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ORIGINAL RESEARCH ARTICLE

Preoperative Comparison of Three Anticholinergic Drug Scales in Older Adult Patients and Development of Postoperative Delirium: A Prospective Observational Study

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Abstract

Background Postoperative delirium (POD) is a frequent and serious complication after surgery. Evidence of a relationship between anticholinergic medication and the development of delirium is inconclusive, but studies on POD are rare.

Objectives The objective of this study was to evaluate the anticholinergic load of preoperative medication in older adult patients and its association with the development of POD.

Methods This investigation was part of the European BioCog project (http://www.biocog.eu), a prospective multicenter observational study in older adult surgical patients (ClinicalTrials.gov identifier: NCT02265263, 15 October 2014). Patients with a Mini–Mental State Examination score ≤ 23 points were excluded. POD was assessed up to 7 days after surgery using the Nursing Delirium Screening Scale, Confusion Assessment Method and a patient chart review. The preoperative anticholinergic load was calculated using the Anticholinergic Drug Scale (ADS), the Anticholinergic Risk Scale (ARS) and the Anticholinergic Cognitive Burden Scale (ACBS), and associations with POD were analyzed using logistic regression analysis adjusting for age, comorbidities, duration of anesthesia and number of drugs used.

Results In total, 837 participants were included for analysis, and 165 patients (19.7%) fulfilled the criteria of POD. After adjusting for confounders, we found no association between preoperative anticholinergic load and the development of POD (ADS [points] odds ratio [OR] 0.928; 95% confidence interval [CI] 0.749–1.150; ARS [points] OR 0.832; 95% CI 0.564–1.227; ACBS [points] OR 1.045; 95% CI 0.842–1.296).

Conclusion This study found no association between the anticholinergic load of drugs used preoperatively and the development of POD in older adult patients without severe preexisting cognitive impairment. Future analyses should examine the influence of intra- and postoperative administration of anticholinergic drugs as well as dosages of and interactions between medications.

1 Introduction

Postoperative delirium (POD) is a common and serious neurocognitive complication, presenting as an acute disturbance in attention and cognition that is not based on a preexisting neurocognitive disorder [1, 2]. POD is associated with increased length of hospitalization [3], impaired functional status [4], long-term cognitive impairments [5–7] and increased short-term and long-term mortality [1]. The incidence of POD is dependent on predisposing risk factors (e.g., age, cognitive impairment, comorbidity or impaired functional status) and precipitating risk factors (e.g., major

Key Points

Depending on the scale used, the anticholinergic load of long-term medications varied considerably.

This study found no association between the anticholinergic load (according to Anticholinergic Drug Scale, Anticholinergic Risk Scale and Anticholinergic Cognitive Burden Scale) of preoperative long-term medication and the development of postoperative delirium in older adult patients.

Future analyses should examine the influence of intra- and postoperative administration of anticholinergic drugs as well as dosages of and interactions between medications.

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surgery) [1, 8]. Older adult patients are particularly at risk of developing POD. The number of older adults undergoing surgery is rising, and demographic changes indicate that this trend will continue. Preoperative optimization, particularly the adaptation of long-term medication, plays an important role in the prevention of delirium.

Given the accumulation of comorbidities in older adults, these patients are more likely to be subject to polypharmacy and inappropriate prescriptions, and anticholinergic adverse effects are frequently described in the literature [9]. Cholinergic neurotransmission plays an important role in cognitive performance [10–13], and associations between anticholinergic adverse effects and the development of dementia or other cognitive disorders have been described [14, 15]. Few studies have evaluated the relationship between anticholinergic medication and the development of delirium. A recent investigation described an association between anticholinergic burden, according to Anticholinergic Drug Scale (ADS) score [16], and the development of POD in older patients with cancer [17]. Overall, studies investigating an association with POD are rare, and the evidence regarding anticholinergic medication is so far inconclusive. Over the years, a number of scales have been developed to simply and efficiently map the anticholinergic burden of drugs, although reviews on this topic [18, 19] have criticized that "variation exists in scale development, in the selection of anticholinergic drugs, and [in] the evaluation of their anticholinergic load" [19].

Preoperative adaptation of long-term medication, especially anticholinergic drugs, would be a feasible option to improve treatment. However, an immediate prerequisite for this is the valid mapping of the anticholinergic load of medications.

The aim of this analysis was to evaluate the preoperative long-term medication of older adult patients according to the most cited anticholinergic scales (ADS, Anticholinergic Risk Scale [ARS] [20] and the Anticholinergic Cognitive Burden Scale [ACBS] [21]) and to investigate an association between scores on these scales and the development of POD.

2 Methods

2.1 Study Design and Population

This investigation was performed as part of the BioCog project (http://www.biocog.eu), a prospective multicenter observational study conducted at the Charité-Universitätsmedizin Berlin, Department of Anesthesiology and Operative Intensive Care Medicine, Berlin, Germany, and the University Medical Center Utrecht, Department of Intensive Care Medicine, Utrecht, Netherlands. The goal of the BioCog study is to establish biomarker panels for risk and clinical outcome prediction of POD and postoperative cognitive dysfunction [22]. The study was approved by the local ethics committees (ref.: EA2/092/14 and 14-469) and conducted in accordance with the declaration of Helsinki (ClinicalTrials.gov: NCT02265263). Written informed consent was obtained from each patient, and all local data privacy regulations were followed.

We included patients who were aged ≥ 65 years, of European descent, undergoing elective surgery with an expected surgical duration ≥ 60 min, and able and willing to provide informed consent and undergo magnetic resonance imaging. Patients with a Mini–Mental State Examination score ≤ 23 points were excluded, as well as those who were homeless or could not be reached by phone or postal services for follow-up examinations. In addition, we excluded participants enrolled in any concurrent prospective interventional clinical study during their hospital stay, those who were accommodated in an institution because of an official or judicial order and those with conditions limiting the conduction of the neurocognitive testing, such as neuropsychiatric conditions, hearing impairment or language barriers.

2.2 Baseline Measurements

The following baseline and perioperative measurements were collected to describe study population: age, sex, physical status according to the American Society of Anesthesiologists (ASA PS), Charlson Comorbidity Index (CCI) [23], duration of anesthesia and site of surgery (intrathoracic/intraabdominal/intrapelvic, peripheral and intracranial operations).

2.3 Postoperative Delirium

POD was defined according to *Diagnostic and Statistical Manual of Mental Disorders 5th Edition* criteria [24]. Patients were considered delirious if they had ≥ 2 cumulative points on the Nursing Delirium Screening Scale and/or a positive Confusion Assessment Method (CAM) score and/or a positive CAM for the Intensive Care Unit (CAM-ICU) score and/or descriptions of delirium on patient chart review (e.g., confused, agitated, drowsy, disorientated, delirious, or received antipsychotic therapy for delirium).

Delirium screening commenced in the recovery room and was repeated twice a day, at 08:00 and 19:00 (± 1 h), up to 7 days after surgery. Delirium assessment was conducted independently of the routine hospital procedures by a research team that was trained and supervised by psychiatrists and other delirium experts.

2.4 Anticholinergic Load

The preoperative anticholinergic load was calculated using the ADS [16], the ARS [20] and the ACBS [21], which are the most cited anticholinergic scales. These all assign a certain number of points to a drug, ranging from "0 points" (no anticholinergic activity) to "3 points" (highest anticholinergic activity). An initial analysis merely determined the presence of any anticholinergic medication listed in each of the scales in the patient medication list. This was followed by an analysis considering the total number of points given for each scale. Long-term medication was determined during the preoperative anesthesia consultation by means of anamnesis or reviewing the patient's medical record or medication prescriptions. Long-term medication included both prescription and over-the-counter medication taken regularly at the time of enrollment.

2.5 Statistical Analysis

Baseline characteristics were expressed as median and 25th quartile and 75th quartile, mean ± standard deviation (SD), or frequencies with percentages. Differences between the groups were tested using the Mann–Whitney *U* test or chi-squared test. The associations between POD and anticholinergic burden (according to ADS, ARS and ACBS) were investigated via multivariable logistic regression analyses, adjusting for possible confounding variables selected a priori, including age, CCI, duration of anesthesia and number of long-term medications. No adjustments were made for multiple testing. All analyses were performed with SPSS Statistics, version 23 (IBM; Armonk, NY, USA) and in the R software environment (R Foundation for Statistical Computing, Vienna, Austria; 2017).

3 Results

A total of 1033 participants were enrolled in two study centers between October 2014 and April 2017. Accounting for early dropouts and missing data, 837 participants could be included in the analysis. Of these, 165 patients (19.7%) developed a POD (Fig. 1). Patients with POD were significantly older, had higher ASA PS and CCI scores and longer duration of anesthesia. Group differences were also seen according to site of surgery. Surgery was most frequently

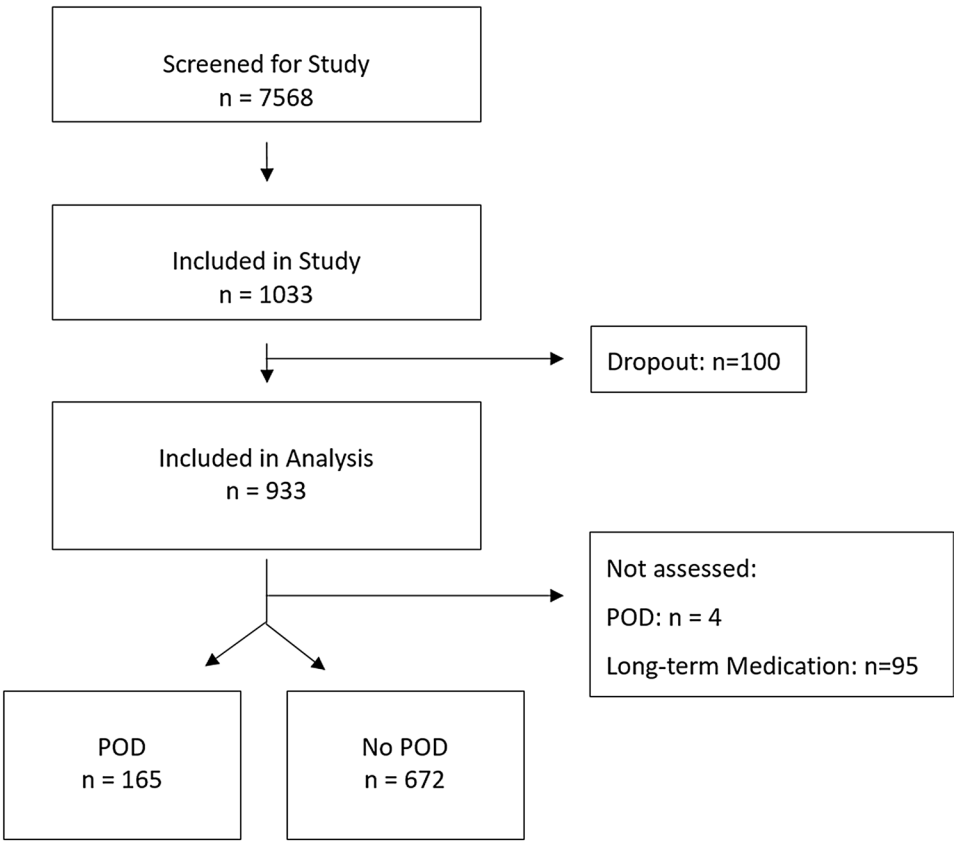

Fig. 1 Flow chart of study participant selection. *POD* postoperative delirium

performed on the musculoskeletal system and digestive tract (see Table S1 in the Electronic Supplementary Material). No sex differences were observed (see Table 1).

In total, 23.8% ($n = 199$) of patients were taking medication with anticholinergic properties preoperatively according to the ADS, 7.2% ($n = 60$) according to the ARS and 28.7% ($n = 240$) according to the ACBS. The mean ± SD anticholinergic load score was 0.4 ± 0.9 points for the ADS, 0.13 ± 0.5 points for the ARS and 0.4 ± 0.8 points for the ACBS. In all three scales, amitriptyline was the most frequently prescribed level III agent. In levels I and II, the most frequently taken agents differed between the scales (Table 2 lists the most frequently taken anticholinergic agents per score and level). There were no differences between subjects with and without POD in the distribution of the most frequently taken drugs per level of the anticholinergic scores. A preoperative adjustment of the anticholinergic medication was not routinely undertaken.

A descriptive analysis showed no differences between patients with and without POD in regard to administration of anticholinergic medication according to ADS, ARS and ACBS or the total score of ADS, ARS or ACBS (Table 3). In addition, when considering confounding factors, anticholinergic load (according to ADS, ARS and ACBS) was not associated with the development of POD in the multivariable logistic regression analyses (ADS, odds ratio [OR] 0.955; 95% confidence interval [CI] 0.621–1.468; ADS [points] OR 0.928; 95% CI 0.749–1.150; ARS OR 0.784; 95% CI 0.376–1.635; ARS [points] OR 0.832; 95% CI 0.564–1.227; ACBS OR 1.132; 95% CI 0.762–1.681; ACBS [points] OR 1.045; 95% CI 0.842–1.296).

Table 2 Distribution of most frequently taken anticholinergic agents per score and level of preoperative long-term medication ($n = 837$ patients)

Scale	Level	*n*	Agent (% within level)
ADS	I	248	Oxycodone (15%), prednisolone (13%), tramadol (11%)
	II	8	Ranitidine (62%), carbamazepine (38%)
	III	24	Amitriptyline (83%)
ARS	I	38	Pramipexole (29%), mirtazapine (21%)
	II	5	Loperamide (60%)
	III	20	Amitriptyline (100%)
ACBS	I	244	Metoprolol (68%)
	II	15	Ipratropium bromide (80%)
	III	26	Amitriptyline (77%)

ACBS Anticholinergic Cognitive Burden Scale, *ADS* Anticholinergic Drug Scale, *ARS* Anticholinergic Risk Scale

4 Discussion

In summary, we did not find an association between anticholinergic load (according to ADS, ARS and ACBS) and the development of POD. This investigation included patients undergoing elective surgery across a wide range of surgical disciplines, of which nearly 20% developed POD. This is in line with other cohorts and investigations [1].

Table 1 Patient characteristics ($n = 837$) for analysis of postoperative delirium

Characteristic	POD ($n = 165$ [19.7%])	No POD ($n = 672$ [80.3%])	*p*-Value
Age (years)	74 (70; 77)	71 (68; 75)	< 0.001[a]
Female sex	79 (47.9)	283 (42.1)	0.180 [b]
ASA PS			
1–2	77 (46.7)	463 (68.9)	< 0.001[b]
3–4	88 (53.3)	209 (31.1)	
Charlson Comorbidity Index	1.86 ± 1.5	1.31 ± 1.5	< 0.001[a]
Duration of anesthesia (min)	306 (211; 473)	168 (105; 255)	< 0.001[a]
Site of surgery			
Intracranial	2 (1.2)	8 (1.2)	
Intrathoracic/intraabdominal/intrapelvic	105 (63.6)	248 (36.9)	< 0.001[b]
Peripheral	58 (35.2)	416 (61.9)	
Number of agents	5.41 ± 3.7	4.44 ± 3.8	0.002[a]

Data are expressed as median (25th quartile; 75th quartile) or as mean ± standard deviation except for categorical data, which are expressed as frequencies (percentages)

ASA PS American Society of Anesthesiologists physical status, *POD* postoperative delirium

$p \leq 0.05$ was considered as statistically significant

[a]Mann–Whitney *U* test between patients with or without POD

[b]Chi-squared test between patients with or without POD

Table 3 Anticholinergic load and postoperative delirium ($n = 837$ patients)

Characteristic	POD ($n = 165$ [19.7%])	No POD ($n = 672$ [80.3%])	p-Value
ADS (points)	0.45 ± 0.92	0.39 ± 0.86	0.484[a]
Anticholinergic medication according to the ADS	42 (25.5)	157 (23.4)	0.572[b]
ARS (points)	0.12 ± 0.50	0.13 ± 0.54	0.973[a]
Anticholinergic medication according to the ARS	12 (7.3)	48 (7.1)	0.954[b]
ACBS (points)	0.53 ± 0.97	0.39 ± 0.77	0.085[a]
Anticholinergic medication according to the ACBS	56 (33.9)	184 (27.4)	0.095[b]

Data are expressed as mean ± standard deviation except for categorical data, which are expressed as frequencies (percentages)

ACBS Anticholinergic Cognitive Burden Scale, *ADS* Anticholinergic Drug Scale, *ARS* Anticholinergic Risk Scale, *POD* postoperative delirium

$p \leq 0.05$ was considered as statistically significant

[a]Mann–Whitney *U* test between patients with or without POD

[b]Chi-squared test between patients with or without POD

Cholinergic neurotransmission plays an important role in cognitive performance, and a leading hypothesis model explains the connection between anticholinergic effects and the pathogenesis of delirium [25]. van Gool et al. [25] hypothesized that cholinergic inhibition could suppress the formation of a vicious cycle where neuroinflammation is maintained by the activation of microglia cells. He postulated that any dysfunction in cholinergic neurotransmission could hinder this mechanism and promote the development of delirium [25]. It is conceivable that anticholinergic adverse effects can promote the development of delirium, as this has already been observed in different settings. For example, associations were reported between the anticholinergic load according to the ACBS and the development of delirium in acutely ill patients [26, 27], between the anticholinergic load according to the ARS and the development of delirium in frail older adults living in a nursing home [28], and between the increase in ARS score and development of delirium in palliative care inpatients [29].

However, our analysis could not confirm an association between anticholinergic load and the development of POD in older surgical patients. This is in line with a study investigating patients aged ≥ 65 years with hip fracture, which could not find an association between a high anticholinergic burden, according to a total score of at least 3 in the clinician-rated ADS, and the development of POD [30]. Furthermore, another study found no association between anticholinergic activity in serum or cerebrospinal fluid, determined according to a muscarinic radio receptor bioassay, and the development of POD [31].

Notably, our results are in contrast with the recently published study on anticholinergic burden and development of POD in older patients with cancer [17], which found an association between anticholinergic burden (ADS) and development of POD. Differing results may be explained by differing target populations (patients with cancer), and generalizability might have been limited by the national design, whereas BioCog was an international multicenter study. Furthermore, in the positive study, 16% of patients were using anticholinergic medication preoperatively and the reported mean ADS score was 0.2 points, whereas preoperative use in our cohort reached 24% and the mean ADS score was 0.4 points. This can be primarily explained by the international design of the BioCog study. The patients treated at the Utrecht study center had significantly higher ADS scores and were significantly more frequently affected by anticholinergic load than the patients treated at the Berlin study center. Lastly, the incidence of POD in the positive study was low at 10%, which could be attributed to patient empowerment through intervention, whereas we observed an incidence of 20% in our cohort.

It must be noted that a well-known issue in the investigation of anticholinergic drugs is that an agent can be rated as having a different level of anticholinergic properties according to the scale used. To deal with this, we calculated the anticholinergic load of the long-term medication using the three most comprehensive scales: ADS, ARS and ACBS. Nevertheless, each scale has advantages and disadvantages that must be taken into account. While the ADS has been validated by a laboratory chemical method showing an association with serum anticholinergic activity, there is no reference in the literature to the establishment of the scale or to the criteria utilized to assign drugs to the different scale levels [16]. Substantial methodological effort was used in the creation of the ARS. After a review of the 500 most commonly prescribed drugs, agents with known potential to cause anticholinergic adverse effects (AEs) were identified and associated with the dissociation constant for the cholinergic receptor. A literature search regarding anticholinergic AEs was then conducted, all information was reviewed by independent assessors and the medication was classified accordingly [20]. The ARS was then validated using both

retrospective and prospective designs via associations with anticholinergic AEs [20]. ACBS was based on a literature review of anticholinergic activity and cognitive function in older patients. The identified drugs were then classified by an interdisciplinary team of experts [21]. The ACBS has not been formally validated.

Consequentially, it is not surprising that reported results differ according to the scale used, with not only total scores varying but also the overall prevalence of anticholinergic load. Despite these differences, the results were similar for all three scales, and no association with POD was observed, likely supporting the validity of the results. However, we cannot rule out that the reason we found no association between anticholinergic load and POD is that the anticholinergic load classification is inappropriate in all three scales. It has been discussed that the intake of any anticholinergic drug or the number of anticholinergic drugs is not as decisive as the combination and subsequent interaction of certain anticholinergic agents [9]. In addition, it seems reasonable to consider the dosage of anticholinergic drugs. To our knowledge, the Drug Burden Index is the only scale that takes dosages into account [32]. The index is based on a mathematical formula that includes the anticholinergic and sedative effects of drugs. In contrast to other anticholinergic scales, there is no positive or negative list of drugs for the index. Instead, drugs are identified using local formulary, which vary between countries. Practical application requires the development of a local list from current approved product information [33]. This makes the practical application of this tool very difficult. Another interesting investigation would be to determine whether patients benefit from preoperative adjustment of anticholinergic drugs in terms of developing POD, preferably employing a randomized controlled trial design. Ultimately, the immediate prerequisite for the development of preventive strategies, in the sense of preoperative adaptation of long-term anticholinergic drugs, remains the valid mapping of the anticholinergic load of the substance.

It is conceivable that factors other than preoperative anticholinergic load have a greater influence on the development of POD. Future analyses should also examine the influence of intra- and postoperative administration of anticholinergic drugs.

A key strength of this study is the prospective multicenter design. POD was characterized by a comprehensive, standardized and validated assessment according to current recommendations. The study database contains further information on possible confounders, and we were able to investigate the associations over a wide range of surgical disciplines, reflecting the setting conditions that apply to routine preoperative risk evaluation.

Nevertheless, some important limitations must be considered. The application of further anticholinergic scales and the consideration of interactions, including dosages, could have provided further insight. A criterion of the parent BioCog study excluded patients with severe preoperative cognitive deficits, although they are known to have a very high risk of developing POD. Although the incidence of POD would probably have been higher if these patients had been included, we do not know whether there would have been an association with preoperative anticholinergic load and POD.

5 Conclusion

Our analysis found no association between preoperative anticholinergic load (according to the ADS, ARS and ACBS) and the development of POD in older surgical patients. Future analyses should examine the influence of intra- and postoperative administration of anticholinergic drugs as well as dosages of and interactions between medications.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40266-021-00839-5.

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Declarations

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Conflict of interest Maria Heinrich is a participant in the Charité Digital Clinician Scientist Program funded by Deutsche Forschungsgemeinschaft. Maria Heinrich, Anika Müller, Andela Cvijan, Rudolf Mörgeli, Jochen Kruppa, Georg Winterer, Arjen J. C. Slooter and Claudia D. Spies have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval This was a prospective multicenter observational study conducted at the clinical study centers Charité-Universitätsmedizin

Berlin, Department of Anesthesiology and Operative Intensive Care Medicine, Berlin, Germany, and the University Medical Center Utrecht, Department of Intensive Care Medicine, Utrecht, Netherlands. The study was approved by the local Ethics Committees (ref.: EA2/092/14 and 14-469) and conducted in accordance with the declaration of Helsinki (ClinicalTrials.gov: NCT02265263).

Consent to participate Written informed consent was obtained from each patient, and all local data privacy regulations were followed.

Consent for publication Written informed consent was obtained from each patient.

Availability of data and material The datasets generated and analyzed during the current study are not publicly available as no consent for this was obtained from participants but are available from the corresponding author on reasonable request.

Code availability Not applicable.

Author contributions Maria Heinrich, Anika Müller, and Rudolf Mörgeli were involved in data collection and plausibility checks. Maria Heinrich, Anika Müller, and Claudia Spies developed the research question. Maria Heinrich and Jochen Kruppa carried out the analyses. The first draft of the manuscript was written by Maria Heinrich, and all authors commented on subsequent versions and read and approved the final manuscript. Georg Winterer, Arjen Slooter, and Claudia Spies designed and directed the BioCog project.

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