Comparative Study Between Haloperidol Versus Olanzapine for The Treatment of Delirium in Intensive Care Unit

Thesis

Submitted for Partial Fulfillment of M.D. Degree in Anesthesiology

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Acknowledgement

First of all, all gratitude is due to **God** *almighty for blessing this work, until it has reached its end, as a part of his generous help, throughout my life.*

Really I can hardly find the words to express my gratitude to **Prof. Dr / Nermin Sadek Nasr** *Professor of Anesthesia and Intensive Care, faculty of medicine, Ain Shams University, for her supervision, continuous help, encouragement throughout this work and tremendous effort she had done in the meticulous revision of the whole work. It is a great honor to work under her guidance and supervision.*

I ask ALLAH to forgive **Prof. Dr /AZZ abd elrashid** *who left our life to the mercy of ALLAH*

Really I can hardly find the words to express my gratitude to **Prof. Dr / Ayman Ahmad Abdellatif,** *Assistant Professor of Anesthesia and Intensive Care, for his continuous directions and meticulous revision throughout the whole work. I really appreciate their patience and support.*

Great thanks to: **Dr./Diaa Eldeen Shalabi Elawadi**, *Lecturer of Anesthesia and Intensive Care, Faculty of Medicine - Ain Shams University. I will never be able to express my feelings and gratitude towards her with simple words, and I wish to be able one day to return apart of what he has offered to me.*

Last but not least, I dedicate this work to my family, whom without their sincere emotional support, pushing me forward this work would not have ever been completed.

Wael Abd El Aziz Mohamed Omran

Contents

List of Abbreviations

APACHE	:	Acute Physiology and Chronic Health Evaluation
CAM-ICU	:	Confusion Assessment Method for the ICU
CYP	:	Cytochrome P
D1	:	Dopaminergic receptors 1
D2	:	Dopaminergic receptors 2
DDS	:	Delirium Detection Score
DRS	:	Delirium Rating Score
DSMB	:	The data safety and monitoring board
DSM-IV	:	Diagnostic and Statistical Manual of Mental Disorders version IV
ECG	:	Electrocardiography
EPS	:	Extrapyramidal symptoms
GABA	:	Gamma-Aminobutyric acid
ICDSC	:	Intensive Care Delirium Screening Checklist
ICU	:	Intensive care unit
K-MMSE	:	Korean version of the Mini Mental Status Examination
NMS	:	Neuroleptic malignant syndrome
PRN	:	Per required need
QTc	:	Corrected QT interval
RASS	:	Richmond Agitation Sedation Scale

List of Tables

List of Tables (Cont.)

List of Figures

Introduction

Delirium is a severe psychiatric syndrome characterized by acute change in consciousness and cognitive function caused by an underlying medical condition (***Adamis et al., 2006).***

Delirium is a form of acute brain dysfunction associated with higher mortality, increased length of hospital stay, increased costs and, long-term cognitive impairment ***(Van den Boogaard et al., 2012).***

Delirium is very common in hospitalized patients. Its prevalence is 10-24% in the adult general medicine population and 37-46% in the general surgical population. In the intensive care unit (ICU) setting, delirium has been reported in up to 87% of patients. Postoperative delirium rates vary widely, ranging from 9% to 87%, depending on patient age and the type of surgery ***(Greene et al., 2009).***

The etiology of delirium is not fully understood and is probably multifactorial. Acute central cholinergic deficiency is one of the most widely accepted explanatory theories, decreased GABA activity, abnormalities in melatonin and serotonin pathways, noradrenergic hyperactivity, inflammation with increased release of Interleukin-I and Interleukin-6 leading to neuronal damage, and cerebral hypoperfusion are other possible pathogenetic mechanisms ***(Hshieh et al., 2008).***

Due to the risk of side effects of haloperidol, particularly extrapyramidal symptoms (EPS), corrected QT interval (QTc) prolongation or torsades de pointes, neuroleptic malignant syndrome,and seizure threshold reduction, other agents that may be utilized include the

atypical anti-psychotics (i.e., risperidone, ziprasidone, quetiapine and olanzapine). Similar to haloperidol, these medications target dopamine receptors, but also target additional neurotransmitter receptors, including serotonin, acetylcholine and norepinephrine. Potential advantages of the atypical anti-psychotics include decreased incidence of EPS, little effect on QTc (except ziprasidone), decreased hypotension, and lower risk of neuroleptic malignant syndrome ***(Lacasse et al., 2006).***

Aim of the Work

The objective of this study was to evaluate and compare the use of Olanzapine in the treatment of delirium in ICU, as regard its efficacy and safety profile compared to Haloperidol.

Definitions:

Delirium is an acute and fluctuating disturbance of consciousness with reduced ability to focus, maintain or shift attention, accompanied by changes in cognition and perceptual disturbances secondary to a general medical condition ***(Morandi et al., 2008).***

Table (1): Diagnostic elements of delirium.

disturbance of	
Attention	Difficulty focusing, easy distractibility
Cognition	Disorganized thinking; incoherent speech; hallucinations; delusions
Behavior	Agitation vs. lethargy; fear; paranoia; irritability
That is	
Acute	Occurs over a few hours, sometimes with short- lived prodromes
Fluctuating	Lucid intervals between episodes, with memory of the events

(Morandi et al., 2008).

Delirium is a form of acute brain dysfunction associated with higher mortality, increased length of hospital stay, increased costs and, long-term cognitive impairment ***(Van den Boogaard et al., 2012).***

Epidmiology:

The prevalence of delirium in the Intensive Care Unit (ICU) is reported to vary from 20 to 80% ***(Burkhart et al., 2010).***

Delirium in the ICU patient is a common consequence of critical illness. It is estimated that up to 50 percent of non-ventilated patients and 80 percent of mechanically ventilated

patients may experience delirium during an ICU stay ***(Thomason et al., 2005).***

Delirium is very common in hospitalized patients. Its prevalence is 10-24% in the adult general medicine population and 37-46% in the general surgical population. In the ICU setting, delirium has been reported in up to 87% of patients. Postoperative delirium rates vary widely, ranging from 9% to 87%, depending on patient age and the type of surgery ***(Greene et al., 2009).***

Classification:

Delirium is subcategorized according to psychomotor symptoms into (hyperactive, hypoactive, or mixed). Hyperactive delirium (in the past referred to as ICU psychosis) is associated with a better overall prognosis ***(Meagher and Trzepacz, 2000).*** It is characterized by agitation, restlessness, attempting to remove catheters, and emotional liability ***(O'Keeffe and Lavan, 1999).*** Hypoactive delirium, which is common and often more deleterious for the patient in the long term, remains unrecognized in 66 to 84% of hospitalized patients. Hypoactivity on the part of a patient does not seem like a problem and may be missed ***(Sanders, 2002),*** this subtype is characterized by withdrawal, flat affect, apathy, lethargy, and decreased responsiveness. Some refer the hypoactive delirium as *encephalopathy* and restrict "delirium" to hyperactive patients. However, using separate terms proves difficult since patients may present with a mixed clinical picture or sequentially experience both subtypes ***(Meagher and Trzepacz, 2000).***

The two most common types of delirium in the ICU are mixed and hypoactive ***(Peterson et al., 2006).*** Hypoactive delirium tends to occur more frequently in older patients compared with other types of delirium and has a worse

prognosis. In patients who underwent elective surgery with postoperative ICU admission, the 6-month mortality was 32% in patients with hypoactive delirium compared with 8.7% in those with other types of delirium ***(Robinson et al., 2011).***

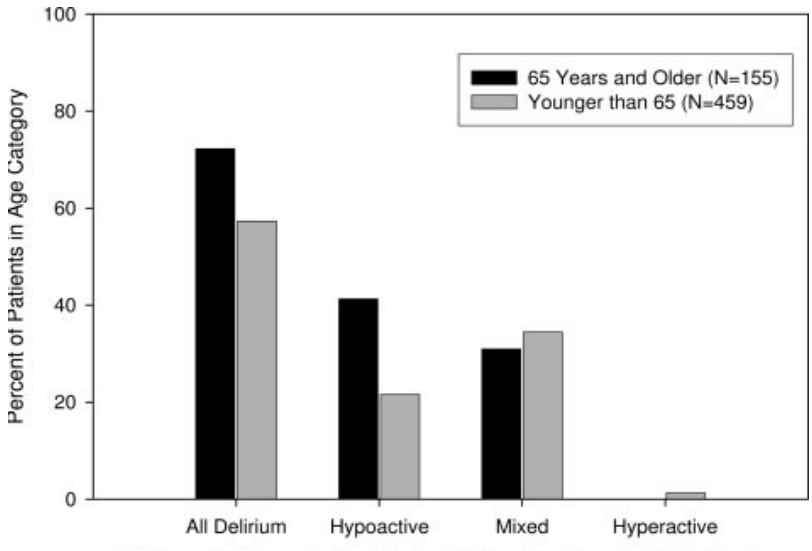

Fig. (1). Delirium subtypes distribution **(Peterson *et al.*, 2006)**

Another important categorization scheme was recently studied in the critical care literature. ICU patients were evaluated for symptoms of delirium and categorized them according to the number of symptoms present. Patients with no symptoms were considered to have 'no delirium', those with four or more symptoms to have 'clinical delirium', and those with one to three symptoms to have 'subsyndromal delirium'. Subsyndromal delirium represents an intermediate state that is different from both clinical delirium and a normal neurologic state **(Ouimet *et al.*, 2007).**

Patients with core symptoms of delirium not reaching full syndromal criteria (subsyndromal delirium) experience outcomes similar to those for the full syndromal illness ***(Marcantonio et al., 2005).***

Risk factors:

Numerous risk factors have been identified for the development of delirium in the ICU. They are summarized in (Table 2).

Table (2): ICU delirium risk factors

Medical history	Age over 70 years Hypertension Congestive cardiac failure Stroke Epilepsy Depression Dementia HIV Renal impairment Hepatic impairment Visual or hearing impairment
Social history	Smoker Alcohol abuse Malnutrition
Environmental	Physical restraints Rectal or urethral catheter Central venous catheter Sleep deprivation
Acute presentation	Disease severity (APACHE II score) Metabolic derangement Hyper- and hypothyroidism Hypo- or hyperglycemia Hyper/hyponatraemia Hyperthermia/Hypothermia Sepsis Hypoxemia Anxiety Uncontrolled pain
Medications	Opiates Benzodiazepines Propofol Anti-cholinergics

(Salluhj et al., 2010).

Patients above 65 years of age have a high incidence of delirium at all levels of hospitalization:10-15% in the general ward,15-50% postoperatively, and nearly 90% in the ICU. What makes the elderly more susceptible to delirium may include cardiovascular and metabolic comorbidity, the intake of large numbers of prescribed medications, a higher sensitivity to acute stress, surgery, and anesthetics, and the prevalence of dementia and other chronic neurologic diseases **(Inouye, 2006).**

Delirium is prevalent among critically ill patients, particularly those that are intubated and mechanically ventilated. In medical, surgical, and trauma ICUs, patients who undergo mechanical ventilation have a prevalence of delirium as high as 80*%* **(Riker *et al.*, 2009),** The need for mechanical ventilation is likely a surrogate of severity of illness, but the tracheal intubation per se, as well as the tight fitting of a non- invasive ventilation mask, may produce sufficient distress (inability to talk, breathlessness, etc.) to trigger delirium. It is important to note that most mechanically ventilated ICU patients are not hypoxemic and may have not been hypoxemic at the time of intubation; the implication that hypoxemia is a common trigger of ICU or perioperative delirium is not based on robust clinical evidence **(Guillamondegui *et al.*, 2011).**

Delirium is not only more frequent in hospitalized patients with multiple medical problems, but it is often the early warning of the onset of a new complication, such as sepsis or congestive heart failure. A number of studies have confirmed the statistical association of indices of severity of illness such as the Acute Physiology And Chronic Health Evaluation Score II (APACHE II) with the development of delirium **(Pisani *et al.*, 2009).**

Benzodiazepines have been consistently associated with the onset of delirium, with no exception among