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ORIGINAL RESEARCH ARTICLE

Haloperidol Use Among Elderly Patients Undergoing Surgery: A Retrospective 1-Year Study in a Hospital Population

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Abstract

Background Haloperidol, frequently used for delirium, can lead to serious side effects, of which QTc prolongation is the most worrisome since it is associated with an increased risk of fatal cardiac arrhythmia.

Objectives The aim of this study was to measure the frequency of haloperidol use after procedures in patients aged ≥65 years in a hospital in the Netherlands.

Methods This was a retrospective study among patients hospitalized in the Netherlands who were aged ≥65 years and who underwent a procedure between January 2008 and January 2009. The hospital's electronic drug database was used to identify the use of haloperidol during hospital admission.

Results A total of 7782 procedures took place in 5946 elderly patients, and 1357 patients were readmitted for a second procedure in the same year. The overall frequency of haloperidol use was 5.4 %. Procedures were classified as elective (90 %) and as major (18 %). A total of 28 % (n = 570) of patients who underwent acute procedures and 24 % (n = 1086) of patients who underwent major procedures received haloperidol. Patients receiving haloperidol had a significantly longer hospital stay (14 vs. 1 day, $p < 0.001$) than patients without haloperidol. Haloperidol users were more likely to have more than one intervention than non-users (16.0 vs. 1.7 %, $p < 0.001$). In multivariable analysis, haloperidol use was associated with older age (odds ratio [OR] 1.09; 95 % confidence interval [CI] 1.07–1.11, $p < 0.001$), acute surgery (OR 2.09; 95 % CI 1.65–2.94, $p < 0.001$), and major procedures (OR 15.4; 95 % CI 11.5–21.5, $p < 0.001$).

Conclusion We show a frequency of haloperidol use of 5.4 %. Based on this high frequency, surveillance of adverse events in hospital should be performed systematically, particularly in the high-risk population that undergoes acute major surgery.

Key Points

The frequency of haloperidol use among hospitalized patients in the Netherlands aged ≥65 years who underwent a procedure between January 2008 and January 2009 was over 5 %.

The percentage of haloperidol users is higher in older patients undergoing acute or major procedures.

Patients using haloperidol experienced a longer hospital stay in this study and are known to have a higher risk of adverse events in the literature.

1 Introduction

In 2005, the US FDA warned clinicians against prescribing antipsychotic medications to patients with dementia-related psychosis, because it would expose patients to an increased risk of death [1]. Mittal et al. [2] showed a 1.3 to 2.0-fold increased risk of stroke and a 1.2 to 1.6-fold increased risk of mortality; these risk ratios are comparable for all antipsychotics. Known immediate side effects of antipsychotics include somnolence, urinary tract infection, urinary

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incontinence, extrapyramidal symptoms, or abnormal gait [3–6]. Antipsychotics are prescribed for many different symptoms and diseases, such as anxiety, psychosis due to schizophrenic disease or depression, and behavioral disturbance in dementia or delirium.

Hospitalized patients with delirium may have a similar or even higher potential for adverse side effects from antipsychotics than more stable patients. The most important known risk factors for postoperative delirium are older age and cognitive or functional impairment [7]. Many older patients with delirium also have dementia; they also usually have an acute medical illness and multiple comorbidities, and are often taking drugs that increase the QTc interval. Yet this issue remains unaddressed, because no published, adequately powered, double-blind, randomized, placebo-controlled trials have examined the safety of antipsychotics in the management of delirium [8]. In addition, no specific recommendations exist for patients with delirium as well as dementia.

Prevalence estimates for delirium during a hospital admission are 10–30 %; thus, it is reasonable to assume that this condition is the single most common cause for the administration of haloperidol in a hospital setting [9, 10]. The scientific evidence for the efficacy of haloperidol in treating delirium is based on a few studies [10]. Five studies evaluated the side effects of haloperidol versus various neuroleptics (e.g., risperidone, olanzapine, quetiapine, and ondansetron) and showed no significant differences in the treatment response for delirium symptoms [11–15].

The 2010 UK National Institute for Health and Care Excellence (NICE) guideline on delirium, which took into account the evidence available at that time, advised limiting the use of antipsychotics for individuals with delirium in distress or at risk to themselves or others. Furthermore, it should be prescribed only after non-pharmacological interventions have been tried, and then only in the lowest possible dose and for the shortest possible time period [16].

The aim of this study was to measure the frequency of haloperidol use after procedures in patients aged ≥65 years in a hospital in the Netherlands. A prerequisite for assessing the risks associated with antipsychotic use in hospitalized patients is to have systems that record the use of these drugs. To address the above gap in the literature, we used electronic pharmacy records to determine the proportion of hospitalized patients aged ≥65 years administered haloperidol after surgical procedures. We studied haloperidol because it is the first-choice medication for delirium in the Netherlands [17].

2 Methods

2.1 Patients

All patients aged ≥65 years who underwent a surgical procedure in the Jeroen Bosch hospital in s–Hertogenbosch in the Netherlands in the period between 1 January 2008 and 1 January 2009 were included. This hospital has 750 beds and is a non-academic, regional teaching hospital with 21 separate medical training specialties. The surgical specialties were gynecology, orthopedics, general surgery, urology, ophthalmology, otorhinolaryngology, oral surgery, neurosurgery, and plastic or reconstructive surgery.

2.2 Study Design

Haloperidol administration during admission was identified using the electronic hospital drug database. Inclusion criteria included patients who took this medication for at least 1 day during their admission period. In the Netherlands, the conventional starting dose for haloperidol is 1 mg. Minor procedures were defined as procedures for which patients were admitted for less than 6 days, and major procedures were defined as a stay longer than 6 days. Procedures were categorized as either acute or elective based on the reason for admission, as classified by the *International Statistical Classification of Diseases and Related Health Problems* – 9th revision (ICD-9).

2.3 Statistical Analysis

We used the Statistical Package for the Social Sciences (SPSS, version 19.0, Chicago, IL, USA) for data analysis. We used *t*-tests and Mann–Whitney *U* tests to test for differences in characteristics in patients with and without haloperidol use. Variables that were not normally distributed were expressed as median scores and interquartile ranges. A two-tailed criterion of $p < 0.05$ was considered statistically significant. We performed univariate and multivariate logistic regression analyses, where haloperidol use was the dependent variable, and age, acute versus elective surgery, minor versus major procedures, and surgical specialty were the independent variables.

3 Results

A total of 7782 procedures occurred in 5946 patients; 145 patients underwent a second procedure during their first admission, and 1357 patients were admitted for at least one additional procedure in the same year. The characteristics of the patients who did and did not use haloperidol are

presented in Table 1. The overall incidence of haloperidol use related to the first procedure in the first admission was 5.4 %. Of these, 323 patients (12 %) received haloperidol throughout the complete admission period. Those administered haloperidol were significantly older (81.2 vs. 74.4 years, $p < 0.001$). In acute procedures ($n = 570$), the percentage of haloperidol use was 28.0 versus 3.1 % in the 5376 elective procedures ($p < 0.001$). In major procedures ($n = 1086$), the percentage was 24.0 versus 1.3 % in 4960 minor procedures ($p < 0.001$).

Patients who received haloperidol had a significantly longer hospital stay (14 vs. 1 day, $p < 0.001$) than patients who did not receive haloperidol. Haloperidol users more often underwent more than one procedure (e.g., they underwent two operations or a biopsy followed by an operation during the admission period [16.0 vs. 1.7 %, $p < 0.001$]) than non-users, but they were less frequently readmitted for a second procedure (12 vs. 23 %, $p < 0.001$).

An overview of the most common procedures per specialty is presented in Table 2; 90 % of procedures were elective and 18 % were major. A total of 29 % of acute procedures and 45 % of major procedures were performed in general surgery. Of these, 15 % of patients received haloperidol. Ophthalmologic surgery was the most frequent type of surgery ($n = 1865$; 31.4 %), and the majority of the ophthalmologic interventions were cataract operations (89.5 %). These were classified as minor procedures, with a haloperidol usage of 0.4 %. Haloperidol use in patients admitted with a fracture was acute: 30 % in surgical patients and 34 % in orthopedic patients. Haloperidol use in orthopedics was 6.4 %, in plastic surgery 0.3 %, in urology 2.4 %, and in gynecology 1.7 %; no patients in the otorhinolaryngology received haloperidol. The odds ratio (OR) of haloperidol administration upon second admission if patients had already been administered haloperidol at first admission was 55 (95 % confidence interval [CI] 27–116).

Table 3 shows the results of the multivariate analysis. Haloperidol use was strongly associated with specialty, specifically general surgery (OR 6.4, 95 % CI 4.0–10.1, $p < 0.001$), acute procedures (OR 1.5, 95 % CI 1.1–2.1, $p < 0.001$), major procedures (OR 8.3, 95 % CI 5.9–11.5, $p < 0.001$), and older age (OR 1.1, 95 % CI 1.08–1.12, $p < 0.001$).

4 Discussion

In this descriptive study of haloperidol use in a hospital population of surgical patients ($N = 5946$) treated over the course of 1 year in a single large hospital in the Netherlands, we found an overall frequency of haloperidol administration of 5.4 %. The hospital is representative of large teaching hospitals in the Netherlands. Haloperidol use in acute and major surgery was much higher than in elective and minor surgery; at least one-quarter of patients who fell into either category received this drug. The fact that haloperidol administration was associated with older age, acute procedures, and major procedures, which are all

Table 1 Characteristics of patients who did and did not receive haloperidol

Variables	Haloperidol ($N = 323$)	No haloperidol ($N = 5623$)	p value
Age (years)	81.2 (65–101)	74.4 (65–104)	<0.001
Male sex (%)	145 ± 45	2409 ± 43	0.47
Specialty (%)			<0.001
Ophthalmology	7 ± 2.2	1858 ± 33	
General surgery	230 ± 71	1269 ± 23	
Orthopedic surgery	66 ± 20	962 ± 17	
Plastic surgery	2 ± 0.6	632 ± 11	
Urology	14 ± 4.3	578 ± 10	
Gynaecology	4 ± 1.2	226 ± 4.0	
Otorhinolaryngology	0 ± 0	70 ± 1.2	
Other[a]	0 ± 0	28 ± 0.5	
Acute procedure (%)	157 ± 49	413 ± 7.3	<0.001
Major procedure (%)	261 ± 81	825 ± 15	<0.001
Length of stay	14 (2–133)	1 (1–142)	<0.001
≥1 Intervention (%)	52 ± 16	93 ± 1.7	<0.001
≥1 Admission (%)	39 ± 12	1318 ± 23	<0.001

Data are presented as mean ± standard deviation for continuous variables with a normal distribution or as median (interquartile range) for variables that are not normally distributed

[a] 'Other' includes cardiology, neurosurgery, and oral surgery

Table 2 Characteristics of the most common surgical procedures, by specialty

Variables	Procedures	Acute (%)	Major (%)	Haloperidol Use
Ophthalmology	1865	1 (0.1)	3 (0.2)	0.4 %
Senile cataract	1670 (89.5 %)			
General	1499	430 (29)	674 (45)	15.3 %
Fracture reposition	318 (21.2 %)			
Biopsy[a]	240 (16 %)			
Digestive tract operations	218 (14.6 %)			
Vascular intervention	200 (13.3 %)			
Inguinal hernia operation	140 (9.3 %)			
Shunt construction	38 (2.5 %)			
Orthopedics	1028	110 (11)	250 (24)	6.4 %
Osteoarthrosis surgery	478 (46.5 %)			
Fracture reposition	86 (8.4 %)			
Removal of plates and correction material	83 (8 %)			
Plastic surgery	634	8 (1.3)	16 (2.5)	0.3 %
Hand surgery due to mononeuritis	124 (19.6 %)			
Biopsy	36 (5.4 %)			
Eye correction surgery	54 (8.5 %)			
Other	386 (60.9 %)			
Urology	592	15 (2.5)	70 (12)	2.4 %
Urethrocystoscopy	320 (54.1 %)			
Prostatectomy	138 (23.3 %)			
Biopsy	34 (5.4 %)			
Gynecology	230	3 (1.3)	69 (30)	1.7 %
Biopsy	91(39.6 %)			
Genital prolapse surgery	78 (33.9 %)			
Otorhinolaryngology	70	0	1 (1.4)	0
Sinusitis surgery	20 (28.6 %)			
Septum rhinoplasty	8 (11.4 %)			
Correction nasal polyp	9 (12.9 %)			
Other[b]	28	3 (11)	3 (11)	0

[a] Biopsy in general surgery includes pulmonary biopsy, lymph nodular explorations, benign exploration of thyroid pathology, rectal polyp excisions, and mamma incision biopsy

[b] 'Other' includes neurosurgery and oral surgery

established risk factors for delirium, suggests that delirium could be the most important indication for its prescription [18]. However, we do not know the indication of haloperidol use, and the known risk factors for delirium—such as operative stress and other drugs used peri- and postoperatively—are not measured in our database. Furthermore, in our study population, a large group of patients were ophthalmologic patients ($n = 1865$), most of whom underwent a cataract procedure; this type of procedure is known to have a low delirium prevalence. It is possible that approximately 0.1 % of patients received haloperidol 1 mg/day prior to procedures if it was known that they had a medical history of serious delirium.

Indeed, a 5.4 % haloperidol administration level is consistent with the typical delirium rates in these groups, as reported in the international literature [16, 17]. Additionally, the multivariate analysis showed that haloperidol use was associated with longer hospital stay, which might be another indirect clue that patients who received haloperidol experienced delirium because delirium is known to be associated with a prolonged hospital stay [19]. Alternatively, the use of haloperidol itself may have contributed to the length of stay.

More broadly, this study shows that large numbers of older people received haloperidol during their hospitalisation for surgery. This level of haloperidol use is notable given the lack of strong evidence for the benefits of this drug in the treatment of delirium. No previous study has investigated the appropriate antipsychotic dosage levels for delirium, and we believe different countries have different antipsychotic dosage strategies [9].

Table 3 Univariate and multivariate analysis of the factors associated with haloperidol use in surgical patients aged >65 years

Factor	Univariate analysis OR (95 % CI)	*p* value	Multivariate analysis OR (95 % CI)	*p* value
Age (years)	1.12 (1.11–1.14)	<0.001	1.1 (1.08–1.12)	<0.001
Specialty (%)				
Other[a]	Reference			
General surgery	22.8 (15.2–34.1)	<0.001	6.4 (4.0–10.1)	<0.001
Orthopedic surgery	8.6 (5.5–13.6)	<0.001	4.0 (2.4–6.5)	<0.001
Acute procedure (%)	11.9 (9.38–15.2)	<0.001	1.5 (1.1–2.1)	<0.001
Major procedure (%)	24.5 (18.4–32.6)	0.004	8.3 (5.9–11.5)	<0.001

CI confidence interval, *OR* odds ratio

[a] All surgeries except general or orthopedic surgery

Importantly, in the last 10 years, more studies have identified a number of risks associated with prescribing antipsychotic drugs during hospital stay, such as a higher risk of pneumonia [20] and or cerebrovascular events. This risk is present even during the first week of antipsychotic use [21]. Furthermore, the initiation of neuroleptics is associated with a 40 % increased risk of a fracture. Delirium is known to be a strong risk factor for dementia, and delirium accelerates cognitive decline in Alzheimer's dementia [22, 23]. In light of this, haloperidol should be prescribed carefully, especially in the absence of scientific medical evidence.

A key strength of this study is the use of a large hospital population dataset analyzed over a 1-year period, providing sufficient power for our study's conclusions. Additionally, electronic records are a reliable way to capture medication use in a hospital setting.

Some limitations should be acknowledged. The study was retrospective; we did not prospectively collect data on indications for haloperidol use. Retrospective analysis of medical charts could yield more relevant information. For example, indications for prescription, such as behavioral disorder or psychotic disorder, could not be taken into account because this detailed information was missing.

Furthermore, the study of adverse events in relation to haloperidol use was beyond the scope of this study. Moreover, we limited this study to haloperidol users and did not investigate other atypical antipsychotics. However, in the Netherlands, haloperidol is the first medication of choice for the treatment of delirium in elderly patients in hospital [17].

5 Conclusion

This study indicates that substantial numbers of older patients undergoing procedures are prescribed haloperidol, with an overall frequency of 5.4 %. The highest use is in older patients undergoing major or acute procedures. This study is the first study to evaluate the use of haloperidol in a large hospital population with various surgical procedures. It is important because of the lack of strong positive evidence in favor of haloperidol use in the treatment of delirium and/or other indications (e.g., behavioral disturbance in dementia), and the potential adverse effects associated with this drug. Given the large-scale use of haloperidol, further research on the benefits, side effects, and costs of this treatment is urgently required.

Compliance with ethical standards

Conflict of interest None of the authors (Prof. A. McLullich, B.C. van Munster, G. Lefeber, H Nijboer) has any conflicts of interest that are directly relevant to the content of this study.

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