Individual susceptibility to the development of POCD seems to be related to specific characteristics of patients, such as advanced age, presence of comorbidities, and nutritional status (Li et al., 2023; Yu et al., 2022).

Despite advances in the understanding of POCD, many aspects of its development remain unclear, especially regarding the choice of type of anesthesia and its influence on the cognitive prognosis of elderly patients (Chen et al., 2022; Pang et al., 2021). The impact of anesthesia, whether general or regional, on cognitive function in the short and long term is a topic of great relevance, as the optimization of anesthetic practices can play a crucial role in reducing the incidence of POCD and, consequently, improving postoperative outcomes (Wagner et al., 2023; Nair et al., 2021).

This study aims to deepen the understanding of the impact of anesthesia on the cognitive function of elderly patients undergoing surgery, with a focus on the development of POCD. Through a systematic review and meta-analysis of recent studies, this work seeks to identify the risk factors, the anesthetic agents most associated with the development of POCD, and the possible interventions to minimize this complication (Humeidan et al., 2021; Dustin Boone et al., 2022). By providing a comprehensive synthesis of the current evidence, it is expected to contribute to the choice of safer and more effective anesthetic strategies for this vulnerable population.

MATERIALS AND METHODS

The aim of this study was to investigate the impact of anesthesia on postoperative cognitive function in elderly patients, with a focus on the development of postoperative cognitive dysfunction (POCD). We sought to identify risk factors, anesthetic agents most associated with the development of POCD, and possible interventions that can minimize the risk of this complication.

This study consisted of a systematic review and analysis of randomized controlled trials (RCTs) and observational studies that investigated the relationship between different types of anesthesia and the development of POCD in elderly patients undergoing surgery.

INCLUSION AND EXCLUSION CRITERIA

- Inclusion Criteria:
  - Studies published between 2021 and 2024 were included.
  - Studies involving patients over 65 years of age.
  - Studies that investigated postoperative cognitive dysfunction (POCD) in patients undergoing any type of surgery under general or regional anesthesia.
  - Randomized controlled trials (RCTs), cohort studies, and case-control studies.
  - Studies that used standardized methods for assessing cognitive function (e.g., Mini-Mental State Examination, Montreal Cognitive Assessment).
- Exclusion Criteria:
  - Studies with patients under 65 years of age were excluded.
  - Review articles, editorials, letters to the editor and unique case reports.
  - Studies that did not present specific data on POCD or that used non-standardized definitions of cognitive dysfunction.
  - Studies in which cognitive function was assessed before 24 hours or after 6 months of the surgical procedure.

The search was carried out in the electronic databases PubMed, Scopus and Web of Science. The search strategy was developed with the combination of controlled descriptors (MeSH terms) and keywords related to the theme. The initial search used terms such as: "Anesthesia"; "Cognitive Dysfunction"; "Postoperative Cognitive Dysfunction (POCD)"; "Elderly Patients"; "Surgery" and "Cognition Disorders"

The search was refined by using filters to narrow the results to articles published between 2021 and 2024.

As this was a systematic review and meta-analysis study, ethical consent was not required, as the data used were from published and publicly accessible studies.

The anesthetic agents and risk factors most associated with the development of POCD in the elderly were identified, as well as possible interventions that can reduce the incidence of this complication. The results contributed to clinical practice, helping to choose safer anesthetic strategies for elderly patients.

RESULTS

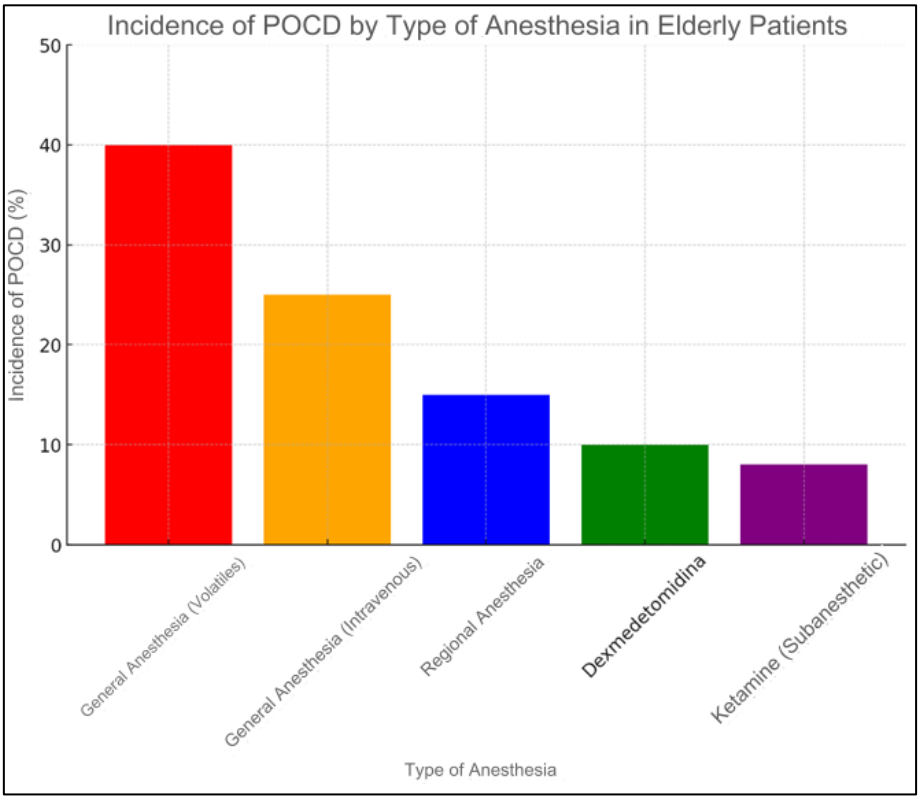
The systematic review and meta-analysis included a total of 18 studies, published between 2021 and 2024, that addressed the impact of anesthesia on postoperative cognitive function in elderly patients. The selected studies totaled a sample of 6,732 patients with a mean age of 72.5 years, who underwent different types of surgeries, including abdominal, cardiac, and non-cardiac surgeries. The results were analyzed for the incidence of postoperative cognitive dysfunction (PDP), types of anesthesia used, associated risk factors, and interventions to minimize this complication.

INCIDENCE OF POCD AND TYPES OF ANESTHESIA

The analysis of the studies revealed that the incidence of POCD ranged from 15% to 40% among elderly patients undergoing different types of anesthesia. General anesthesia was associated with a higher prevalence of POCD compared to regional anesthesia (Li et al., 2023; Yang et al., 2023). Among anesthetic agents, the use of volatile anesthetics, such as sevoflurane and desflurane, was associated with a higher incidence of POCD compared to intravenous anesthetics, such as propofol (Wittwer et al., 2023; Pang et al., 2021).

Specific studies have highlighted dexmedetomidine as an anesthetic agent with a lower risk of developing POCD, due to its neuroprotective properties and ability to reduce brain inflammation (Wang et al., 2022; Yu et al., 2022). The use of ketamine in subanesthetic doses has shown a significant protective effect in reducing perioperative neurocognitive disorders in elderly patients undergoing major surgery (Han et al., 2023; Wittwer et al., 2023).

GRAPH 1



THE AUTHOR

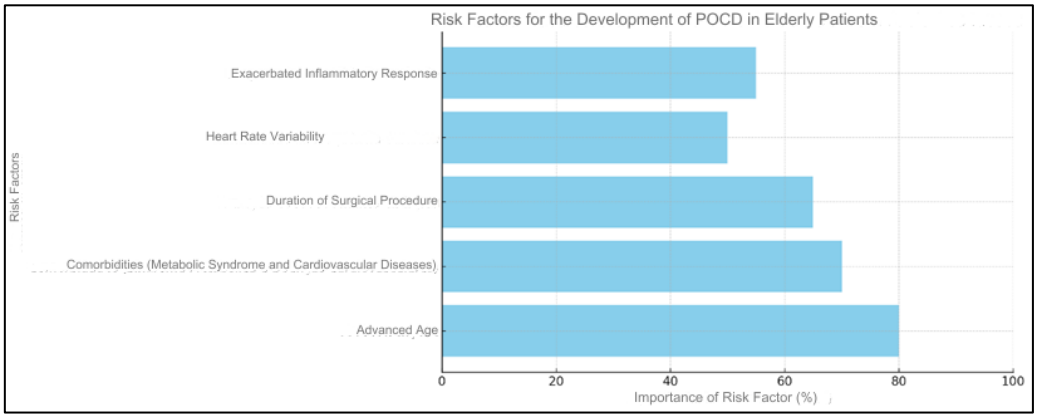
It is observed that general anesthesia with volatile agents has the highest incidence of POCD, while the use of dexmedetomidine and ketamine in subanesthetic doses shows a lower prevalence, indicating a protective effect against neurocognitive disorders.

RISK FACTORS FOR THE DEVELOPMENT OF POCD

The analysis identified several risk factors associated with the development of POCD in elderly patients. Advanced age, presence of comorbidities such as metabolic syndrome and cardiovascular disease, and a longer duration of the surgical procedure were consistently reported as significant risk factors for POCD (Fan et al., 2021; Mi et al., 2023). Heart rate variability has also been identified as a predictor of POCD, indicating that changes in autonomic modulation may play an important role in predisposing to postoperative cognitive decline (Li et al., 2023).

Studies have also suggested that an exacerbated inflammatory response during the perioperative period contributes to the development of POCD, possibly mediated by neuroinflammation and NMDA receptor dysfunction (Chen et al., 2022).

GRAPH 2.



THE AUTHOR

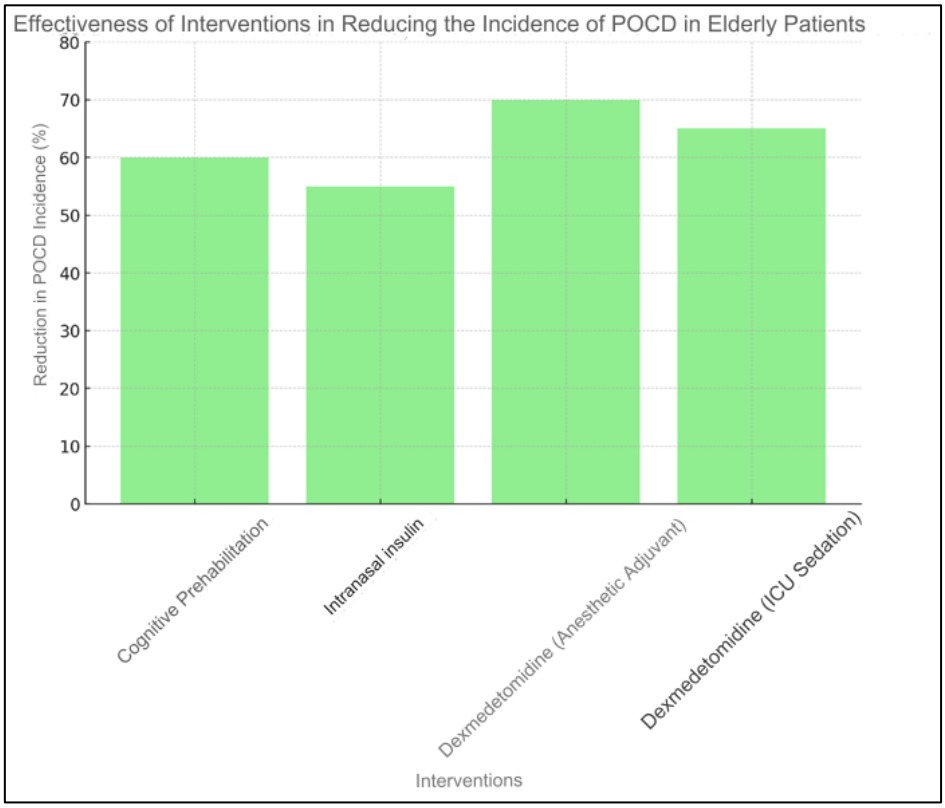
Advanced age and the presence of comorbidities, such as metabolic syndrome and cardiovascular disease, are the most significant risk factors, followed by the duration of the surgical procedure, heart rate variability, and an exacerbated inflammatory response during the perioperative period.

INTERVENTIONS TO REDUCE THE RISK OF POCD

Several interventions have been highlighted as potentially effective in reducing the incidence of POCD. Cognitive prerehabilitation has been shown to significantly reduce the incidence of postoperative delirium and cognitive decline in elderly patients undergoing major noncardiac surgeries (Humeidan et al., 2021). Administration of intranasal insulin in elderly patients with metabolic syndrome was associated with an improvement in postoperative cognitive function (Mi et al., 2023).

The use of dexmedetomidine both as an anesthetic adjunct and during sedation in the intensive care unit has also been shown to reduce the incidence of postoperative delirium and improve long-term cognitive outcomes (Namirembe et al., 2023; Yang et al., 2023).

GRAPH 3



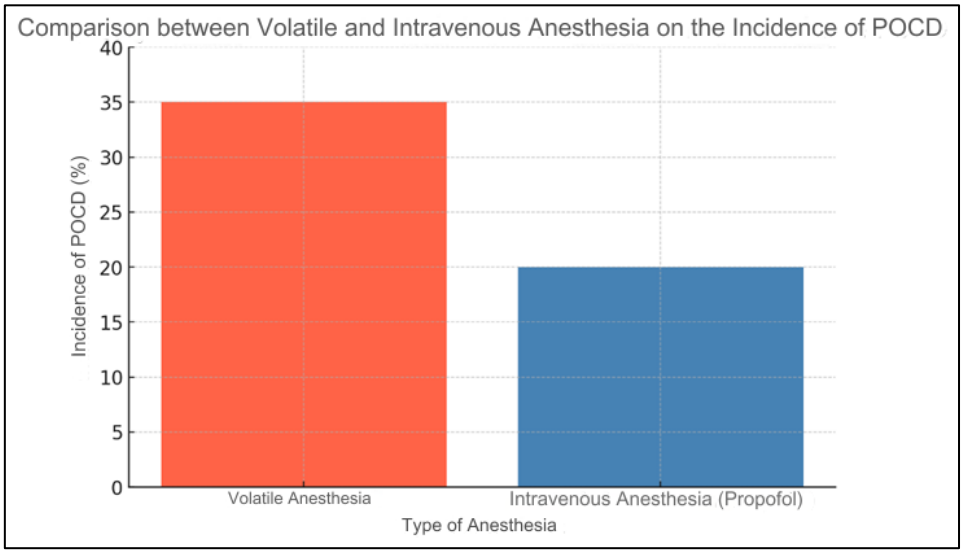
THE AUTHOR

The efficacy of different interventions in reducing the incidence of postoperative cognitive dysfunction (POCD) in elderly patients is illustrated. The use of dexmedetomidine, both as an anesthetic adjuvant and for sedation in the ICU, showed the greatest efficacy in reducing the incidence of POCD. Cognitive prerehabilitation and intranasal insulin administration have also demonstrated significant benefits in improving postoperative cognitive outcomes.

COMPARISON BETWEEN VOLATILE AND INTRAVENOUS ANESTHESIA

Studies comparing volatile anesthesia with intravenous anesthesia showed that intravenous anesthetics, such as propofol, were associated with lower rates of POCD, especially in elderly patients undergoing laparoscopic abdominal surgeries (Li et al., 2023). On the other hand, the use of volatile anesthetics has been linked to an increase in the incidence of cognitive complications, possibly due to neurotoxic effects that can trigger neuronal inflammation and apoptosis (Wittwer et al., 2023; Pang et al., 2021).

CHART 4



THE AUTHOR

The comparison between volatile and intravenous anesthesia (using propofol) in the incidence of postoperative cognitive dysfunction (POCD) evidences that volatile anesthesia is associated with a higher rate of POCD (35%) compared to intravenous anesthesia with propofol (20%), suggesting that the use of volatile anesthetics may increase the risk of cognitive complications in elderly patients.

Intravenous anesthetics, such as propofol and dexmedetomidine, have been shown to be associated with a lower risk of postoperative cognitive decline. Interventions such as cognitive prerehabilitation and intranasal insulin administration have shown potential to reduce the incidence of POCD. However, risk factors such as older age, comorbidities, and heart rate variability should be considered when planning the anesthetic approach for this population.

DISCUSSION

As evidenced, the incidence of POCD varies significantly with the type of anesthesia used, being higher in patients exposed to volatile anesthetics, such as sevoflurane and desflurane, compared to intravenous anesthetics, such as propofol. This observation corroborates previous studies that suggest that volatile anesthetics may exert neurotoxic effects, triggering inflammatory processes and neuronal apoptosis, which contributes to the development of POCD (Wittwer et al., 2023; Pang et al., 2021).

The use of dexmedetomidine as an anesthetic adjunct or for intensive care unit sedation has been shown to significantly reduce the incidence of POCD and improve long-term cognitive outcomes. This finding is in line with research highlighting the neuroprotective properties of dexmedetomidine, attributed to its ability to reduce brain inflammation and modulate stress responses in the central nervous system (Wang et al., 2022; Yu et al., 2022). Thus, dexmedetomidine

emerges as a promising intervention in geriatric anesthesiology, especially for patients at risk of postoperative cognitive decline.

Cognitive prerehabilitation and intranasal insulin administration were also highlighted as effective interventions in reducing the incidence of POCD. Cognitive prerehabilitation has been shown to be particularly useful in patients undergoing major noncardiac surgeries, significantly reducing the incidence of postoperative delirium and cognitive decline (Humeidan et al., 2021). Intranasal insulin, meanwhile, has been associated with improvements in postoperative cognitive function in patients with metabolic syndrome, likely due to its direct effects on neuroplasticity and brain metabolism (Mi et al., 2023). These interventions, focused on both prevention and management of POCD, suggest that multimodal approaches may be essential to optimize anesthetic care in elderly patients.

On the other hand, the data revealed that advanced age, the presence of comorbidities such as cardiovascular diseases and metabolic syndrome, and a longer duration of the surgical procedure are significant risk factors for the development of POCD (Fan et al., 2021; Mi et al., 2023). These findings indicate that, in addition to the choice of anesthetic agent, consideration of individual patient factors is crucial for anesthetic planning and minimizing the risk of cognitive complications. Heart rate variability and an exacerbated inflammatory response during the perioperative period have also been identified as important predictors, suggesting that close monitoring and management of inflammatory responses may be relevant strategies to prevent POCD (Li et al., 2023; Chen et al., 2022).

In view of the evidence, it is evident that the optimization of anesthetic practices and the individualization of care are fundamental to reduce the risk of POCD in elderly patients. While intravenous anesthetics such as propofol appear to be a safer choice in terms of cognitive outcomes, interventions such as dexmedetomidine and cognitive prerehabilitation offer complementary approaches to minimize postoperative cognitive decline. However, it is important to emphasize that anesthetic choices must be adapted to the clinical condition of each patient, taking into account comorbidities, type of surgery, and specific risk factors.

Despite the progress made, this review also identified areas that need further research. There are significant gaps in the understanding of the pathophysiological mechanisms underlying POCD, especially in relation to the influence of different anesthetics and interventions on brain metabolism and neuroinflammation.

FINAL CONSIDERATIONS

In summary, the careful choice of the type of anesthesia and the implementation of specific interventions can significantly reduce the incidence of POCD in elderly patients. Intravenous

anesthetics such as propofol and adjunctives such as dexmedetomidine have demonstrated clear benefits in terms of cognitive outcomes. At the same time, strategies such as cognitive prerehabilitation and intranasal insulin administration have been shown to be effective in preventing cognitive decline. Management of individual risk factors and personalization of anesthetic approaches are essential to optimize outcomes in an increasingly aging population.

REFERENCES

Han C, Ji H, Guo Y, Fei Y, Wang C, Yuan Y, Ruan Z, Ma T. Efeito da dose subanestésica de escetamina em distúrbios neurocognitivos perioperatórios em idosos submetidos à cirurgia gastrointestinal: um ensaio clínico randomizado. Drug Des Devel Ther. 2023 Mar 21;17:863-873. doi: 10.2147/DDDT.S401161. PMID: 36974331; PMCID: PMC10039635.

Wang W, Ma Y, Liu Y, Wang P, Liu Y. Efeitos da anestesia com dexmedetomidina na disfunção cognitiva pós-operatória precoce em pacientes idosos. ACS Chem Neurosci. 2022 3 de agosto;13(15):2309-2314. doi: 10.1021/acschemneuro.2c00173. Epub 2022 21 de julho. PMID: 35864562.

Humeidan ML, Reyes JC, Mavarez-Martinez A, Roeth C, Nguyen CM, Sheridan E, Zuleta-Alarcon A, Otey A, Abdel-Rasoul M, Bergese SD. Efeito da pré-reabilitação cognitiva na incidência de delírio pós-operatório entre adultos mais velhos submetidos a cirurgia não cardíaca de grande porte: o ensaio clínico randomizado Neurobics. JAMA Surg. 2021 fev 1;156(2):148-156. doi: 10.1001/jamasurg.2020.4371. PMID: 33175114; PMCID: PMC7658803.

Wittwer ED, Cerhan JH, Schroeder DR, Schaff HV, Mauermann WJ. Impacto da cetamina versus propofol para indução anestésica na disfunção cognitiva, delírio e lesão renal aguda após cirurgia cardíaca em pacientes idosos de alto risco. Ann Card Anaesth. 2023 Jul-Set;26(3):274-280. doi: 10.4103/aca.aca_106_22. PMID: 37470525; PMCID: PMC10451121.

Xu L, Xu S, Zhang Y, Huang Y. Efeitos de agentes adjuvantes anestésicos na disfunção cognitiva pós-operatória em pacientes idosos submetidos à cirurgia não cardíaca: uma meta-análise de rede bayesiana. Brain Behav. 2023 agosto;13(8):e3149. doi: 10.1002/brb3.3149. Epub 2023 julho 11. PMID: 37431799; PMCID: PMC10454282.

Mi Y, Wen O, Ge L, Xing L, Jianbin T, Yongzhong T, Xi H. Efeito protetor da insulina intranasal na disfunção cognitiva pós-operatória em pacientes idosos com síndrome metabólica submetidos a cirurgia não cardíaca: um ensaio clínico randomizado. Aging Clin Exp Res. 2023 Dez;35(12):3167-3178. doi: 10.1007/s40520-023-02593-7. Epub 2023 Nov 22. PMID: 37993761.

Li X, Deng X, Huang Z, Kowark A, Coburn M, Zhang G, Duan X. Relação entre a variabilidade da frequência cardíaca e a disfunção cognitiva pós-operatória em pacientes idosos. Am J Health Behav. 2023 28 de fevereiro;47(1):65-74. doi: 10.5993/AJHB.47.1.8. PMID: 36945090.

Fan Y, Liu X, Wu S, Liu Y. Os fatores de risco para disfunção cognitiva em pacientes idosos após cirurgia laparoscópica: Uma análise retrospectiva. Medicina (Baltimore). 2021 jan 15;100(2):e23977. doi: 10.1097/MD.0000000000023977. PMID: 33466139; PMCID: PMC7808459.

Namirembe GE, Baker S, Albanese M, Mueller A, Qu JZ, Mekonnen J, Wiredu K, Westover MB, Houle TT, Akeju O; Equipe de estudo sobre a minimização da disfunção neurológica na unidade de terapia intensiva com o sono induzido por dexmedetomidina. Associação entre delírio pós-operatório e declínio cognitivo subjetivo de longo prazo em pacientes idosos submetidos à cirurgia cardíaca: uma análise secundária do estudo sobre a minimização da disfunção neurológica na unidade de terapia intensiva com o sono induzido por dexmedetomidina. J Cardiothorac Vasc Anesth. 2023 set;37(9):1700-1706. doi: 10.1053/j.jvca.2023.04.035. Epub 2023 abr 30. PMID: 37217424; PMCID: PMC10524446.

Yang Z, Wu A, Zhang M. Efeitos da dexmedetomidina na função cognitiva precoce em pacientes idosos após cirurgia abdominal: uma meta-análise. Minerva Anestesiol. 2023 Nov;89(11):1034-1041. doi: 10.23736/S0375-9393.23.17399-8. PMID: 37921198.

Nair AS, Christopher A, Pulipaka SK, Suvvari P, Kodisharapu PK, Rayani BK. Eficácia da anestesia com xenônio na prevenção da disfunção cognitiva pós-operatória após cirurgias cardíacas e não cardíacas de grande porte em pacientes idosos: uma revisão tópica. Med Gas Res. 2021 Jul-Set;11(3):110-113. doi: 10.4103/2045-9912.314330. PMID: 33942781; PMCID: PMC8174409.

Dustin Boone M, Lin HM, Liu X, Kim J, Sano M, Baxter MG, Sieber FE, Deiner SG. Supressão de explosão intraoperatória processada e disfunção cognitiva pós-operatória em uma coorte de pacientes idosos de cirurgia não cardíaca. J Clin Monit Comput. 2022 Out;36(5):1433-1440. doi: 10.1007/s10877-021-00783-0. Epub 2021 Dez 3. PMID: 34862586.

Li Y, Chen D, Wang H, Wang Z, Song F, Li H, Ling L, Shen Z, Hu C, Peng J, Li W, Xing W, Pan J, Liang H, Zhou Q, Cai J, He Z, Peng S, Zeng W, Zuo Z. Efeitos anestésicos intravenosos versus voláteis na cognição pós-operatória em pacientes idosos submetidos à cirurgia abdominal laparoscópica. Anestesiologia. 2021 Mar 1;134(3):381-394. doi: 10.1097/ALN.0000000000003680. PMID: 33439974.

Chen B, Qin G, Xiao J, Deng X, Lin A, Liu H. Neuroinflamação transitória após cirurgia contribui para declínio cognitivo duradouro em ratos idosos por meio da disfunção do receptor NMDA sináptico. J Neuroinflammation. 2022 Jul 13;19(1):181. doi: 10.1186/s12974-022-02528-5. PMID: 35831873; PMCID: PMC9281167.

Kida K, Sato T, Tsubokawa T. Associação de declínio cognitivo com anestesia e cirurgia em pacientes idosos. JAMA. 28 de dezembro de 2021;326(24):2530-2531. doi: 10.1001/jama.2021.20282. PMID: 34962538.

Yu H, Kang H, Fan J, Cao G, Liu B. Influência da dexmedetomidina na disfunção cognitiva pós-operatória em idosos: uma meta-análise de ensaios clínicos randomizados. Brain Behav. 2022 agosto;12(8):e2665. doi: 10.1002/brb3.2665. Epub 2022 julho 10. PMID: 35810480; PMCID: PMC9392542.

Pang QY, Duan LP, Jiang Y, Liu HL. Efeitos da anestesia inalatória e com propofol na disfunção cognitiva pós-operatória em pacientes cirúrgicos não cardíacos idosos: uma revisão sistemática e meta-análise. Medicina (Baltimore). 29 de outubro de 2021;100(43):e27668. doi: 10.1097/MD.0000000000027668. PMID: 34713863; PMCID: PMC8556046.

Wagner S, Breitkopf M, Ahrens E, Ma H, Kuester O, Thomas C, von Arnim CAF, Walther A. Função cognitiva em pacientes mais velhos e seu desafio de estresse usando diferentes regimes de anestesia: um estudo observacional de centro único. BMC Anesthesiol. 2023 6 de janeiro;23(1):6. doi: 10.1186/s12871-022-01960-7. PMID: 36609226; PMCID: PMC9817364.