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Cognitive Protection After Cataract Surgery: Examining Ketamine and Dexmedetomidine in the Elderly

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Abstract

Background: Cataract surgery has risen dramatically in the US as a reflection of the growing geriatric population. Despite its safety and efficacy, elderly patients remain vulnerable to postoperative cognitive dysfunction (POCD). Previous studies have shown ketamine and dexmedetomidine to have neuroprotective effects. This study aims to examine its association with POCD using the TriNetX database, mirroring a prior randomized trial and assessing outcomes at 1 week, 3 months, and 1 year postoperatively.

Methods: We conducted a retrospective cohort study using the TriNetX US Collaborative Network, analyzing patients aged 65-85 who underwent cataract surgery prior to June 2025. Using ICD-10 codes, POCD was defined as the new onset diagnosis of delirium, dementia, encephalopathy, or depressive disorders at 1 week, 3 months, and 1 year post surgery. Exclusion criteria included pre-existing cognitive impairment, psychiatric illness, psychotropic use, anesthesia allergies, and severe visual impairment. Propensity score matching adjusted for demographics and ASA II/III risk profiles based on common comorbidities. Outcomes were compared using risk difference, risk ratio, and odds ratio metrics.

Results: In matched ketamine cohorts (n = 3,733 each), POCD occurred in 0.308% *vs*. 0.705% at 3 months (p = 0.0182; RR = 2.29) and in 1.315% *vs*. 2.312% at 1 year (p = 0.0016; RR = 1.76), favoring ketamine. In matched dexmedetomidine cohorts (n = 8,569 each), 1-year POCD was 1.797% *vs*. 2.389% (p = 0.0094; RR = 1.33), also favoring the treatment group.

Conclusion: These findings suggest that both ketamine and dexmedetomidine may reduce the risk of POCD in elderly patients undergoing cataract surgery. While short-term effects were not significant, reductions in POCD incidence became apparent by three months and persisted through one year. This supports prior evidence of potential neuroprotective effects of these agents and highlights their relevance in perioperative planning for older adults. Further prospective studies are warranted to validate these associations and clarify underlying mechanisms.

Summary: This retrospective TriNetX study examined ketamine and dexmedetomidine use during cataract surgery in patients aged 65–85. Only ketamine was associated with reduced POCD at 3 months, but both agents were associated with reduced POCD at 1 year. Findings suggest an added cognitive benefit of these anesthetics in geriatric patients.

Keywords: Cataract Surgery; Postoperative Cognitive Dysfunction (POCD); Cognitive Protection; Elderly Patients; Anesthesia in Geriatrics

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Introduction

As the United States population continues to age at an ever-growing pace, healthcare professionals must be well-equipped to address the ailments that often afflict this demographic. According to the 2020 US Census, the population aged 65 and older increased by 15.5 million from the previous Census (2010), reaching a total of 55.8 million, which is 16.8% of the population. This was noted to be the fastest rate of population growth within this demographic in a decade, from 1880

to 1890 [1]. As of today, the US population is now older than it has ever been. Between 1980 and 2022, the median age of the population increased from 30.0 to 38.9, and this trend is projected to rise, with the geriatric population expected to reach 82 million by 2050 [2]. As this population grows, so too will the myriad of health problems that will flood the healthcare system and pose a significant healthcare cost.

Cataracts are an example of the many health problems that impact older populations and are also very common within this demographic. According to the NIH National Eye Institute, after the age of 40, the proteins in the lens will start to break down and clump together, creating the cloudiness effect. The etiology for the disease is so common that more than half of all Americans aged 80 or older either have cataracts or have had surgery for treatment [3]. Surgery remains the only effective treatment for cataracts. Currently, more than 3.5 million cataract operations are performed annually in the US, and as age remains a primary risk factor, the number of cataract diagnoses is expected to increase by 50 million by 2050 [4].

Even more so, the prevalence of psychiatric disorders within the geriatric population is ever-growing and may be underreported. Approximately 20% of older adults have a diagnosable psychiatric disorder, including but not limited to personality disorders, anxiety disorders, mood disorders, and substance use disorders [5]. Compounded with these findings, cataracts have been shown to diminish quality of life. Studies have indicated that self-reported visual impairment is associated with a greater likelihood of developing dementia over time, and elderly individuals living with cataracts and who have suffered falls are closely linked to depression and other mental health issues [6, 7]. Fortunately, cataract surgery remains the most effective measure to cure cataracts, as well as handling the consequences that come along with it. Cataract extraction has shown improvement in emotion and a reduction in falls altogether, and was associated with a lower risk of dementia development [7, 8].

While cataract surgery is generally considered safe and effective, older adults remain particularly vulnerable to risks associated with surgery and anesthesia. Postoperative cognitive dysfunction (POCD), a decline in memory, attention, or executive function following surgery, is a well-documented complication in the geriatric population, with age being a major risk factor [9]. The pathophysiology of POCD is multifactorial, often linked to neuroinflammation, oxidative stress, and anesthetic neurotoxicity [10]. General and sedative anesthetics, including those used during ophthalmic procedures, have been implicated in short- and long-term cognitive changes, especially in older adults with pre-existing vulnerabilities [11]. Several studies have reported an increased incidence of cognitive decline and even dementia following surgery, prompting growing interest in anesthetic choice as a modifiable risk factor [12]. As cataract surgeries increase among aging adults, identifying anesthetics that preserve cognitive integrity is essential to perioperative planning.

Ketamine has emerged as a common analgesic for cataract surgery. Sedation with ketamine during cataract surgery does not influence intraocular pressure, and patients report no pain during the administration of the anesthesia or postoperatively [13]. On the contrary, there is some dispute about the use of dexmedetomidine for cataract surgery. While reports mention reduced intraocular pressure and higher patient satisfaction, dexmedetomidine was also accompanied by cardiac depression and delayed recovery [14, 15].

In a 2023 randomized controlled trial, Oribey et al. investigated the neuroprotective effects of ketamine and dexmedetomidine in elderly patients undergoing cataract extraction. Participants were randomized into ketamine, dexmedetomidine, or normal saline groups. In comparison to the controls, both analgesics significantly reduced the incidence of postoperative cognitive dysfunction at 1 week and 3 months following surgery [16]. This evidence of cognitive dysfunction reduction provided a framework for a retrospective cohort study on TriNetX. Clinical protocol was mirrored, focusing on similar drug exposures and follow-up intervals at 1 week, 3 months, and 1 year to validate and extend these findings to longer-term trajectories.

Methods

Queries were built via the TriNetX database focusing on the US Collaborative Network. Patients who reported receiving cataract surgery before June 2025 and within the age of 65-85 were initially brought into the TriNetX query. Records of patients receiving extracapsular cataract removal with insertion of intraocular lens prosthesis or replacement of lens in either the right or left eye were pulled for our inclusion criteria. Cohorts were then created by patients who received ketamine on the day of the surgery or one day prior, and patients who did not receive ketamine. Separate cohorts were created by patients who received dexmedetomidine on the day of the surgery or one day prior and patients who did not receive dexmedetomidine. Queries were not built to focus on using ketamine or dexmedetomidine only during surgery.

Oriby et al., define POCD based on performance changes in the Mini-Mental State Examination (MMSE), with a decline of 2 or more points from the preoperative MMSE score [16]. Because cognitive testing data are not available in TriNetX, we constructed a proxy definition for POCD using a composite of ICD-10 codes that represent new-onset neurocognitive and psychiatric diagnoses. POCD was defined as the first occurrence, one week, three months, or one year after surgery, of any of the following conditions, including: dementia, delirium, other and/or unspecified mental disorder, encephalopathy, depressive episode and major depressive disorder. This coding-based approach aligns with real-world EHR methodologies for POCD surveillance in large datasets. Table 1 contains the ICD-10 codes used in our query to define our outcomes. Any patient with a record of the following outcomes prior to the follow-up window was excluded from the analysis.

Exclusion criteria included patients with pre-existing cognitive impairment in order to prevent confounding outcomes. This included patients with Alzheimer's disease and senile degeneration of the brain. Patients with severe psychiatric disorders, such as schizophrenia, schizotypal disorder, delusional disorders, schizoaffective disorder, unspecified psychosis, bipolar disorder, depressive episode, and major depressive disorder, were also removed because of its affect on cognition. Patients who received psychotropic medications like antipsychotics and antidepressants before the surgery were also excluded from our analysis. Furthermore patients who had anesthesia-related complications or allergies, as well as severe visual impairment were part of our exclusion criteria. Table 2 lists all of the ICD-10 and ATC codes used in the query to define our exclusion criteria.

Prior to analysis, a cohort that included the analgesic of study was compared to its respective counterpart and then matched within the TriNetX database. Propensity score matching was done by demographics (eg. age, sex, race/ethnicity) and following the

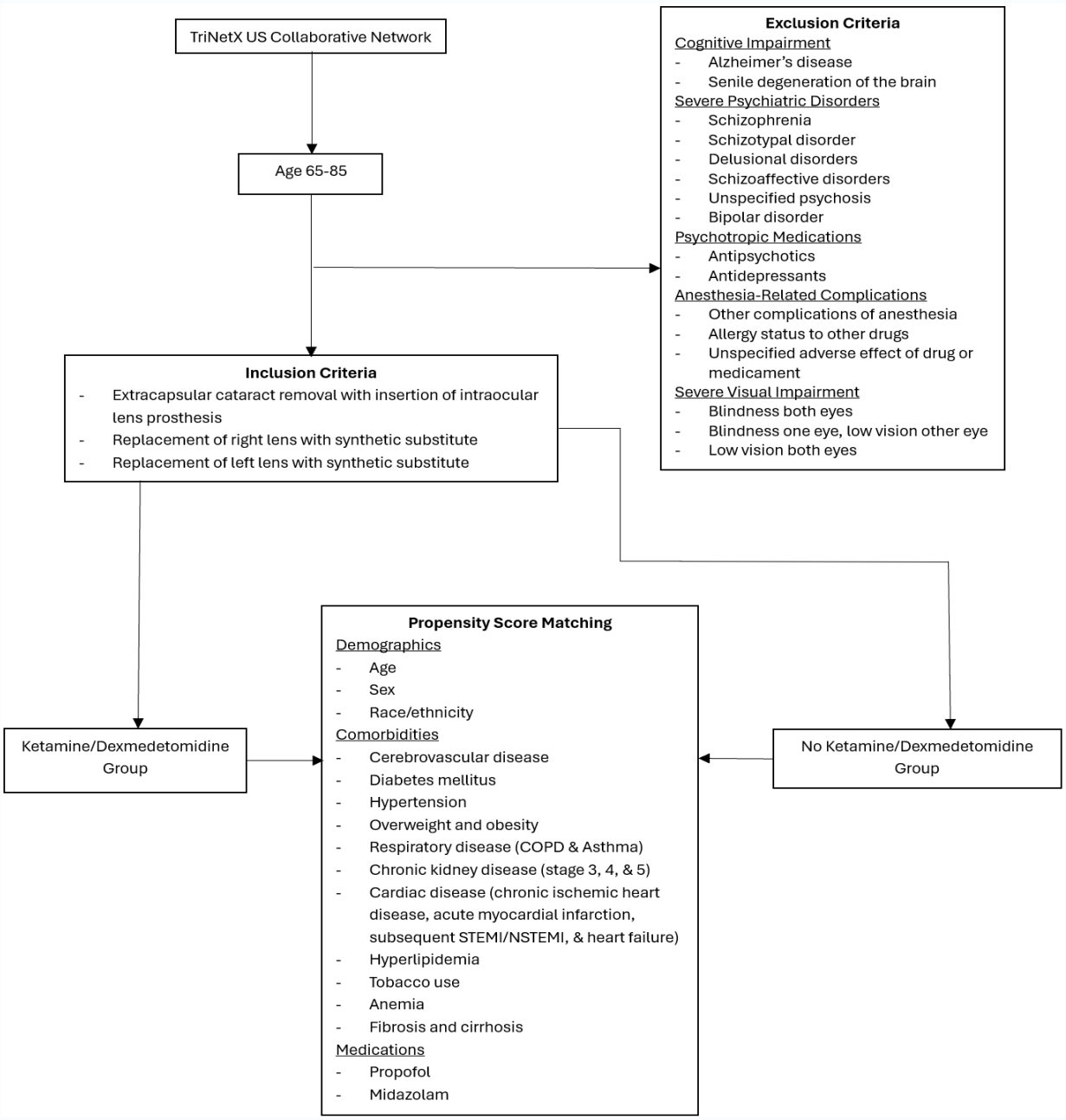

Figure 1: Cohort selection and matching strategy using the TriNetX U.S. Collaborative Network.

American Society of Anesthesiologists (ASA) Physical Status Classification System. The ASA Physical Status Classification System provides standardized criteria to assess a patient's preoperative physical health, ranging from ASA I (healthy) to ASA VI (brain dead organ donor) [17]. This classification helped approximate patient risk by matching on comorbidities typically associated with ASA II and III. The following conditions included history of cerebrovascular disease, diabetes melitus, hypertension, obesity, respiratory diseases, chronic kidney disease, cardiac disease, lipid disorders, tobacco use, anemia, and liver disease. Medications like propofol and midazolam were also taken into account for matching to adjust for potential anesthetic variation. Table 3 lists all the ICD-10 and RxNorm codes used for matching.

Outcomes were compared after matching both cohorts. "Measures of Association" was selected to compare the risks of experiencing the outcome between the two cohorts. Risk difference, risk ratio, and odds ratio was obtained in the analysis. Our set time window was between one day after surgery and one week, three months, and one year after surgery. Patients with the outcomes prior to the window were not included in our study (Figure 1).

Results

Before propensity score matching, 342,535 patients were pulled in the no-ketamine cohorts, while 3,807 were pulled from the ketamine cohort. After matching, there were 3,733 patients found within each cohort, however, patients were removed in the no-ketamine cohort (n = 187) and the ketamine cohort (n = 160) since our outcome was noted prior to the surgery. Cohorts were followed up for one week,

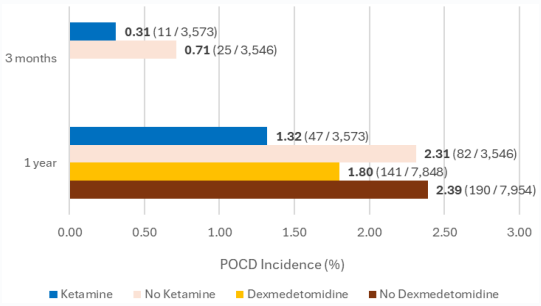

Figure 2: Incidence of Postoperative Cognitive Dysfunction (POCD) at 3 Months and 1 Year Post-Cataract Surgery.

three months, and one year post-surgery.

After one week, there was no statistically significant difference in the comparisons between ketamine cohorts. Following up three months post-surgery, a total of 7,119 patients met the inclusion criteria with the propensity score matching (no-ketamine cohort n = 3,546 and ketamine cohort n = 3,573). A record of POCD occurred in 11 patients (0.308%) in the ketamine cohort, compared to 25 patients (0.705%) in the no-ketamine cohort.The absolute risk difference was 0.397% (95% CI: 0.067%, 0.727%), indicating a lower incidence of POCD in the ketamine cohort. This difference reached statistical significance (z = 2.362, p = 0.0182). The risk ratio was 2.29 (95% CI: 1.129, 4.647) and the odds ratio was 2.299 (95% CI: 1.13, 4.68), both results suggesting that patients in the no-ketamine cohort had over twice the risk of developing POCD in comparison to the ketamine cohort.

Results followed this trend after one year post-surgery, with a total of 82 patients in the no-ketamine cohort indicating POCD (2.312%) compared to 47 patients in the ketamine cohort (1.315%). The absolute risk difference was 0.997% (95% CI: 0.377%, 1.617%, z = 3.153, p = 0.0016), still favoring prior results that patients in the ketamine cohort had a lower incidence of POCD compared to the no-ketamine cohort. The risk ratio was 1.758 (95% CI: 1.232, 2.509) and the odds ratio was 1.776 (1.237, 2.55), further indicating that patients in the no-ketamine cohort had a higher risk of developing POCD even one year after surgery. These trends across time points are visually summarized in Figure 1, which illustrates the incidence of POCD at 1 week, 3 months, and 1 year in patients who received ketamine compared to those who did not.

When observing our dexmedetomidine cohorts, before matching there were 324,207 patients in the dexmedetomidine cohort and 8,569 in the dexmedetomidine cohort. After matching, 8,569 patients were found in both cohorts, with 615 patients removed from the no-dexmedetomidine cohort and 721 patients removed from the dexmedetomidine cohort due to outcomes being present prior to the window.

Follow up after one week and three months did not show statistical significance between cohorts. After a year post-surgery, a total of 15,801 patients met the inclusion criteria with the propensity score matching (no-dexmedetomidine cohort n = 7,954 and dexmedetomidine cohort n = 7,848). During this follow-up, 190 patients who were on dexmedetomidine reported to have POCD in the no dexmedetomidine cohort (2.389%) in comparison to the 141 patients in the dexmedetomidine cohort (1.797%). The risk difference was 0.592% (95% CI: 0.146%, 1.038%, z = 2.599, p = 0.0094), indicating that patients who were not on dexmedetomidine had a higher incidence of POCD a year post-surgery in comparison to those who were on the algesic. Both the risk ratio and odds ratio was 1.33 (95% CI: 1.072, 1.649) and 1.338 (95% CI: 1.073, 1.667) respectively, further stating a higher risk for POCD in patients who were not on the analgesic.These findings are depicted in Figure 2, which shows the incidence of POCD at 1 week, 3 months, and 1 year among patients who received dexmedetomidine compared to controls.

Discussion

This large retrospective cohort study evaluated the impact of intraoperative ketamine and dexmedetomidine use on postoperative cognitive dysfunction (POCD) within a matched population. Among the ketamine cohorts, the incidence of POCD was significantly lower both at three months (0.308% *vs.* 0.705%; p = 0.0182) and one year post-surgery (1.315% *vs.* 2.312%; p = 0.0016) compared to the no-ketamine group. The absolute risk difference at one year was 0.997%, with a risk ratio of 1.76 and an odds ratio of 1.78, indicating that patients not receiving ketamine had nearly twice the risk of POCD. Similarly, dexmedetomidine exposure was associated with a significantly lower incidence of POCD at one year (1.797% *vs.* 2.389%; p = 0.0094), with an absolute risk difference of 0.592%. Risk and odds ratios (1.33 and 1.34, respectively) further supported this protective effect. While short-term follow-up did not reveal statistically significant differences for dexmedetomidine, the long-term findings underscore the potential cognitive benefits of both agents in the perioperative setting.

Ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, has been shown to attenuate glutamate-induced excitotoxicity and modulate the neuroinflammatory response—mechanisms that are increasingly implicated in the pathogenesis of POCD [18, 19]. In our study, patients exposed to ketamine intraoperatively had significantly lower rates of POCD at both three months and one year postoperatively, with a risk reduction of nearly 1% at one year. These findings support earlier reports suggesting that ketamine may reduce the incidence of POCD, particularly in high-risk surgical populations [10, 20]. Furthermore, ketamine has been shown to modulate systemic cytokines and neuroinflammatory pathways, including the inhibition of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), both of which are elevated during surgical stress and are associated with postoperative cognitive decline [21, 22]. This suggests that even sub-anesthetic or intraoperative doses of ketamine may exert meaningful neuroprotective effects over time.

Dexmedetomidine, a selective α2-adrenergic receptor agonist, has gained prominence due to its sedative and analgesic properties that do not cause significant respiratory depression. In addition to its hemodynamic stability, it is known for reducing systemic inflammation and neuroinflammatory mediators, important contributors to POCD [23, 24]. Our findings of significantly lower POCD rates at one year among patients who received dexmedetomidine mirror those of several randomized controlled trials that have reported decreased incidence of delirium and cognitive impairment with its use [25]. One study showed that dexmedetomidine reduces POCD in elderly patients undergoing non-cardiac surgery, attributing the benefit to reduced IL-6 levels and preservation of blood-brain barrier integrity [26]. Although our study did not show a significant benefit at one week or three months, the year-long reduction supports the hypothesis that dexmedetomidine may facilitate long-term neuroprotection, possibly through anti-apoptotic signaling and attenuation of microglial

activation [27].

While the absolute risk reductions observed for ketamine (0.997%) and dexmedetomidine (0.592%) may appear modest, their clinical significance is amplified when considered in the broader context of POCD. Postoperative cognitive dysfunction has been associated with increased morbidity, prolonged recovery, reduced quality of life, and even elevated mortality risk in older adults [28]. One prospective study demonstrated that patients developing POCD at three months postoperatively were more likely to experience functional dependence and had a higher risk of early retirement [29]. Given the large surgical volumes globally, even small reductions in POCD rates translate into meaningful public health benefits. Moreover, both ketamine and dexmedetomidine are already widely used anesthetics, making their targeted application for POCD prevention a feasible and cost-effective intervention with potentially high yield.

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Limitations and Future Directions

This study has several limitations inherent to retrospective analyses. Despite robust propensity score matching, residual confounding cannot be excluded. Our reliance on electronic health record coding for POCD diagnoses may underestimate true incidence, as subtle cognitive changes are often underdiagnosed or misclassified [32]. Additionally, we lacked detailed information on anesthetic dosage, intraoperative duration, and concurrent medications, which could modulate POCD risk. Future research should focus on prospective, randomized trials incorporating objective neuropsychological testing, biomarkers of neuroinflammation, and imaging to elucidate the mechanisms underlying anesthetic-related cognitive protection. Moreover, evaluating whether a combination of ketamine and dexmedetomidine provides synergistic neuroprotection would be a valuable next step.

Conclusion

In conclusion, our study provides compelling evidence that intraoperative use of ketamine and dexmedetomidine is associated with a statistically and clinically significant reduction in postoperative cognitive dysfunction at one year. Given the increasing awareness of POCD's burden and the growing elderly surgical population, these findings highlight a modifiable perioperative factor with long-term implications. As anesthetic protocols continue to evolve, the integration of neuroprotective strategies—particularly those already in clinical use—offers a promising avenue to safeguard cognitive function in surgical patients. Further investigation through prospective trials will be critical to validate these results and optimize anesthetic regimens for cognitive outcomes.

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