Prevention of Delirium in Intensive Care Using low dose risperidone prophylaxis: A randomised placebo controlled trial

Dissertation submitted to The Tamil Nadu Dr. MGR Medical University, in part fulfilment of the requirement for MD Branch I General Medicine Final Examination to be held in May 2019

Certificate

We hereby declare that the dissertation entitles “Prevention of Delirium in Intensive Care using low dose risperidone prophylaxis: a randomised placebo controlled trial” is bonafide work done by Dr Amita Jacob, Department of General Medicine, Christian Medical College, Vellore, India, and is submitted to the Tamil Nadu Dr MGR Medical University. It has not been submitted in part or in full to any other university.

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Certificate

I hereby declare that the dissertation entitles "Prevention of Delirium in Intensive Care using low dose risperidone prophylaxis: a randomised placebo controlled trial" is bonafide work done by Dr Amita Jacob under my guidance at the Department of General Medicine, Christian Medical College, Vellore, India and is submitted to the Tamil Nadu Dr MGR Medical University. It has not been submitted in part or in full to any other university.

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Professor of Medicine

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Declaration

I hereby declare that the dissertation entitles "Prevention of Delirium in Intensive Care using low dose risperidone prophylaxis: a randomised placebo controlled trial" is bonafide work done by me under the guidance of Dr O.C. Abraham, Professor of Medicine, at the Department of General Medicine, Christian Medical College, Vellore, India and is submitted to the Tamil Nadu Dr MGR Medical University. It has not been submitted in part or in full to any other university.

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IRB Approval

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Prevention of Delirium in Intensive Care using low dose risperidone prophylaxis: a randomized placebo controlled trial (PREDELIC trial)
Dr Amita Jacob, PG Registrar, General Medicine, Dr. O.C Abraham, General Medicine, Dr. J.V Peter, Critical Care

Ref: IRB Min No: 10226 [INTERVEN] dated 24.08.2016

Dear Dr Amita Jacob,

The Institutional Review Board (**Silver**, Research and Ethics Committee) of the Christian Medical College, Vellore, reviewed and discussed your project titled "Prevention of Delirium in Intensive Care using low dose risperidone prophylaxis: a randomized placebo controlled trial (PREDELIC trial)" on August 24th 2016.

The Committee reviewed the following documents

1. IRB Application form
2. CV's of Drs. Shirley Suzana, Joy and Shanmugam Shivakumar.
3. Information Sheet and Consent Form
4. Data Sheet
5. No. of Documents 1 – 4

The following Institutional Review Board (**Silver**, Research & Ethics Committee) members were present at the meeting held on August 24th 2016 in the CREST/SACN Conference Room, Christian Medical College, Bagayam, Vellore 632002.

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We approve the project to be conducted as presented.

The Institutional Ethics Committee expects to be informed about the progress of the project, any **adverse events** occurring in the course of the project, any **amendments in the protocol and the patient information / informed consent**. On completion of the study you are expected to submit a copy of the **final report**. Respective forms can be downloaded from the following link: http://172.16.11.136/Research/IRB_Polices.html in the CMC Intranet and in the CMC website link address: http://www.cmch-vellore.edu/static/research/Index.html

Kindly provide the total number of patients enrolled in your study and the total number of withdrawals for the study entitled: "Prevention of Delirium in Intensive Care using low dose risperidone prophylaxis: a randomized placebo controlled trial (PREDELIC trial)" on a monthly basis. Please send copies of this to the Research Office (research@cmcvellore.ac.in).

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Fluid Grant Allocation:

A sum of 54,000/- INR (Rupees Fifty Four Thousand Only) will be granted for 2 years.

Yours sincerely

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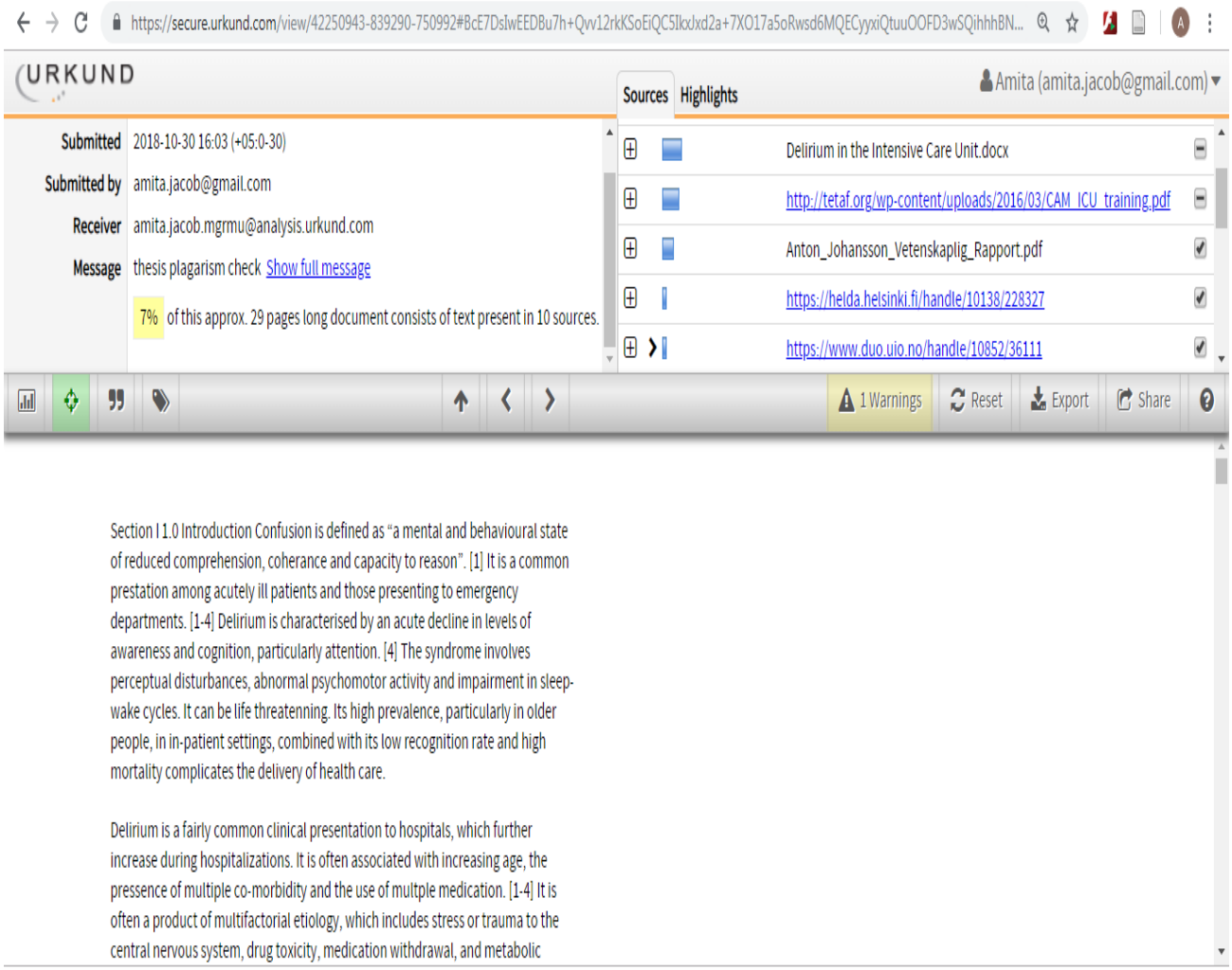

Section I 1.0 Introduction Confusion is defined as "a mental and behavioural state of reduced comprehension, coherance and capacity to reason". [1] It is a common prestation among acutely ill patients and those presenting to emergency departments. [1-4] Delirium is characterised by an acute decline in levels of awareness and cognition, particularly attention. [4] The syndrome involves perceptual disturbances, abnormal psychomotor activity and impairment in sleep-wake cycles. It can be life threatenning. Its high prevalence, particularly in older people, in in-patient settings, combined with its low recognition rate and high mortality complicates the delivery of health care.

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List of Abbreviations used

APA	American Psychiatric Association
CAMICU	Confusion Assessment Method-Intensive Care Unit Scale
DSM 5	Diagnostic and Statistical Manual 5
ICD-10	International Classification of diseases 10
RASS	Richmond Agitation-Sedation Score
RCT	Randomised controlled trial
WHO	World Health Organization

Section

1.0 Introduction

Confusion is defined as “a mental and behavioural state of reduced comprehension, coherence and capacity to reason”. [1] It is a common presentation among acutely ill patients and those presenting to emergency departments. [1-4] Delirium is characterised by an acute decline in levels of awareness and cognition, particularly attention. [4] The syndrome involves perceptual disturbances, abnormal psychomotor activity and impairment in sleep-wake cycles. It can be life threatening. Its high prevalence, particularly in older people, in in-patient settings, combined with its low recognition rate and high mortality complicates the delivery of health care.

Delirium is a fairly common clinical presentation to hospitals, which further increase during hospitalizations. It is often associated with increasing age, the presence of multiple co-morbidities and the use of multiple medications. [1-4] It is often a product of multifactorial aetiology, which includes stress or trauma to the central nervous system, drug toxicity, medication withdrawal, and metabolic disorders secondary to organ failure. The multiple aetiologies result in a poor understanding of its pathophysiology and complicate its management. [1-4]

Delirium is a particularly commonly prevalent and serious problem in patients admitted to in Intensive Care Units (ICUs). A prevalence as high as 60 to 70 % has been reported. [5, 6] Delirium has been found to be associated with worsen

short term and long term patient outcomes. There are several factors that make the ICU patient at risk for delirium, the most common being medications used for pain relief and sedation. A significant proportion of patients with delirium are distressed and agitated, which can precipitate accidental removal of endotracheal tubes or of intravascular catheters used for monitoring or administration of life-sustaining medications. Pain is the most common experience recalled by patients. [7] The development of delirium complicates the delivery of health care as its impacts many aspects of care. Table 1.1 records the burden of delirium. [4]

Table 1.1: Burden of Delirium

Increased morbidity
Increased hospitalization
Increased nursing care
Increased length of stay
Increased risk of cognitive decline
Increased risk of functional decline
Increased mortality
Delay in postoperative mobilization
Delay in early rehabilitation
Increased need for home care services
Increased rate of nursing home placements
Increased distress for family and caregivers
Barrier to closure in terminally ill patients

2. Review of Literature

The literature is reviewed under the following heads: definition, history, comparative nosology, incidence and prevalence, risk factors, protective factors, pathophysiology, aetiologies, diagnosis, pathology and laboratory findings, differential diagnosis, clinical features, assessment, course and prognosis, prevention, treatment and Indian work. These are briefly highlighted.

2.1. Definition

The core symptoms of delirium are a disturbance of awareness that is associated with a change in attention. It develops rapidly usually within a few hours to days and has a fluctuating course. [1-4] The fifth edition of the Diagnostic and Statistical (DSM) Manual considers delirium as a disturbance of awareness and attention. [8] This definition differs from the fourth edition of the DSM[9], which considered it as a disturbance of consciousness with inattention, accompanied by a change in cognition or perceptual disturbance.

The World Health Organization's International Classification of Diseases 10^{th} edition defines delirium as an etiologically non-specific syndrome characterised by concurrent disturbance of consciousness and attention, perception, thinking, memory, psychomotor behaviour, emotion and the sleep-wake cycle. [10]

2.2. History

The earliest descriptions of delirium are found in Greek literature, in the writings of Hippocrates.[4] Tradition suggests that the term was first used in the medical context by Celsus, who employed it to describe a spectrum of mental disorders from general insanity to acute and transient mental disturbance. Several centuries later, Phillip Barrough in 1583, clarified the concept of delirium and suggested that it was due to a derangement of a combination of internal senses, which included imagination, memory and cognition.

In the 18th century, Erasmus Darwin noted that the state constituted an "interruption of voluntary power" while John Hunter defined delirium as a cessation of consciousness. James Sims distinguished two variants of delirium, which fit in with the modern concepts of hypoactive and hyperactive delirium. Rees localised the unique aetiology of delirium within the brain in 1818.

George Engel and John Romanao, through the use of electroencephalograms in the 20th century, demonstrated that delirium was due to a reduction in metabolic activity of the brain. They documented decreased background activity on EEG, which corresponded with reduced cognition, attention and memory. [4]

2.3. Comparative Nosology

The diverse, multiple and complex aetiologies causing delirium are reflected in the use of varied terminology [1-3] (Table 2.1). General medicine and medical subspecialties favour terms like encephalitis (which refer to inflammation of the

brain parenchyma, distinct from that of the meninges) and encephalopathy (which refers to disorders of the brain secondary to metabolic problems and organ failure). Psychiatrists employed the term acute confusional state prior to DSM, and now prefer the term delirium.

Table 2.1: Terms describing delirium

Acute confusional state
Acute brain failure
Encephalitis
Encephalopathy
Intensive care unit psychosis
Toxic metabolic state
Central nervous system toxicity
Para neoplastic limbic encephalitis
Sun downing
Cerebral insufficiency
Organic brain syndrome
Delirium

2.4. Incidence and prevalence

Delirium is common in intensive care settings [1-4] and its prevalence has ranged between 16%-89%. [5, 6, 8] It is a common presentation in older people

with the highest rates among geriatric populations. Community studies have documented a prevalence rate of 1% among people over 55 years and 13% among those over 85 years of age.[4] Studies in elderly patients in emergency room setting have documented rates between 5 to 10% with higher prevalence of 15 to20% among those admitted to medical wards.

Delirium has also been recorded in 10-15% of general surgical patients, 30% of patients after open heart surgery and over 50% in those with hip fractures. Prevalence in Intensive Care Units has been shown to be between over 70% and over 80% among patients at end of life care. [1-4]

The incidence of delirium in patients who are free of delirium at admission has been reported as 5 to 10%, although higher rates (20-30%) have also been documented. [4]

2.5. Risk Factors

Advanced age, the presence of more than one condition associated with coma, treatment with sedative medications, a neurologic diagnosis, and increased severity of illness are risk factors. [1-4]. It is useful to conceptualise risk factors for delirium into 2 categories: (i) predisposing factors, and, (ii) precipitating factors. [11]

Table 2.2 lists common predisposing factors. Demographic characteristics, cognitive and functional status, sensory impairment, decreased oral intake, drugs and co-existing medical conditions predispose people to delirium.[1-4] Managing predisposing factors is crucial in preventing delirium and reducing morbidity and mortality associated with it.

Table 2.2: Common predisposing factors for delirium

Demographic characteristics	Age 65 years and older Male sex
Cognitive status	Dementia Cognitive impairment History of delirium
Functional status	Functional dependence Immobility History of falls Low level of activity
Sensory impairment	Hearing Vision
Decreased oral intake	Dehydration Malnutrition
Drugs	Treatment with psychotropic medication Treatment with drugs with

	anticholinergic properties Alcohol abuse
Co-existing medical conditions	Severe medical disease Metabolic abnormalities Chronic renal or hepatic disease Stroke Neurological disease Human Immunodeficiency virus infection Fractures or trauma Terminal diseases

Table 2.3 documents common precipitating factors for delirium, which include particular medication, primary neurologic diseases, intercurrent illnesses, surgery and environmental stress. [1-4]

Table 2.3: Common precipitating factors for delirium

Drugs	Sedative hypnotics Narcotics, Anticholinergic drugs Polypharmacy Alcohol or drug withdrawal
Primary neurologic disease	Stroke, non-dominant hemisphere Intracranial bleeding Meningitis or encephalitis
Intercurrent illnesses	Infections Iatrogenic complications Severe acute illnesses Hypoxia Hyponatremia Dehydration Shock Anemia Fever or hypothermia Poor nutritional status Low serum albumin levels Metabolic derangements
Surgery	Orthopaedic surgery Cardiac Surgery Prolonged cardiopulmonary bypass Non-cardiac surgery
Environmental	Admission to Intensive Care Unit Use of physical restraints Use of bladder catheter Use of multiple procedures Pain, Emotional stress Prolonged sleep deprivation

2.6 Protective factors

Good premorbid functioning before delirium predicts better outcomes. The significant morbidity and mortality associated with the condition demands the use of preventive strategies, early recognition and intervention. Education programs for clinicians, critical care staff, surgeons, geriatricians etc. and liaising with psychiatric units have been recommended. Focus on nutrition, increased rehabilitation and attention to hearing and vision impairment has been suggested as approaches to protect people from developing delirium. [1-4]

2.7 Pathophysiology

The pathophysiology (also termed pathogenesis, pathobiology) of delirium is currently poorly understood. [1-4] The majority of studies examining the pathogenesis of delirium were done in non-ICU patients. Further research is needed to explain complex interaction between causative factors of delirium in critically-ill patients. Although there have been attempts to find final common pathway, multiple aetiologies suggest more than one mechanism in the production of the condition. The pathophysiology of delirium is dependent of its causation. [5] Consequently, it is difficult to characterize its specific pathology. The pathophysiologic mechanisms of delirium remain unclear despite improved diagnosis and potential treatments.

Contemporary thinking on the pathophysiology of delirium suggests that it is a complex process, triggered by many different stimuli, which result in the

activation of one or more pathophysiological mechanisms. [3] There are seven prominent pathophysiological theories for the aetiology of delirium [3] and include: (i) Neuroinflamatory hypothesis, (ii) Neuronal aging hypothesis, (iii) Neurotransmitter hypothesis, (iv) Oxidative stress hypothesis, (v) Neuroendocrine hypothesis, (vi) Diurnal dysregulation of melatonin or dysregulation hypothesis, (vii) Network disconnectivity hypothesis. They are briefly mentioned.

2.7.1. Neuroinflamatory hypothesis and the role of Inflammation

Inflammation plays a contributory role in the dysfunction of multiple organs caused by critical illness. [3] Inflammatory abnormalities induced by endotoxin and cytokines are likely to contribute to the development of ICU delirium. Inflammatory mediators produced during critical illness (Tumour necrosis factor-α, Interleukin-1, Interleukin-2 Interleukin-6) cause a cascade of endothelial damage, thrombin formation, and micro-vascular complications. These inflammatory mediators cross the blood-brain barrier and increase vascular permeability in the brain. Inflammation may cause brain dysfunction by decreasing cerebral blood flow via the formation of micro-aggregates of platelets, fibrin and neutrophils; by constricting cerebral vasculature by α_1-adrenoceptor activation; or by neurotransmitter inactivation.

2.7.2. Neuronal aging hypothesis

Older age has been identified as an independent risk factor for delirium. [1-4] Physiologic and anatomic changes associated with aging in the brain may make it susceptible to exogenous insults, which trigger acute inflammatory responses. [3] In addition, the aging brain may mount a significant inflammatory response when stimulated by peripheral inflammatory states. The presence of apolipoprotein E (APOE) A4 allele is associated with increased risk of postoperative cognitive dysfunction and delirium in the elderly, possibly working through increased inflammation and or reduced cholinergic activity.

2.7.3. Neurotransmitter hypothesis and neurotransmitter imbalance

Delirium may be a neurobehavioral manifestation of imbalances in the synthesis, release, and activation of neurotransmitters that control cognitive function, behaviour, and mood. [3, 4] Derangements of many neurotransmitter systems maybe involved in the pathophysiology of delirium. Dopamine and acetylcholine are the most strongly implicated. These neurotransmitters have opposing effects. Dopamine increases neuronal excitability while acetylcholine decreases it. An imbalance of these chemicals can result in neuronal instability and variable neurotransmission. Increased levels of dopamine or decreased levels of acetylcholine have been associated with delirium. [12] Cholinergic deficiency may be a final common pathway. Anticholinergic drugs can induce delirium, while physostigmine, a cholinergic agent is useful in reversing delirium associated with anticholinergic medication. Dopaminergic drugs (e.g. L-dopa

and bupropion) are recognised precipitants of delirium, while dopamine antagonists (e.g. antipsychotic medication) are effective in its treatment.

The increased risk of delirium associated with the use of Gamma Aminobutyric Acid (GABA) agonists has led to the belief that the GABAergic neurotransmitter systems play a contributory role. Elevated levels of ammonia, associated with hepatic encephalopathy, contribute to increased levels of glutamate and glutamine, which are precursors of GABA. [3, 4]

Glutamate, through its excitatory neurotoxic effects, mediated via N-methyl-D-aspartate (NMDA) receptors is associated with delirium. NMDA antagonists (E.g. ketamine and phencyclidine) are known to cause delirium. [3, 4] Other neurotransmitters are likely to play a role in the pathogenesis of delirium as well, including serotonin, norepinephrine and endorphins.

2.7.4. Oxidative stress hypothesis

Multiple and diverse stimuli can increase oxygen consumption and can decrease oxygen delivery to the brain resulting in increased energy expenditure, reduce oxidative metabolism and consequent central nervous system (CNS) dysfunction.[3] Nutritional deficiencies may add to the complex aetiology.

2.7.5. Neuroendocrine hypothesis

Delirium may be caused by neuronal damage by high levels of glucocorticoids by activation of hypothalamic-pituitary-adrenal axis in response to physiologic stress due to infections, surgery or trauma or due to the administration of exogenous glucocorticoids. [3]

2.7.6. Dysregulation hypothesis

Delirium may be caused by disruption of circadian cycles, which can be induced by sleep deprivation. Melatonin and other neurotransmitter derangements are said to be contributory. [3]

2.7.7 Network disconnectivity hypothesis

Many insults to the brain can result in dysfunction and disconnection between the many neural networks responsible for brain function. Particular network breakdown due to stressors such as aging, sleep deprivation, infection, inflammation, and medication exposure result in different presentations of delirium. [3]

Delirium research has recently begun to use neuroimaging. These contribute to the evidence that delirium may be caused by widespread brain dysfunction and may lead to cell death in the CNS. Studies have shown that delirious patients experienced reduced overall cerebral blood mainly in the subcortical and occipital regions. Global hypoperfusion of the brain indicated the presence of

wide- spread cerebral dysfunction and could potentially cause long-term cognitive damage and changes that are associated with prolonged delirious states. Prolonged alteration in CNS perfusion may begin to trigger apoptotic mechanisms including autophagy which can lead to permanent damage.

The long-term sequelae of delirium including impaired cognition, functioning and behavioural changes are well documented. Increased brain atrophy has been demonstrated in geriatric patients in delirium in comparison to matched controls. The degree of atrophy correlated to the patients' score on a Mini Mental-State Examination (MMSE) scores. A positive association between the duration of delirium in the ICU and both cerebral atrophy and cerebral white-matter disruption has been documented using magnetic resonance imaging techniques. [13,14] However, these preliminary studies do not reveal the directionality of causation; delirium in the ICU either gives rise to alterations in brain structure or the presence of such changes increase susceptibility to delirium.

In summary, no single theory adequately explains the aetiology of delirium. Many aetiologies are interrelated, can occur in different combinations, in different patients and can vary over the course of delirium in the same patient. [3]

2.8. Aetiologies

Delirium is a syndrome, that can have diverse medical causes (E.g. infections, metabolic disturbance, hepatic and renal failure) or be due to medication (E.g. benzodiazepines) or substance intoxication or withdrawal (E.g. alcohol). Multiple aetiologies for delirium can co-exist. [5, 6, 8]

2.8.1. Common aetiologies

Table 2.4 list common aetiologies of delirium and include toxins, metabolic conditions, infections, endocrine, cerebrovascular, autoimmune, neoplastic disorders, seizure disorders, terminal end-of-life delirium and hospitalization. [1-2]

Table 2.4: Common aetiologies of delirium

Toxins	Prescription medicines especially with anticholinergic properties, narcotics, benzodiazepines Drugs of abuse: alcohol intoxication and withdrawal, opiates, ecstasy, lysergic acid diethylamide (LSD), gamma hydrobutyrate, phencyclidine (PCP), ketamine, cocaine, etc. Poisons: Inhalants, carbon monoxide, ethylene glycol, pesticides
Metabolic conditions	Electrolyte disturbances: hypoglycaemia, hyperglycaemia, hyponatremia, hypernatremia, hypocalcaemia, hypomagnesaemia Temperature dysregulation: hypothermia and hyperthermia Pulmonary failure: hypoxemia, hypercarbia

	Liver failure/hepatic encephalopathy Renal failure/uraemia Cardiac failure Vitamin deficiencies: B12, thiamine, foliate, niacin Dehydration and malnutrition Anemia
Infections	Systemic infections: urinary tract infections, pneumonia, skin and soft tissue infections, sepsis CNS infections: meningitis, encephalitis, brain abscess
Endocrine conditions	Thyroid: Hyperthyroidism, hypothyroidism Parathyroid: Hyperparathyroidism Adrenal insufficiency
Cerebrovascular disorders	Global hypoperfusion states Hypertensive encephalopathy Focal ischemic strokes and haemorrhages- non dominant parietal and thalamic lesions
Autoimmune disorders	CNS Vasculitis Cerebral lupus Neurologic Para neoplastic syndromes
Seizure-related disorders	Non-convulsive status epilepticus Intermittent seizures with prolonged post-ictal states
Neoplastic disorders	Diffuse metastasis to the brain Gliomatosis cerebri Carcinomatous meningitis CNS lymphoma
Hospitalization	
End-of-life delirium	

The syndrome of delirium is caused by diverse aetiologies. Multiple causes can combine to cause delirium. The common aetiologies are highlighted and include (i) sedative and analgesics, (ii) substance intoxication, (iii) substance withdrawal, (iv) Post-surgery

2.8.2. Sedatives and analgesics

In the ICU, patients often receive prolonged exposure to sedatives and analgesics, often at high doses. More than 90% of patients requiring invasive ventilation in intensive care units are administered benzodiazepines during admission to relieve agitation and prevent removal of invasive devices. Sedatives and analgesics are the leading modifiable iatrogenic risk factors for developing delirium in the intensive care unit. Multiple studies had documented benzodiazepine use as an independent risk factor for ICU delirium. Narcotics (morphine and meperidine) are also a risk factor among both medical and surgical patients. Benzodiazepines, narcotics, and other psychoactive drugs taken together are associated with a 3- to 11-fold increase in risk for delirium in ICU patients. Surveys suggest that delirium is frequently treated with lorazepam by a significant number of ICU professionals. The quantity and dosing of these drugs are often based on clinical experience rather than on evidence-based guidelines. Doses may not be modified taking into account the age, comorbid conditions and individual variability of patients and this may result in over-sedation, especially in vulnerable elderly patients. [1-4]

2.8.3. *Substance intoxication*

Many chemical agents are associated with delirium. Intoxication with a variety of drugs of abuse is causal. For example, intoxication with cocaine, angel dust (PCP), heroin, alcohol, nitrous oxide, amphetamine and its derivatives (like Speed and Ecstasy), marijuana, etc. can present with delirium. Herbal preparations are also known to result in impaired cognition and delirium [1-4].

2.8.4. Substance withdrawal

Many substance of abuse can result in delirium during withdrawal states. Alcohol, benzodiazepines, opioids, and some over the counter medications can result in withdrawal delirium. Alcohol withdrawal results in delirium tremens where delirium is associated with severe tremor. Opioid withdrawal delirium is accompanied with other withdrawal symptoms which include flu-like symptoms, gastrointestinal cramping, diarrhoea, diaphoresis, autonomic hyperactivity and craving. [1-4]

2.8.5. Post-operative delirium

The post-operative period of many major surgical procedures can result in delirium. The incidence of delirium after open heart surgery, coronary artery bypass graft, hip joint replacement and other major neurosurgical procedures is common.

2.9. Clinical features

Delirium is a clinical syndrome characterized by a disturbance of attention and awareness associated with neurocognitive dysfunction (E.g. deficits in memory, disorientation, language, visuo-spatial ability or perception), is often acute in onset. [8] The disturbance in attention includes a reduced ability to direct, focus, sustain and shift attention. The reduced awareness implies reduced orientation to the environment. The disturbance develops over a short period of time, usually hours or a few days. [1-4] it represents a change from baseline attention and awareness and tends to fluctuate during the course of the day. It may be associated with additional disturbance in cognition like memory deficit (impairment in recent memory), disorientation (to time and place), abnormal perception (misinterpretations, illusions, hallucinations, often visual), and problems in language and visuo-spatial ability.

Delirium is associated with a disturbance in the sleep-wake cycle, which includes daytime sleepiness, night-time agitation, difficulty in falling asleep, excessive sleepiness through the day and wakefulness through the night.[8] The patients may exhibit emotional disturbances, such as anxiety, fear, depression, irritability, anger, euphoria and apathy. The individuals may shout, scream, curse, mutter, moan, etc.

The syndrome is not due to severely reduced levels of arousal such as coma. There should be evidence from history, physical examination, or laboratory

findings that the disturbance is due to a direct physiological consequence of a medical condition, substance intoxication or withdrawal or exposure to a toxin or is due to multiple aetiologies.

2.9.1. Clinical subtypes

Delirium presentations have been categorized into hyperactive and hypoactive. [1-4, 8, 15]

2.9.1.1. Hyperactive delirium: The hyperactive variety is characterized by increased levels of psychomotor activity that may be associated with lability or fluctuations of mood, agitation, and refusal to cooperate with medical care. [1-4, 8, 15] Individuals with hypoactive delirium present with reduced psychomotor activity that may be accompanied by sluggishness and lethargy that approaches stupor and constitutes a more challenging clinical diagnosis. Clinical presentations can also present with a mixed level of activity with fluctuations in level or normal level of psychomotor activity with disturbance of attention and awareness. The condition is usually acute and lasts for a few hours or days. However, occasionally it can be persistent lasting weeks and months. Hyperactive delirium has been associated with a better prognosis than hypoactive delirium in non-critically ill patient. However association has not been evaluated thoroughly among ICU patients.

2.9.1.2. Hypoactive delirium: Hypoactive delirium is characterized by a decrease in responsiveness, withdrawal, and apathy. [1-4, 8, 15] The prevalence of hypoactive delirium in intensive care ill patients contributes to clinicians' lack of recognition of delirium. In one cohort of intensive care unit patients 43.5% of patients had purely hypoactive delirium.

2.9.1.3. Mixed delirium: Patients may have features of both hypo and hyperactive delirium. In a cohort of medical ICU patients 54.1% had mixed delirium of patients had purely hypoactive delirium. [15]

Delirium is associated with poor clinical outcomes in critically ill patients, routine monitoring using valid and reliable delirium diagnosis instruments is recommended in all ICUs so that the prognostic significance of delirium does not go unnoticed.

2.9.1.3. Subsyndromal Delirium

Ouimet et al [16] found that many ICU patients fulfilled some but not all the clinical criteria for a diagnosis of delirium by DSM IV.[9] This sub-syndromal delirium represents an intermediate state on the spectrum between clinical delirium and a normal neurologic state. Subsyndromal delirium also carries a poorer prognosis compared to people without such cognitive dysfunction. [17]

2.10. Diagnosis

The diagnosis of delirium is often missed particularly when patients present with hypoactive delirium.[1-4] A high index of suspicion, good histories, daily mental state examinations and the use of formal instruments to rate the syndrome are crucial for diagnosis.

Diagnostic criteria like the Diagnostic and Standard Manual IV [9] have been the clinical gold standard for diagnosis of delirium. The American Psychiatric Association Diagnostic and Statistical Manual 5 criteria, the current standard for delirium [8], are listed in Table 2.5. The 5 point criteria need to be satisfied in order to make a diagnosis of delirium. In addition, the manual also has specifiers to identify particular aetiologies and clinical variations.

Table 2.5: American Psychiatric Association Diagnostic and Statistical Manual 5 criteria of delirium

A. Disturbance in attention (i.e., reduced ability to direct, focus, sustain, and shift attention) and awareness (reduced orientation to the environment).
B. The disturbance develops over a short period of time (usually hours to a few days), represents an acute change from baseline attention and awareness, and tends to fluctuate in severity during the course of a day.
C. An additional disturbance in cognition (e.g. memory deficit, disorientation, language, visuo-spatial ability, or perception).

D. The disturbances in Criteria A and C are not better explained by a pre-existing, established or evolving neurocognitive disorder and do not occur in the context of a severely reduced level of arousal such as coma.

E. There is evidence from the history, physical examination or laboratory findings that the disturbance is a direct physiological consequence of another medical condition, substance intoxication or withdrawal (i.e. due to a drug of abuse or to a medication), or exposure to a toxin, or is due to multiple aetiologies.

Specifiers:

(1) substance intoxication delirium, (2) substance withdrawal delirium, (3) medication-induced delirium, (4) delirium due to another medical condition, (5) delirium due to multiple etiologies, (6) acute, (7) persistent, (8) hyperactive, (9) hypoactive, (10) mixed level of activity

The Confusion Assessment Method (CAM) Diagnostic algorithm [1, 18] is listed in Table 2.6.

Table 2.6: The Confusion Assessment Method (CAM) Diagnostic algorithm

The diagnosis of delirium requires the presence of features1 and 2 and of either feature 3 and 4.
Feature 1. Acute onset and fluctuating course

Is there evidence of an acute change from the patient's baseline? Did the (abnormal) behaviour fluctuate during the day? Feature 2: Inattention Did the patient have difficulty focusing attention? Feature 3: Disorganised thinking Was the patient's thinking disorganised or incoherent? Feature 4 Altered level of consciousness Was the patient alert? (as opposed to lethargic, stuporous, comatose)

2.10.1. Recognition and diagnosis

Delirium is considered a commonly occurring and serious event in critically ill patients. As there is no diagnostic test (blood, electrophysiological, or imaging test) for delirium, its identification is purely clinical, making it a clinical diagnosis. [5]

Delirium is said to be unidentified in about 75% of patients with the condition in ICU.[5] On the other hand, active screening by research nurses have identified 64% of patients diagnosed with delirium by psychiatrists, neurologists or geriatricians.[19]

2.10.2 Differential diagnosis

History, clinical examination and laboratory studies are useful in distinguishing delirium from other causes of global cognitive impairment like dementia,

depression and psychosis. [1-4] Dementia is usually of gradual onset, persists for over a month, is usually progressive and is not associated with reduced alertness until its terminal stage. However, delirium can be superimposed on dementia and demands caution as there is considerable overlap in presentations. The diagnosis of dementia should be deferred until after the resolution of the acute confusional state.

Depression can resemble hypoactive delirium. [4] However, clouding of consciousness is seldom present in depression. Psychosis is a differential for hyperactive delirium, however, the hallucinations tend to be auditory rather than visual and the delusions persistent compared to delirium. [4]

2.11 Instruments and rating scales

Formal cognitive assessments involve the use of standard screening and diagnostic instruments and rating scales. [20] These instruments are listed in Table 2.7.

Table 2.7: List of instruments to assess delirium

Aim	Instrument
Instruments for assessment of arousability of the patient	Richmond Agitation Sedation Scale (RASS)[21]
Instruments for screening for premorbid cognitive disturbances	Informant Questionnaire on cognitive decline in the elderly (IQCODE) [22,23]
Screening Instruments	NEECHAM Confusion Scale [24] Nursing Delirium Screening Scale [25] Delirium Observation Screening Scale [26] Delirium Observation Scale [27] Intensive care delirium screening checklist [28] Pediatric Anesthesia Emergence Delirium scale[29] Global Attentiveness Rating [30]
Diagnostic Instruments	Delirium Symptom Interview [31] Saskatoon Delirium Checklist [32] Delirium Rating Scale-revised version [33] Memorial Delirium Assessment Scale [34] Confusion Assessment Method (CAM) [35] Confusion Assessment Method-ICU [36,37] Pediatrics CAM-ICU [38]

Table 2.8 documents some characteristics of delirium instruments including the criteria on which the scale was based, the number of items, qualifications of the rater, time taken for administration, and its usefulness in screening, diagnosis and severity rating.

Table 2.8: Characteristics of delirium instruments

Scale	Criteria	Items	Rater	Time (min)	Screening	Diagnosis	Severity
CAC-A		25	Nurse	<5		x	
CAC-B		58	Nurse			x	
CAM	DSMIIIR	9	Clinician	<5	x	x	X
CSE	Research	22	Clinician	<30		x	X
CTD	DSMIIIR	9	Researcher	10-15			
DAS	DSMIII	8	Doctor				X
DI	DSMIIIR	7	Researcher	5-10			X
DOSS	DSMIV		Researcher	5-10	x		
DOS	Dsmiv		Nurse	<5	x		

CAC-A Clinical Assessment Confusion [39, 40]

CAC-B Clinical Assessment Confusion, [39, 40]

CAM Confusion Assessment Method [35]

CSE Confusion State Evaluation [41]

CTD Cognitive Test for Delirium [42, 43]

DAS Delirium Assessment Scale [44]

DI Delirium Index [45]

DOSS Delirium Observation Screening Scale [26]

DOS Delirium Observation Scale [27]

The older studies employed the Mini Mental State Examination [46] to assess cognitive function, while the newer scales are specific for evaluating delirium. These scales differ on the criteria on which they were based (E.g. DSM III [47], DSM IIIR[48]), the number of items, the time taken to administer the scale, the qualifications of the rater and their use for screening, diagnosis and for rating severity.[20]

Instruments, which are used to identify delirium, test cognitive domains of standard diagnostic criteria. Delirium Detection Scale (DDS) and the Memorial Delirium Assessment Scale (MDAS) are employed to assess delirium symptom severity. The CAM-ICU scale can be used even on non-verbal ventilated patients in the ICU and has a pooled sensitivity of 80% with a sensitivity of 95.9%. [49] Using a structured format, this tool evaluates four features, namely, acute onset or fluctuating course, inattention, disorganized thinking, and altered level of consciousness. When administered by bedside nurses with no formal psychiatric training, the CAM-ICU has been demonstrated to have high accuracy (sensitivity of 93% to 100% and specificity of 98% to 100%) and inter-rater reliability (K = 0.96). [37]

2.12. Pathologies and laboratory examination

The diverse causes of delirium result in varied abnormalities. Delirium may be the only sign of illness in some patients, while in others the abnormalities may be obvious clinically. The extent of laboratory evaluation is often determined by the clinical context. Table 2.9 documents the commonly employed laboratory parameters to rule out or confirm abnormality/disease. [1-4] Infection, dehydration and metabolic abnormalities account for over 97% of cases of fever and delirium.

Table 2.9: Clinical abnormalities commonly suspected and tests ordered

Abnormalities suspected	**Tests ordered**
Pneumonia	Chest X-ray
Cardiac ischemia	ECG
Blood chemistry	Electrolytes, glucose, Arterial blood, gas, calcium, magnesium, renal, thyroid and liver function tests
Anaemia and Leucocytosis for infection	Complete Blood Counts, Urine analysis, Urine and blood cultures,
HIV, Syphilis	Serology
Meningitis, encephalitis	CSF Examination
Seizures	EEG
Focal abnormalities	Neuroimaging
Second tier evaluation	Vitamin B12, folate, thiamine levels;

	Serum Ammonia, Auto-immune serology (ANA, complement levels, Para neoplastic serology, etc.)

2.13. Course and prognosis

Delirium has a significant impact on patients admitted to ICUs. The diagnosis of delirium in patients admitted to ICUs results in worse outcomes and more complications during hospital stay.

These include:

(i) Increased duration of hospitalization (50)

(ii) Higher health care costs [51]

(iii) Longer duration of mechanical ventilation [6]

(iv) Increased mortality (estimated as a 10% increase in the relative risk of death for each day of delirium) (50,52]

(v) Increased complications including self-extubation and removal of catheters [53]

(vi) Decreased long-term cognitive function (54).

(vii) A longer duration of delirium while in ICU has been significantly associated with increased post-discharge sleep disturbance (53).

(viii) Delirium incidence showed a trend toward association with increased functional disability in the year following discharge (53).

Since delirium is associated with worse clinical outcomes in critically ill patients, routine monitoring using reliable and valuable screening tools is recommended in all intensive care units. Delirium must be recognized early for appropriate treatment and prognostication for ICU patients.

2.14. Treatment

The treatment of delirium in ICUs consists of a combination of non-pharmacologic and pharmacologic management in addition to the treatment of the underlying cause identified.

2.14.1. Treatment of underlying conditions

Almost any medical condition can precipitate delirium in a susceptible patient; critically ill patients may have multiple underlying conditions are often present. If an underlying precipitating illness is identified, specific therapy for that medical condition is required to reduce duration and severity of delirium [1-4]

Common precipitating conditions include:

(i) Metabolic encephalopathy

(ii) Fluid and electrolyte disturbances (dehydration, hyponatremia or hypernatremia, hypo or hypercalcemia)

(iii) Infections (sepsis, urinary tract, respiratory tract, skin and soft-tissue)

(iv) Organ failure (uraemia, liver failure, hypoxemia/hypercarbia)

(v) Hypoglycaemia

(vi) Drug toxicity - Drug toxicity causes or contributes to up to 30% of all cases of delirium. Delirium can occur even at "therapeutic" levels of drugs.

(vii) Withdrawal from alcohol and sedatives

Correction of metabolic encephalopathies, management of fluid and electrolyte imbalance, treatment of infections with antibiotics, correction of hypoglycaemia, dialysis for renal failure, supportive treatments for organ failure and drug intoxication, physostigmine for anticholinergic intoxication, thiamine and benzodiazepines for Wernicke encephalopathy and delirium tremens are necessary

2.14.2. Supportive Medical Care and Non-pharmacological Interventions

A delirious patient is at higher risk for complications of immobility and confusion including aspiration and skin break-down. Specific interventions addressing these known complications are required in delirious patients [1-4].

Mild symptoms may respond to interpersonal and environmental manipulations. Intensive care units often have high ambient noise, lack of windows and restraint use, often contributes to worsening confusion. Specialized departments that address these issues have improved the outcomes in at-risk patients (55).

Calm and safe environments are crucial. Repeated reassurance and verbal re-orientation can lessen agitation. The presence of relatives and other familiar persons at the bedside can also decrease confusion. Provision of hearing and vision aids and paper and pencils for communication are useful. The use of environmental cues and daytime activities need to be encouraged to produce normal sleep-wake cycles. Psychosocial support from both family and staff is cardinal.

Physical restraint of patients should be used only as a last resort. Restraint of agitated patients can worsen and prolong delirium as well as cause complications such as loss of mobility, pressure ulcers and aspiration. (56). Pain management and early mobilization are important.

2.1.4.3. Pharmacological Interventions

Strong evidence for the use of antipsychotic medication in managing delirium is lacking [57] and suggests caution in their use. Psychotropic medication should be reserved for patients who are severely disturbed. Haloperidol is currently recommended as the drug of choice for the treatment of ICU delirium by the Society of Critical Care Medicine and American Psychiatric Association. The optimal dosage has not been defined in clinical trials. SCCM guidelines recommend a starting dose of 2 mg intravenously which can be repeated if agitation persists. Higher doses are commonly used for patients with acute

agitation. However, haloperidol and first generation antipsychotics cause extrapyramidal symptoms.

Atypical antipsychotics (e.g. risperidone, ziprasidone, quetiapine, olanzapine) may also be useful in the treatment of delirium. Only preliminary data exist regarding their use in the critically ill. These medications target dopamine receptors as well as receptors for other neurotransmitters (Serotonin, acetylcholine, nor-epinephrine). Small trials show a similar effect to haloperidol in the treatment of delirium with fewer side effects (Table 2.10).

Table 2.10: Trials of use of antipsychotic medication in treatment of delirium

Authors	**Study design**	**Drugs used**	**Outcome**
Maneeton B; 2013; Drug Des Devel Ther [58]	Double blind, RCT in hospitalized patient with delirium	Haloperidol vs. quetiapine	1.Severity of delirium 2. Equally effective
Yoon HJ et al; 2013; BMC Psych [59]	Double blind, RCT in hospitalized patients with delirium	Haloperidol vs. risperidone, quetiapine and olanzapine	1.Severitiy of delirium 2. Equally effective
Devlin JW et al	Double Blind.	Quetiapine 50mg	1.Time to

2011; Crit Care [60]	Placebo Controlled, RCT in ICU patients with delirium	every 12 h vs. placebo	resolution of delirium 2.Drug superior to placebo

Patients treated with antipsychotics should be closely monitored for adverse effects. These include hypotension, dystonia, extrapyramidal effects, malignant hyperthermia, glucose and lipid dysregulation, laryngeal spasm and anticholinergic effects (dry mouth, constipation, and urinary retention). These medications should be avoided in patients with prolonged QT intervals due to the risk of Torsades des Pointes.

There has been an association observed between antipsychotic use and increased mortality in elderly patients. [61, 62] However no study of ICU patients has demonstrated any increased risk of death due to antipsychotic use. In one study haloperidol was associated with significantly lower hospital mortality among ICU patients. [63]

The equivalence of **oral** antipsychotics is as follows:
Haloperidol 2 mg = risperidone 3 mg= quetiapine 300 mg (from Maudsley Prescribing Guideline 2015) [64] Delivery by intravenous route results in 3-5 time the oral dose a there is no first pass metabolism in the liver.

2.15. Prevention

A variety of factors common in critically ill patients predispose to delirium. These include infection, pain, use of sedation, metabolic derangements, and hypoxemia. Hence, patients should regularly be evaluated and treated for the above to decrease its risk.

NICE guidelines recommend preventive interventions to manage cognitive impairment or disorientation (orienting cues, cognitively stimulating activities, visits from family and friends), dehydration or constipation (fluid intake), hypoxia (monitor saturation levels), immobility (early mobilization), infection (antibiotics), multiple medication (avoid polypharmacy), pain (monitor and manage), poor nutrition (monitor and manage), sensory impairment (resolve reversible causes, aides) and sleep disturbance (environment, schedules).[65]

Delirium prevention should involve multicomponent interventions. [1-4, 66] It can be divided into pharmacologic and non-pharmacologic methods

2.15.1 Non-pharmacologic interventions

Sleep deprivation and disturbance of the circadian rhythm is a major risk factor for delirium. Interruptions in REM sleep are the most significant. Improvement in sleep quality by noise and light reduction and reducing night-time procedures was associated with improved sleep and a reduced incidence of delirium in the ICU.[67,68] Immobility is another risk factor for delirium that can be avoided

by regular physical and occupational therapy.[69] Other factors worsening delirium include visual and hearing impairments, cognitive impairments and dehydration.

Multi-component interventions including a repeated reorientation of the patient and provision of cognitively stimulating activities; non-pharmacologic sleep protocol; early mobilization activities and range of motion exercises; timely removal of catheters and physical restraints; use of eyeglasses, magnifying lenses, and hearing aids; and early correction of dehydration have been shown to be effective in older hospitalized patients [18] and post-operative patients [70] but have not been evaluated in the ICU. Many of these interventions are routinely employed in many ICUs.

Schweickert WD et al [71] performed a randomised controlled trial in 104 ICU patients and found that early physical and occupational therapy almost halved the delirium rates. Even more recently, implementation of the ABCDE delirium prevention bundle, which incorporated awakening and breathing co-ordination, delirium monitoring and physiotherapy, was found to have a 20% decrease in delirium. (72]

2.15.2. Pharmacological interventions

Pharmacological interventions for delirium can be divided into the rational use of sedation and analgesia and the use of antipsychotic medication.

2.15.2.1. Rational Use of sedation and analgesia

Deep sedation has been associated with a higher incidence of delirium. [68, 73] Benzodiazepines in particular seem to worsen delirium when given in high doses compare to other sedatives. [75] One of the reasons for higher doses of sedation is agitation due to pain. Hence, adequate analgesics as well as daily pain monitoring is recommended for all ICU patients.[74] The use of dexmedetomidine [75.76] for sedation have been associated with less ICU delirium that other sedatives. Ketamine also appears to improve rates of delirium in post-operative patients. [77]

2.15.2.2. Pharmacological prophylaxis

Currently no medication is recommended for prevention of delirium in an ICU setting as the evidence from systematic reviews and meta-analysis is inconclusive. [78] Both Haloperidol and atypical antipsychotics have been successfully used to prevent delirium in the post-operative setting. [1-4, 80, 81] However, evidence is limited in non-surgical patients and there have been no high-quality trials that are positive for delirium prevention with antipsychotics outside the postoperative period. [5] A Cochrane review concluded that there is currently no conclusive evidence that anti-psychotic medication reduces the incidence of delirium among critically ill.[81] Well designed, placebo-controlled, randomised trials are required to inform critical care clinicians

regarding the efficacy and safety of antipsychotics in the prevention and treatment of ICU delirium.

Haloperidol is a typical antipsychotic. It blocks D_2 dopamine receptors which results in a decrease in hallucinations, delusions, and unstructured thought patterns. In a non-randomised before/after project for prevention of delirium. [82] Prophylactic haloperidol in medical and surgical ICU patients decreased the incidence and duration of delirium as well as showing an improvement in 28 day mortality. However, another randomized control trial looking at the effect of prophylactic haloperidol on critically ill patients showed no difference in 28 day mortality or incidence of delirium between treatment and control groups. The evidence is summarised in Table 2.11.

Table 2.11: RCTs using Haloperidol for Delirium prophylaxis

Author	Study Design	Dose	Outcome
Wang et al, 2012 Crit Care Med. [79]	Double Blind, Placebo Controlled, RCT Post-operative patients	0.5 mg IV bolus followed by continuous infusion at a rate of 0.1 mg/h for 12 hrs.	1. Primary end point - incidence of delirium within the first 7 days after surgery. 2.Drug superior to placebo
Girard et al 2010 Crit Care Med. [83]	Double Blind, Placebo Controlled, RCT in ventilated	Oral haloperidol (average 15mg/day) or ziprasidone (average 113.3	1.Primary end point was the number of days patients were alive without delirium or

	surgical patients	mg/day) or placebo every 6 hrs. for up to 14 days	coma; 2.No difference
Van den Boogaard et al 2018; *JAMA* [84]	Double Blind, Placebo Controlled, RCT ICU patients	1or 2mg IV haloperidol thrice daily	1.Survival at 28 days 2.No difference
Kalisvaart KJ et al 2005; J Am Geriatric Soc.[85]	Double Blind, Placebo Controlled, RCT Elderly patient after hip surgery	1.5mg/ day haloperidol for 3 days	1. Incidence of post-op delirium 2. No difference
Al-Quadeebh NS et al 2016; Critical Care Medicine[86]	Double Blind, Placebo Controlled, RCT ICU patients with subsyndromal delirium	1mg IV haloperidol every 6 hours	1.Incidence of delirium 2.No difference Hours per day spent agitated lower in treatment group

The introduction of second generation atypical antipsychotics led to their use in the prevention of delirium. There is currently no evidence regarding the use of atypical anti-psychotic medication for the prophylaxis of delirium among medical ICU patients. There is some evidence that these medications can reduce delirium in post-operative patients (Table 2.12).

Table 2.12: Evidence of atypical antipsychotic use in prevention of delirium

Authors	Study design	Drug and dose	Outcomes
Prakanrattana U 2007; Anaesth Intensive care [87]	Double-blind, Placebo controlled RCT; Post cardiac surgery patients	Risperidone 1mg stat	1.Incidence of delirium 2.Drug superior to placebo
Larsen KA et al 2010; Psychosomatics[88]	Double-blind, Placebo controlled RCT; Elderly patients post joint replacement	Olanzapine 10mg perioperatively	1.Incidence of delirium 2.Drug superior to placebo
Tahir et al J 2010 Psychosom Res. [89]	Double-blind, Placebo controlled RCT	Quetiapine vs. placebo	1. .Incidence of delirium 2.Drug superior to placebo but underpowered

The evidence for using haloperidol and atypical antipsychotic for preventing delirium is inconclusive.

Dexmedetomidine is a newer α_2-receptor agonist. [1] It may prove to be an alternative to benzodiazepines as a sedative agent that is less likely to cause delirium. Pilot studies suggest that there may be decrease in delirium and increase days with normal neurological state (no coma or delirium) compared to sedation with lorazepan. Larger trials are warranted to evaluate the efficacy and safety of this agent.

2.16. Delirium research from India

Cross-sectional, case-control, cohort and randomised trials were identified using a PubMed search using terms “delirium” and “India”. These are briefly mentioned under the following head: (i) prevalence and risk factors, (ii) clinical features, (iii) aetiology and pathogenesis, (iv) diagnosis,
(v) treatment, (vi) prevention

Studies from India have examined the incidence and prevalence of delirium in different settings and have documented different rates:

(i) delirium in ICU prevalence - 68% prevalence [90]

(ii) delirium in post-operative patients undergoing major abdominal surgery for malignancy 4% [91]

(iii) delirium in ICU incidence 59.6% [92]

(iv) Delirium was seen in 17.5% patients after cardiac surgery. [93]

(v) Incidence and prevalence rate of delirium were 24.4% and 53.6% respectively tertiary care hospital [94].

Studies in India have documented risk factors for developing delirium

(i) Advanced age, addictions, respiratory complications and sepsis were found to be significant associations with post-operative delirium among patient undergoing major abdominal surgery for malignancy. [91]

(ii) Heavy drinking, continuous pattern of drinking, past history of delirium, alcohol-induced psychosis, and presence of cognitive deficits (emerged as strong predictors of Alcohol Withdrawal Delirium Tremens in people with alcohol dependence [95].

(iii) History of hypertension, carotid artery disease, noninvasive ventilation use, ICU stay more than 10 days and poor postoperative pain control was associated with post cardiac surgical delirium [93]

Studies have recorded clinical presentations of delirium

(i) Common symptoms were disturbances in attention (100%), thought process abnormality (100%), fluctuation in symptoms (97.33%) disturbance in, sleep-wake cycle, language disturbance (94.7%), disorientation (81.33%), and short-term memory impairments (73.33%). No patient had delusions and very few (5.3%) reported perceptual disturbances. Hypoactive delirium was the most common subtype (45.33%), followed by hyperactive subtype (37.33%) and a few patients had mixed subtype of delirium (17.33%). [94]

(ii) The majority of cases were of hypoactive delirium type (85.72%) after cardiac surgery [93]

(iii) Delirium in children described sleep wake cycle disturbance and cognitive dysfunction, with a small minority reporting delusions and hallucinations [96]

Investigations of delirium in the Indian context have employed screening instruments to identify delirium:

(i) Confusion Assessment Method for the ICU (CAM-ICU) was reported to have higher sensitivity than Intensive Care Delirium Screening Checklist (ICDSC) when used to diagnose delirium in an Indian ICU setting [97]

Studies which have formally validated delirium instruments:

(i) Validated the Intensive Care Delirium Screening Checklist [98]

(ii) Validation of memorial Delirium Assessment Scale [99]

Studies of consultation liaison psychiatric referral have also been done.

(i) Referral rate from ICUs to psychiatrists was very low, 1.71% over a 10 year period. [92]

(ii) Average time to referral was 5.3±9.1 (range=0-56) days. Prevalent delirium at admission, sleep-wake disturbance, and specialty of referral were significant predictors of delayed diagnosis.[100]

Studies from India have also examined outcomes.

(i) Postoperative delirium is associated with higher mortality. [91]

(ii) Comprehensive inpatient treatment resulted in higher abstinence rate in people with alcohol dependence compared to those who only received treatment in Emergency Departments [101]

(iii) Increased mortality document in people with delirium; age and the use of restraints were risk factors for mortality [102]

(iv) Delirium associated with longer ICU stay and mortality among cardiac patients [103]

(v) Delirium associated with increased mortality and hospitalization. [104]

(vi) Increased distress among caregivers of patients with delirium [105]

(vii) One-third of the caregivers (36.11%) of people with delirium attributed the symptoms of delirium to non-organic causes like supernatural beliefs, emotional stress resulting from physical illness or various social factors, attention seeking behavior, or a result of religious disobedience.[106]

Studies on treatment

(i) Single-blind randomised trial of Quetiapine vs. haloperidol in the prevention of delirium. Flexible dosing regimen (haloperidol: 0.25-1.25 mg; quetiapine 12.5-75 mg/d) was used. Both drugs were equally effective in treating delirium. [107]

(ii) Single blind study comparing haloperidol, risperidone and olanzapine in preventing delirium showed non-statistically significant differences [108]

Studies on prevention

(iii) Orally given melatonin 3 mg in organophosphate compound poisoning patients has been shown to reduce the duration of delirium and the requirement of sedation and analgesia. This study was a randomized trial using a total of 56 patients [109]

(iv) RCT using dexmedetomidine as an adjunct in cardiac anesthesia produce non statistically significant trend in reducing post-operative delirium [110]

(v) A questionnaire survey of ICU practice across India by the Indian Society of Critical Care Medicine (ISCCM) and the Indian Society of Anesthesiologists (ISA) suggests while awareness of issues related to prevention of delirium was high compliance with best practice was low. Monitoring for delirium, early mobilization and use of analgesia was low while benzodiazepine use as a sedative was high. [111]

2.17. Conclusion

Prevention of delirium is crucial for critically ill patients; Multiple strategies are employed including monitoring, management of pain and agitation, use of sedation and analgesia. The management of established delirium involves correcting precipitating factors and the use of low dose antipsychotic medication (e.g. halorperidol, risperidone, etc.) and benzodiazepines (midazolam, etc.).

Data on the prophylactic use of antipsychotic medication in the prevention of delirium in ICUs is inconclusive, demanding further research.

Section 3

3.0. Aims and objectives

The aim of the study was examine the efficacy of oral risperidone in the prevention of delirium in Medical Intensive Care Unit at the Christian Medical College, Vellore.

The null hypothesis was that there is no difference between oral risperidone and placebo in preventing delirium in patients admitted to the medical intensive care unit.

Section 4

4.0. Method

The study attempted to examine the efficacy of oral risperidone and compare it with a placebo in the prevention of delirium in patients admitted to the intensive care unit. The methodology is based on the CONSORT checklist [112] and is discussed under the following subheadings:

4.1. Trial design

The study design chosen to address the question of efficacy of oral risperidone in the prevention of delirium was a randomized controlled trial. It employed a placebo-controlled arm and was double blind. The patients recruited for the trial were followed up for the development of delirium.

4.2. Setting

The study was undertaken in a 2,500-bed, university-affiliated, private teaching hospital in semi-urban India. The Medical Intensive Care unit has a total of 24 beds with 12 in the high dependency section and 12 in the intensive care section.

The I.C.U follows a semi-open model in which patient care is shared by an admitting team and the ICU team. The admitting unit (in this instance, a medical unit with internal medicine doctors designated as “medical doctors”) takes overall responsibility in terms of extent of care, antibiotic therapy, transfusions, and other treatments. The ICU team, comprised of full-time intensive care

specialists (members designated as “ICU doctors”), manages critical care aspects such as ventilation, hemodynamic support, and renal replacement therapy.

4.3. Participants

The study included consecutive patients with non-neurological problems admitted to the medical ICU, aged 18 years or more with an expected ICU length of stay > 1 day.

4.3.1. Inclusion Criteria: Consecutive adults (18>years) admitted into the medical intensive care unit

4.3.2. Exclusion Criteria:

(i) No informed consent obtained

(ii) Neurological disease (including post-cardiopulmonary resuscitation patients)

(iii) Coma due to drug overdose

(iv) Alcohol withdrawal syndrome

(v) Antipsychotic therapy over the last 30 days

(vi) Pregnancy/breast feeding

(vii) Documented delirium prior to ICU admission

(viii) Difficulty in CAM-ICU assessment (serious auditory or visual disorders, severely mentally disabled; serious receptive aphasia)

(ix) ICU-stay less than one day

(x) Moribund and not expected to survive two days

(xi) Known allergy to Risperidone

(xii) Severe haemodynamic instability (vasopressor dose/inotrope dose>20mcg/min)

(xiii)Liver failure (Child Pugh Class B or C)

(xiv) Renal failure (Stage 3 KDIGO)

4.4. Intervention and Comparator agent:

The following intervention and comparator agents were used

4.4.1 Intervention:

Oral Risperidone 1mg twice daily per orally for the duration of their ICU stay. The review of literature revealed a range of risperidone doses being used for prophylaxis of delirium. It ranged from 1-2 mg per day oral to 2 mg three times a day intravenous. It was decided to use a lower dose for prophylaxis.

4.4.2. Comparator: Placebo daily for the same duration. The placebo was manufactured by the Pharmacy department and was identical in appearance to the intervention as the trial was double blind.

Other modifiable factors predisposing to delirium such electrolyte imbalance, infection and dehydration were actively screened for and treated by the treating physicians as part of routine clinical practice.

The CMC Medical ICU does not currently use any prophylaxis for delirium.

4.5. Outcome

The primary and secondary outcomes are described below:

4.5.1. Primary Outcome: The incidence of delirium in the study patients as measured by the Confusion Assessment Method-ICU Scale score.

4.5.1.1. CAM-ICU Scale [36,37] and score

This is a validated diagnostic tool for delirium for patients in the ICU. It was designed for use by non-psychiatrists at the bedside. It can be administered to all patient with an adequate level of consciousness i.e. patients who have are briefly arousable to call (corresponding to a Richmond Agitation-Sedation [21] score of >-3). This includes those who are on mechanical ventilation since as per current teaching the target level of sedation for these patients is 0 to -1 (i.e. alert and calm to drowsy with sustained arousal on call).

The score assesses four criteria: (i) fluctuation in mental status from baseline (ii) inattention (iii) altered level of consciousness, and (iv) disorganized thinking.

Baseline mental status is the patient's pre-hospital mental status. If the patient is young (<65 years) without a history of stroke or other neuropsychiatric disease then it can be presumed to be normal. For older patients or those with a history of neurological disease pre-hospital status must be assessed by detailed discussion with the patient's family or care-givers.

The CAM-ICU Manual [113] suggests the following steps in its use (Table 4.1)

Table 4.1 Assessing Consciousness: Linking Level of Consciousness & Delirium Monitoring

Step 1 Level of Consciousness: RASS*

Scale	Label	Description	
+4	COMBATIVE	Combative, violent, immediate danger to staff	
+3	VERY AGITATED	Pulls to remove tubes or catheters; aggressive	
+2	AGITATED	Frequent non-purposeful movement, fights ventilator	
+1	RESTLESS	Anxious, apprehensive, movements not	

		aggressive	
0	ALERT & CALM	Spontaneously pays attention to caregiver	
-1	DROWSY	Not fully alert, but has sustained awakening to voice (eye opening & contact >10 sec)	Voice
-2	LIGHT SEDATION	Briefly awakens to voice (eyes open & contact <10 sec)	Voice
-3	MODERATE SEDATION	Movement or eye opening to voice (no eye contact)	
If RASS is ≥ -3 proceed to CAM-ICU (Is patient CAM-ICU positive or negative?)			
-4	DEEP SEDATION	No response to voice, but movement or eye opening to physical stimulation	Touch
-5	UNAROUSABLE	No response to voice or physical stimulation	Touch
If RASS is -4 or -5→STOP (patient unconscious), RECHECK later			

Step 2 Content of Consciousness: CAM-ICU

Feature 1:	Acute change or fluctuating course of mental status
AND	
Feature 2:	Inattention
AND	
Feature 3:	Altered level of consciousness
OR	
Feature 4:	Disorganized thinking

All participants were screened for delirium daily by the primary investigator using the CAM-ICU instrument.

The manual has detailed instructions on its use. This scale is currently not routinely used in the CMC medical ICU. However, we have successfully piloted it on patients admitted in the ICU.

4.5.2. Secondary Outcome(s):

The following were the secondary outcomes:

(i) Ventilator free days

(ii) Self-extubation rate

(iii) Duration of ICU stay

(iv) Duration of hospital stay

(v) Mortality at 28 days

The patients were screened daily for the development of delirium using the CAM-ICU scale. There were no changes made to the outcome criteria after study was cleared by the Institutional Review Board.

Patients who developed delirium were given treatment for the same at the discretion of the treating physicians. All patients were followed up for 28 days after enrolment. All deaths and adverse events occurring were recorded.

4.6. Sample size:

Sample size was calculated using the following values:

Alpha 0.05

Beta 0.02

Delirium in controls group 60%

Delirium in intervention group 30%

Sample required 42 in each arm

Kelsey JL, Whittemore AS, Evans AS,Thompson WD. [114]

4.7. Randomization:

Randomization procedure is described under the following heads: (i) Sequence generation, (ii) Allocation concealment, (iii) Implementation.

4.7.1.Sequence generation

The pharmacists, department of pharmacy services, CMC, Vellore, used a computer generated the randomization sequence with block randomization in blocks of 4. The allocation ratio was 1:1 intervention and control groups.

4.7.2. Allocation concealment

The study medication was stored in sequentially labelled containers for use. Allocation was concealed from the all investigators, participants and the treating physicians.

4.7.3. Implementation

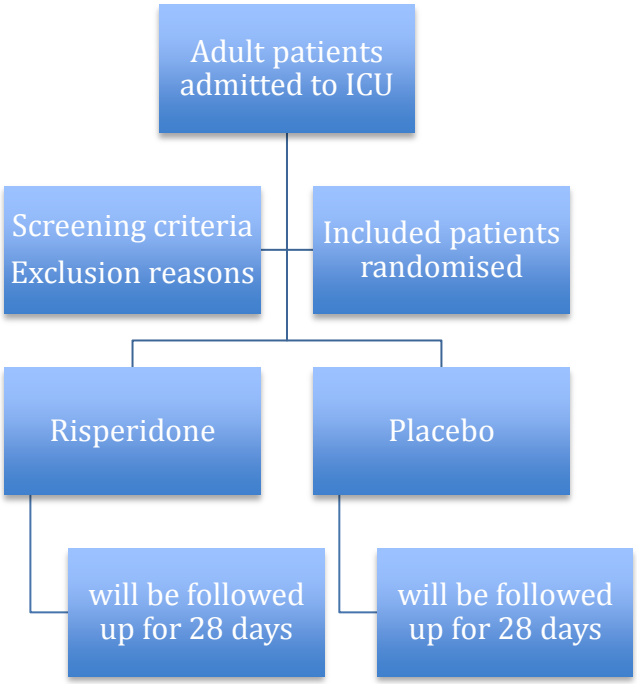
The pharmacist generated the randomization sequence, prepared identical solutions of medication and placebo and stored them in sequentially labelled containers. Both treatment and placebo were stored in similar unmarked packaging. All patients, who satisfy study criteria, were randomized in a 1:1 allocation ratio into intervention and control groups within 24 hours of ICU admission.

The author (AJ) recruited the patients and allocated interventions. The interventions were administered orally.

4.8. Blinding and masking:

The patients, care providers and investigators were all blinded after assignment to treatment and control groups. Both treatment and placebo were administered in similar unmarked packaging.

4.9. Detailed diagrammatic algorithm of the study (Figure 4.1)



4.10. Early stopping rules

The following conditions/criteria were considered for withdrawal of participants:

(i) Severe hemodynamic stability

(ii) Adverse effects related to trial medication

(iii) Renal failure with KIDGO stage III acute kidney injury

(iv) At the discretion of the treating physician

As risperidone is currently licensed for use in the management of delirium in ICUs, premature stopping of trial was not anticipated.

4.11. Statistical analysis

Mean and standard deviation were calculated for continuous variables, while frequencies and percentages obtained for categorical data. Normally distributed variables were tested using the student t test for comparison and the Mann-Whitney U test was employed for non-normally distributed variables. Categorical and binary variables were analysed using the Chi-squared test. Odds ratios and confidence intervals were also calculated.

Baseline variables were compared between those who received risperidone and those who received placebo to check if the two groups differed.

Secondary outcome measures and adverse effects were also compared between the two groups.

Statistical analysis was performed using SPSS version 16.

4.12. Ethics and consent

The Institutional Review Board of the Christian Medical College, Vellore,

Cleared the study protocol (Included).

The informed consent process was initiated immediately after ICU admission.

Written informed consent was taken from the individuals or the immediate

Family of all participants. Family members who were eligible to give consent

include the patient's parents, siblings, spouse and adult children. (Appendix).

4.13 Trial Registration

The trial was registered on the Clinical Trial Registration Database with registration

Number CTRI/2018/10/015955.

5.0 Results

The results of the study are described below under the following subheadings:

1. Overview of the trial

2. Baseline characteristics of the study population

3. Comparison of the baseline characteristics of the treatment and control groups

4. Comparison of drugs used in both groups

5. Outcomes

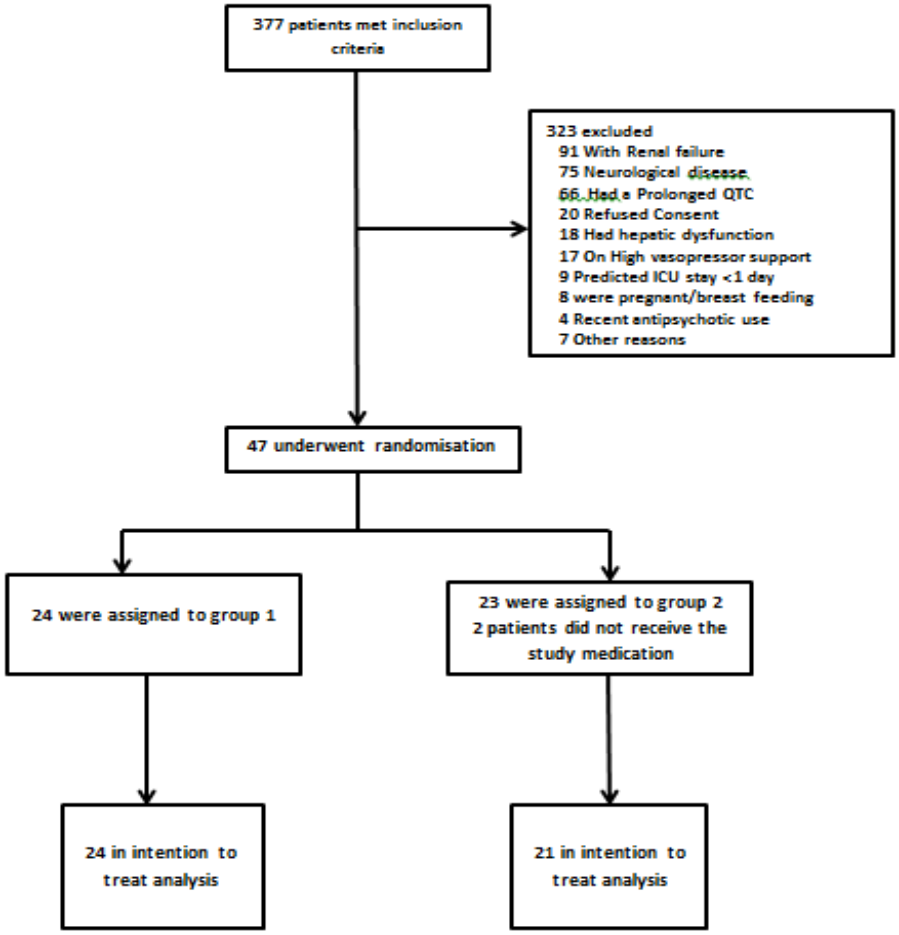
6. Risk factors for delirium

7. Outcomes in patients with delirium

5.1. Overview of the trial

The overview of the trial/ CONSORT Flow diagram is shown in Figure 5.1
An overview of the trial is given in Fig 5.1. During the study 370 patients met the inclusion criteria. 323 patients were excluded before randomisation. 20 patients refused consent. 24 and 23 patients were randomised into group 1 and group 2 respectively. In group 2, 2 patients did not receive even one dose of the study medication. The remaining patients were included in the intention to treat analysis.

Fig.5.1 CONSORT Flow diagram



5.2 Excluded patients

The details of patients who met exclusion criteria are discussed under the following heads: (i) Differences on socio-demographic characteristics between those who participated in the trial and those who did not, (ii) Reasons for patient exclusion.

5.2.1 Comparison of demographic characteristics between included and excluded patients

Table 5.1 documents comparison of demographic characteristics of included and excluded patients. The differences between the two groups on age and sex distribution were not statistically significant.

Table 5.1 Comparison of socio-demographic variables between included and excluded patients

Demography	**Excluded**	**Included**	**Chi sq. value; df; p-value**
Age >40 years	215(64.8)	23(52.3)	4.329; 2; 0.115
Sex- Male	190(59.0)	28(63.3)	1.134; 4; 0.889

5.2.2 Reasons for patient exclusion

The reasons for patient exclusion are recorded in Table 5.2.

Table 5.2. Reasons for patient exclusion

Reason for exclusion	**N (%)**
High Vasopressor support	17(4.5)
Renal failure	91(24.1)
Neurological disease	75(19.9)
Prolonged QTc	66(17.5)
Hepatic dysfunction	18(4.8)
Recent antipsychotic use	4(1.1)
Pregnancy/Breast feeding	8(2.1)
Predicted ICU stay <1 day	10(2.7)
Refused Consent	20(5.3)
Other	9(2.7)
Total	332

The most common reasons for exclusion of patients were renal failure, neurological disease and a prolonged QT interval on their ECGs.

5.3. Study population

The baseline characteristics of the study population are given in Tables 5.3 and 5.4. The study population was predominantly male with and average age of 41.2. Most patients were admitted in the medical high dependency unit. The most common illnesses requiring admission were respiratory and infectious diseases.

Most patients had at least one comorbid illness. The majority of patients were admitted to the intensive care unit within 36 hours of hospitalisation.

Table 5.3. Baseline characteristics of study population- categorical variables

Characteristic	**N=45**	**%**
Sex- Male	29	64.4
HDU admission	31	67.4
Diagnosis		
Infection	26	56.5
Cardiac disease	9	19.6
Renal disease	14	30.4
Poisoning	17	37
Malignancy	2	4.3
Respiratory disease	34	73.9
Gastrointestinal disease	7	15.2
Metabolic disease	5	10.9
Hepatic disease	2	4.3
Comorbid illnesses	18	39.1
Diabetes	15	32.6
Hypertension	10	21.7
Chronic renal disease	3	6.5
Heart disease	3	6.5
Malignancy	1	2.2

Autoimmune disease	3	6.5
Chronic lung disease	2	4.3
Chronic liver disease	0	0
Respiratory failure	40	88.9
Type 1 Respiratory failure	35	87.5
Type 2 Respiratory failure	5	12.5
Ventilation	36	80
Non-invasive	15	41.7
Invasive	22	47.8
Hypotension	19	42.2
Vasopressor requirement	19	42.3

Respiratory failure was common with many patients requiring ventilation. Hypotension requiring vasopressors was present in 42.3% of patients. They had an average APACHE II score of 12.07 and an average SOFA score of 4.5.

Table 5.4 Socio-demographic and clinical characteristics of the sample

Characteristics	Mean	Standard deviation
Age(years)	41.2	17.09
Day in hospital	1.5	1.48
APACHE II	12.07	5.87
SOFA	4.58	2.95
Haemoglobin	11.8	3.25
Total WBC count	14233	7361
Neutrophil %	80.64	16.26
Lymphocyte %	289580	48746.5
Creatinine	1.23	0.63
Urea	39.7	24.9
Total Bilirubin	1.20	1.27
Direct Bilirubin	0.74	1.11
Protein	6.56	1.02
Albumin	3.23	0.89
SGOT	59.2	53.9
SGPT	51.25	72.8
Alk. Phosphatase	134.82	94.3
Sodium	134.82	5.7
Potassium	3.91	0.83
Bicarbonate	16.36	5.01

5.4. Comparison of the treatment and control groups at baseline

Baseline socio-demographic and clinical characteristic of the two groups are compared and recorded in Table 5.5 and Table 5.6

Table 5.5.Baseleine comparison of treatment and control groups-continuous variables

Characteristic	Risperidone Mean (SD)	Control Mean(SD)	T-value; df; p value
Age	40.79(18.34)	41.67(15.96)	-0.169;43;0.866
Day in hospital	1.75(1.89)	1.35(0.74)	0.888;42;0.38
APACHE II	10.82(5.63)	13.38(5.97)	-1.448; 41; 0.155
SOFA	4.63(3.2)	4.52(2.74)	0.123; 41; 0.902
Haemoglobin	11.41(3.08)	12.24(3.45)	-0.856; 43; 0.397
Total WBC	13108(7718.35)	15519(6888)	-1.099; 43; 0.278
DC Neutrophil	78.09(17.38)	83.45(12.37)	-1.14;40;0.261
DC Lymphocytes	13.42(10.35)	8.63(4.87)	1.904; 38; 0.313
Platelets	214880(134130)	374950(69837)	-1.102; 43; 0.277
Creatinine	1.25(0.73)	1.20(0.52)	0.264; 43; 0.793
Urea	40.13(22.27)	39.35(28.36)	0.102;42;0.92
Total bilirubin	1.41(1.55)	0.97(0.82)	1.123;41;0.268
Direct bilirubin	0.98(1.42)	0.48(0.47)	1.481;41;0.146
Protein	6.35(0.84)	6.8(1.16)	-1.527;41;0.135
Albumin	3.01(0.84)	3.50(0.89)	-1.863; 41;0.70

SGOT	62.04(58.83)	56.10(48.95)	0.357;41;0.723
SGPT	56.26(91.75)	45.5(43.64)	0.479;41;0.635
Alk Phos	138.04(1114.83)	101.00(60.14)	1.29;41;0.203
Sodium	133.39(4.43)	136(6.72)	-1.61;31;0.118
Potassium	3.91(0.78)	3.92(0.90)	-0.47;30;0.963
Bicarbonate	16.82(5.83)	15.8(3.95)	0.135;31;0.573

There were no statistically significant differences between the treatment and control groups at baseline.

Table 5.6- Baseline comparison of treatment and control groups- categorical variables

Characteristic	**Risperidone N (%)**	**Control N (%)**	**Chi squared value; df; p value**
Sex- Male	16(66.7)	13(61.9)	0.111;1; 0.739
HDU admission	15 (62.5)	16 (76.2)	0.979;1; 0.322
Diagnosis			
Infection	16 (61.5)	10 (38.5)	1.666; 1; 0.197
Cardiac disease	5 (21.7)	4 (19)	0.49; 1; 0.824
Renal disease	7 (0)	7 (0)	0.91; 1; 0.763
Poisoning	8 (33.3)	9 (42.9)	0.432; 1; 0.511
Malignancy	2 (8.3)	0 (0)	1.832; 1; 0.176
Respiratory disease	20 (83.3)	14 (66.7)	1.684; 1; 0.194

Gastrointestinal disease	4 (16.7)	3 (14.3)	0.48; 1; 0.826
Hepatic disease	3 (12.5)	2 (9.5)	0.1; 1; 0.751
Metabolic disease	5 (20.8)	4 (19)	0.22; 1; 0.81
Autoimmune disease	1 (4.2)	1 (4.8)	0.1; 1; 0.751
Comorbid illnesses	10 (45.5)	8 (40)	0.239; 1; 0.625
Diabetes	6 (27.3)	9 (45)	1.149; 1; 0.284
Hypertension	5 (22.7)	5 (23.8)	0.07; 1; 0.933
Chronic kidney disease	0 (0)	0 (0)	-
Heart disease	3 (13)	0 (0)	2.940; 1; 0.084
Malignancy	1 (4.3)	0 (0)	0.934; 1; 0.334
Autoimmune disease	3 (12.5)	0 (0)	2.683; 1; 0.101
Chronic lung disease	0 (0)	2 (9.5)	2.295; 1; 0.130
Respiratory failure	20 (83.3)	20 (95.2)	1.607; 1; 0.205
Type 1 RF	16 (45.7)	19 (54.3)	2.057; 1; 0.151
Type 2 RF	5 (25)	1 (5)	3.137; 1; 0.077
Ventilation	18 (75)	18 (85.7)	0.84; 1; 0.37
Non-invasive	7 (46.7)	8 (53.3)	0.114; 1; 0.735
Invasive	11 (64.7)	11 (61.1)	0.48; 1; 0.826
Hypotension	9 (37.5)	10 (47.6)	0.322; 1; 0.57
Vasopressor requirement	9 (37.5)	10 (47.6)	0.322; 1; 0.57

There were no statistically significant differences between the treatment and control groups at baseline. Group 1(Risperidone) had a numerically higher number of patients admitted with infectious and respiratory disease while group 2 (Placebo) had higher percentages requiring ventilation and vasopressor support. However, these differences were not statistically significant.

5.5. Drugs received by treatment and control groups during the study

Table 5.7 documents the drugs received in ICU by the two groups. More patients in group 2 received benzodiazepines and sedatives though this difference was not statistically significant. The most common benzodiazepines received were midazolam and the most common opioid was fentanyl. Very few received antipsychotics for agitation. Dexmedetiodine was used frequently for sedation.

Table 5.7 Medication used during ICU admission

Drug	Treatment	Control	Chi-sq.; df; p
Benzodiazepines	13(54.2)	15(71.4)	1.42;1;0.233
Midazolam	11(45.8)	12(57.1)	0.573;1;0.449
Lorazepam	2(8.3)	2(9.5)	0.20;1;0.889
Opioids	12(50)	12(57)	0.23;1;0.632
Fentanyl	12(50)	9(42.9)	0.23;1;0.632
Morphine	2(8.3)	1(4.8)	0.23;1;0.632
Tramadol	3(12.5)	1(4.8)	0.828;1;0.363
Sedatives	9(37.5)	13(61.9)	2.67;1;0.102
Propofol	2(8.3)	3(14.3)	0.402;1;0.526

Ketamine	2(8.3)	6(28.6)	3.138;1;0.076
Dexmed	7(29.2)	9(42.9)	0.916;1;0.338
Antipsychotics	2(8.3)	4(19)	1.113;1;0.292
Haloperidol	2(8.3)	3(14.3)	0.402;1;0.526
Atypical antipsychotics	2(8.3)	1(4.8)	0.23;1;0.632

5.6 Outcomes

The primary, secondary and safety outcomes between the risperidone and placebo groups are compered.

5.6.1. Comparison of primary outcome

Primary Outcomes are compared in Table 5.8. Patients were analysed according to intention to treat analysis. 2 patients died while still sedated and comatose and hence they could not be assessed for delirium. They were analysed in 3 ways

1. Best case scenario: Assuming both to be delirium-free
2. Worst case scenario: Assuming both to be have delirium
3. Per protocol analysis: Excluding both patients

Table 5.8 Primary outcome

Outcome	Risperidone	Control	Chi-sq.; df; p value
Delirium			
ITT: Best case scenario	9(37.5)	9(42.9)	0.134; 1;0.714
ITT: Worst case scenario	9(37.5)	12(57.1)	1.736; 1; 0.188
Per protocol analysis	9(37.5)	9(50)	0.656;1;0.418
Mortality at discharge	3(14.3)	2(10.5)	0.129; 1; 0.720
Mortality at 28 days	3(14.3)	2(10.5)	0.129; 1; 0.720

The differences between the two groups on the different analysis did not reach statistical significance.

5.6.2 Comparison of secondary outcomes

The secondary outcomes between the two groups are compared in Table 5.9.

Table 5.9 Secondary Outcomes

Secondary Outcomes	Risperidone	Control	T value; df; P value
Day of delirium	1.2(0.45)	1.5(1.37)	-0.463; 9; 0.654
ICU stay	6.64(5.31)	6.95(4.83)	-0.199; 40; 0.843
Ventilator-free days	22.42(8.3)	22.92(8.03)	-0.176; 31; 0.861
Duration of ventilation	3.31(4.06)	5.33(5.36)	-1.065;23; 0.298
Hospital stay	13.26(5.93)	21.0(20.07)	-1.611; 21.11; 0.122

There was no significant difference between incidence of delirium in both groups in both intention to treat and per protocol analysis. There was no difference in mortality or any of the other secondary outcomes.

5.6.3. Safety Outcomes

Table 5.10 documents the comparison of safety outcomes.

Table 5.10 Safety Outcomes

Safety Outcomes	**Risperidone**	**Control**	**Chi-square; df; p value**
Any adverse effect	1(4.2)	3(14.3)	1.416; 1; 0.234
QTc Prolongation	1(4.2)	2(9.5)	0.517; 1;0.472
Neurological	0(0)	1(4.8)	1.169; 1; 0.280
Complications	3(14.3)	3(15.8)	0.018; 1; 0.894

There were no significant differences in safety outcomes between groups. One patient in the control group developed neurological adverse effects due to which the study drug was discontinued. The drug was discontinued early in 3 patients at the request of the treating physician.

5.7. Risk factors for delirium

Table 5.11 Risk factors for delirium

Risk factors	Present	Absent	Chi-sq. ; df; p value
HDU stay	**15(57.7)**	**3(21.4)**	**4.835; 1; 0.028**
Infection	10(40.0)	8(47.1)	0.206; 1; 0.65
Cardiac disease	2(22.2)	15(46.9)	1.759; 1;0.185
Renal disease	5(38.5)	13(44.8)	0.149; 1; 0.748
Hepatic disease	2(40.0)	16(43.2)	0.019; 1; 0.891
Gastrointestinal	2(28.6)	16(45.7)	0.7; 1; 0.403
Poisoning	**10(66.7)**	**8(29.6)**	**5.40; 1; 0.02**
Comorbidities	10(52.6)	8(36.4)	1.096; 1; 0.295
Respiratory failure	17(45.9)	1(20)	1.211; 1; 0.271
Hypotension	9(52.9)	9(36.0)	1.186; 1; 0.276
Ventilation	16(48.5)	2(22.2)	1.992; 1; 0.158
Invasive ventilation	**13(65.0)**	**2(16.7)**	**7.036; 1; 0.008**
Benzodiazepine use	**14(56.0)**	**4(23.5)**	**4.356;1; 0.037**
Opioid use	13(59.1)	5(25.0)	4.972; 1; 0.26
Dexmed use	5(33.3)	13(48.1)	0.864; 1; 0.353
Antipsychotic use	3(50.0)	15(41.7)	0.146; 1; 0.703

Risk factors for delirium in the study population were also assessed and are listed in Table 5.11. Admission in the high dependency unit, diagnosis of poisoning, benzodiazepine use and use of invasive ventilation correlated significantly with occurrence of delirium.

5.8. Outcomes with delirium

The outcomes of patients who developed delirium were compared with those who did not. These results are shown in Table 5.12 and 5.13. The patients with delirium had longer ICU and hospital admission with a higher rate of nosocomial complications. There was no difference in mortality between the 2 groups.

Table.5.12 Outcomes with delirium- categorical variables

Outcome	**Delirium**	**No delirium**	**Chi sq.; df; p value**
Mortality at discharge	2(11.1)	1(4.3)	0.681; 1; 0.409
Mortality at 28 days	2(12.5)	2(4.5)	0.806; 1; 0.369
Complications	**5(31.2)**	**0(0)**	**7.917; 1; 0.005**

Table.5.13 Outcomes with delirium- continuous variables

Outcome	Delirium	No delirium	T value; df; p value
ICU stay(days)	10.2(6.4)	4.5(2.3)	-3.289; 16.56; 0.004
Duration of ventilation	8.25(6.11)	1.94(1.34)	-2.887; 1; 0.022
Ventilator-free days	18.44(8.54)	25.31(5.82)	2.212; 11.12; 0.049
Hospital stay	23.67(18.14)	12.909(11.51)	-2.21; 35; 0.034

The ICU stay, duration of ventilation and hospital stay days were significant in the delirium group. The ventilator free days were significantly higher in the no delirium group.

6.0 Discussion

6.1. Introduction

Delirium in intensive care units is a complex problem, whose pathophysiology is poorly understood. It complicates critical illness and occurs in about one-third of patients admitted to ICUs [115]. The fact that hypoactive delirium is much more common than agitated delirium also means poor rates of recognition. Patients who experience such acute confusional states are at higher risk for mechanical ventilation, and are more likely to develop long term cognitive impairment. [116]

The increased morbidity, length of stay, cost, use of resources, higher mortality and poorer course and outcome mandate improved understanding, prevention and management protocols [115].

Although the risk factors and natural history of delirium have been well studied extensively, the evidence for the use of pharmacological medication is scanty. This study attempted to examine the efficacy of oral risperidone in preventing delirium among patients admitted to the Medical ICU.

6.2. Strengths of the study

The study compared oral risperidone 1 mg twice a day and compared it against identical placebo. The investigation was a randomized controlled trial with a comparator placebo arm. It was double blind with patients, physicians and investigators were unaware of treatment allocation. It employed standard and objective outcome assessment criteria.

6.3. Limitations of the study

The limitation of the study is its small sample size. The study population consisted of critically ill adults and the routine use of anti-psychotic medication is uncommon. This study excluded many of the more seriously ill patients in view of safety concerns about possible side effects (though rare). In addition informed consent from relatives of sick patients is difficult. They are often not in a position to understand the issue and give informed consent.

6.4. Implications

As with other studies on the prevention of delirium [115, 116] this investigation resulted in the following implications regarding the treatment of delirious patients:

6.4.1 Excluded patients

This is study excluded many seriously ill patients with multi-organ dysfunction at high risk for delirium. Its results may not be representative of all intensive care patients at risk for delirium. The results of the study may only apply to a small, relatively stable fraction of the patients usually admitted to an intensive care unit.

6.4.2. Study population

The study population had an APACHE II score was 12.07 which corresponds to a predicted mortality of 14.6%. Most patients had normal or near normal liver and renal function with a low burden cardiac disease. Less than half of all patients required vasopressor support while most required either invasive or non-invasive ventilation. These are characteristics which defer from the general population requiring admission to a medical ICU.

6.4.3 Comparison of treatment and control groups at baseline

There were no statistically significant differences between the groups. However despite randomisation and likely due to the small sample size there were non-significant differences between 2 groups, with more infections in the treatment group and more respiratory disease in the control group.

6.4.4 Drugs received in ICU

There were no statistically significant differences between the medications received in both groups. However a higher percentage of patients from the control group received benzodiazepines and other sedatives during their ICU stay. This can be both a cause and effect of a higher rate of delirium in this group.

6.5 Outcomes

(i) The negative results of the study are in keeping with many other trials which have shown that antipsychotic medication are not useful in preventing delirium in the ICU [83-86] and contradict other Investigations which have shown the usefulness of prophylactic antipsychotic medication [87-89]. The results of this study, although underpowered, support the overall conclusion that antipsychotic medication is not the simple answer to prevent delirium in ICUs. [115]

(ii) The treatment group had a lower rate of delirium compared to the control group. However this difference was not statistically significant due to the small numbers studied. A larger study is required to confirm the same.

(iii) The delirium is a heterogeneous problem which may not be managed with a single solution

(iv) The study and its negative results of using risperidone also bring into to focus non-pharmacological management of delirium. Avoiding excessive sedation, benzodiazepines, nocturnal noise and stimulation, and maintaining a day-night schedule, reducing noise, providing ear plugs, eye patches, early mobilization, repeated attempts at reorientation, music therapy are standard recommendations and should be enforced in all ICUs.

(v) Ease of detection of delirium: The investigation piloted the use of CAM-ICU as a method to screen for and identify delirium. Its routine use in the study, its ease of use showed that the identification of delirium can become a quick and routine procedure in the ICU. While agitated and hyperactive delirium in patients is often recognised, the more common hypoactive variety of acute confusional state also needs to be identified and managed.

6.6 Risk factors for delirium

This study identified risk factors for delirium including benzodiazepine use, invasive ventilation and admission for poisoning. Benzodiazepine use has

previously been linked to higher rates of delirium which suggests a need for limiting its use in ICU as far as possible.

6.7 Outcomes among patients with delirium

Patients with delirium had longer ICU and hospital stays as well as a higher rate of nosocomial complications including nosocomial infections and bed sores. This is in keeping with existing literature and supports the need for effective strategies to prevent and treat delirium in the intensive care unit.

7.0 Recommendations

Despite its small sample size and negative results the study, the study has positive outcomes:

(i) It has demonstrated the routine use of CAM-ICU to identify delirium. Its routine use is recommended.

(ii) It has also emphasised on the fact that there are no single or simple solutions to preventing delirium in ICUs shifting the focus to non-pharmacological management protocols to prevent delirium.

(iii) Delirium had a significantly adverse impact on length of ICU and hospital stay and complications.

While the results of and a recent large multicentre RCT (which used haloperidol prophylaxis) [84] are negative, it is still unclear if other medication have a role in preventing delirium. For example, a large trial is currently studying the use of exogenous melatonin in the prevention of delirium in patients with advanced malignancies. [117]

8.0 Summary

1. Delirium, common in the Intensive Care Units, often under recognised. It is a complex problem, yet poorly understood. It is a final common pathway seen in a variety of critical illnesses and under different environmental conditions. It complicates many critical illnesses and occurs in about one-third of patients admitted to ICUs. The increased morbidity, length of stay, cost, use of resources, higher mortality and poorer course and outcome mandate improved understanding, prevention and management protocols.

2. Although the risk factors and natural history of delirium have been well studied extensively, the evidence for the use of pharmacological medication is scanty. This study attempted to examine the efficacy of oral risperidone in preventing delirium among patients admitted to the Medical ICU.

3. The study used randomised controlled trial methodology to compare oral risperidone 1 mg twice a day and compared it against identical placebo. It was double blind with patients, physicians and investigators were unaware of treatment allocation, employed standard and objective outcome assessment criteria and used standard statistical tests to compare outcome.

4. The results did not reveal any difference between risperidone and placebo in preventing delirium. However, the trial had a small sample size. Nevertheless, the negative results of the study are in keeping with many other trials which have shown that antipsychotic medication are not useful in preventing delirium in the ICU [83-86] and supports the overall conclusion that antipsychotic medication is not the simple answer to prevent delirium in ICUs.[115]

5. The study piloted the use of CAM-ICU as a method to screen for and identify delirium. It sensitized the ICU staff and can now be routinely used to identify delirium. The study and its negative results of using risperidone also bring into to focus non-pharmacological management protocols for preventing delirium.

Appendix

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Appendix.1 Patient information sheet

Department of Medicine
Christian Medical College, Vellore

PREDELIC TRIAL- PATIENT INFORMARION SHEET

What is delirium?

Delirium, is a clinical condition where the person has difficulty in attention and concentration and which results in mental confusion. Such confusion and agitation means that the person is not aware of his surroundings and will not be cooperative for treatment. Delirium is a common problem that affects patients admitted to the intensive care units (ICU).

Patients who develop delirium have greater cognitive problems after discharge from hospital, usually have a longer period of hospitalization resulting in higher cost of care and are also at an increased risk of death. Delirium is worsened by infections, certain medications and is more common among older people.

The treatment of delirium includes the management of the underlying medical condition and the use of certain medications like risperidone. While such medication helps people in whom delirium occurs, there is limited scientific evidence to use such strategies to prevent the condition. There have been a few studies done in a small number of people, where medications like risperidone are shown to be useful in preventing delirium. However, there is no definitive evidence to support the routine use of such medication to prevent delirium in ICU.

What is risperidone?

Risperidone is a newer medication, which is now routinely employed in clinical practice. It is routinely used to treat confusion and agitation in people and is used to treat certain forms mental illness. It is routinely use to treat established delirium in hospitalised patients. It is licenced for use in India.

What is the aim of this study?

This study aims to investigate the effectiveness of the medicine risperidone in preventing delirium from occurring to patients admitted in the ICU. Half the patients who join the study will be given a small dose of risperidone, while the rest will receive a placebo.

What will happen if my relative joins the study?

All patients who join this study will be provided standard treatment and care in the ICU. However, half of the patients in the study will receive a low dose of risperidone 1mg twice daily and the other half will receive placebo (dummy) tablets. Neither you nor the treating doctors will know which patients are receiving the active treatment or placebo (dummy) tablets. All the patients

will be checked daily to see if they have delirium and will be monitored for side-effects. The medicine will be stopped once the patient leaves the ICU. In case any patient develops delirium despite treatment the study medication will be stopped and the delirium will be treated using standard treatment protocol.

What are the possible side effects of risperidone?

Risperidone is a relatively safe medicine with few side effects at low dose. However, these may include dry mouth, dizziness, headache and somnolence. All patients will be routinely monitored to check their vital signs.

What will happen is you develop any study related injury?

We do not expect any injury to happen but if you do develop any side effects or problems due to the study medication, these will be treated free of cost to you. However, we are unable to provide monetary compensation to you.

Will you have to pay for the study tablets?

Both risperidone and the placebo (dummy tablet) will be given free for the period of hospitalization in ICU.

Will your personal details be kept confidential?

Yes. Your personal details will be kept confidential. If the results if the study are published in a medical journal, you will not be identified by name in any publication or presentation of the study results. However, your medical notes may be reviewed by people associated with the study.

Can I withdraw from this study after it starts?

Your relatives participation in this study is entirely voluntary. You can withdraw consent for the study at any time and this will not affect your relative's care and treatment.

Appendix 2: Consent form

PREDELIC Trial: Informed Consent Form for Subjects

Informed Consent form to participate in a research study

Study Title: Prevention of Delirium in ICU using low-dose risperidone

Subject's Name: _____

Date of Birth / Age: _____

(i) I confirm that I have read and understood the information sheet dated _____ for the above study and have had the opportunity to ask questions. [ ]

(ii) I understand that my participation in the study is voluntary and that I amfree to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. [ ]

(iii) I understand that the Ethics Committee and the regulatory authorities will not need my permission to look at my health records both in respect of the current study and any further research that may be conducted in relation to it, even if I withdraw from the trial. I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published. [ ]

(iv) I agree not to restrict the use of any data or results that arise from this study provided such a use is only for scientific purpose(s).[ ]

(v) I agree to take part in the above study. [ ]

Signature (or Thumb impression) of the Subject/Legally Acceptable

Date: _____/_____/_____

Signatory's Name: _____ Signature:

Appendix 3: Data collection sheet

[Type text]

1) Serial Number:
2) Name:
3) Age: 4.)Sex: (1)M (2)F
5) Hospital No.:
6) Date of Admission:
7)Day in hospital:
8)MICU/MHDU

6)DIAGNOSIS (Specify):	
6a)Infection (1)Yes (2)No	6f) Respiratory (1)Yes (2)No
6b)Cardiac (1)Yes (2)No	6g)Gastrointestinal (1)Yes (2)No
6c) Renal (1)Yes (2)No	6h)Hepatic (1)Yes (2)No
6d)Poisoning (1)Yes (2)No	6i)Autoimmune (1)Yes (2)No
6e)Malignancy (1)Yes (2)No	6j)Metabolic (1)Yes (2)No

7. CO-MORBIDITIES:

7a)Diabetes (1)Yes(2)No	7d)Malignancy (1)Yes(2)No	7g)Chronic respiratory (1)Yes(2)No
7b)Hypertension (1)Yes(2)No	7e)Autoimmune (1)Yes(2)No	7h)Chronic liver (1)Yes(2)No
7c)Chronic renal (1)Yes(2)No	7f)Cardiac (1)Yes(2)No	7i)Other _____ (1)Yes(2)No

8. APACHE II SCORE:

9. SOFA score:

10. Respiratory failure: 1)Yes 2)No

10A. If yes 1)Type 1 2)Type 2

11. Hypotension: 1)Yes 2)No

11A. If yes, requiring vaspressors? 1)Yes 2)No

13. Ventilation during admission: 1)Yes 2)No

13A. If yes: 1)Invasive- ET

2)Invasive- tracheostomy 3)Non-invasive

12.BASELINE INVESTIGATIONS

12A. Haemoglobin	12H. APTT	12O. SGOT
12B. Total WBC	12I. Creatinine	12P. SGPT
12C. WBC Neutrphils	12J. Urea	12Q. Alkaline Phosphatase
12D. WBC Lymphocytes	12K. Total Bilirubin	12R. Calcium
12E. Platelets	12L. Direct Bilirubin	12S. Phosphate
12F. PT	12M. Total Protein	12T. Albumin
12G. INR	12N. Total Albumin	12U. Magnesium

DRUGS	Drug Name	Duration	Dose
13)Benzodiazepines	**13a**		
	13b		
	13c		
14)Analgesics	**14a**		
	14b		
	14c		
15)Antibiotics	**15a**		
	15b		
	15c		
16)Others	**16a**		
	16b		
	16c		

PREDILIC DATA SHEET

OUTCOMES:

Day	Time	RASS score	CAM-ICU score	Delirium Yes/No	Sodium <130-1 >149-2	Urea	pH	Calcium	SOFA	Fever	Procedure	Risk Factor for Delirium Yes/No
1												
2												
3												
4												
5												
6												
7												
8												
9												
10												
11												
12												
13												
14												
Total Days												

SOFA Score	1	2	3	4
P/F ratio	<400	<300	<220	<100
Platelets x10^3/mm^3	<150	<100	<50	<20
Bilirubin (mg/dl)	1.2-1.9	2.0-5.9	6.0-11.9	>12
Hypotension MAP<70*	Nil	Dopa<5 or dobut	Dop>5 or Norep<0.1 or Adr<0.1 mcg/kg/min	Dop>15 or Norep>0.1 or Adr>0.1
GCS	13-14	10-12	6-9	<6
Creatinine (mg/dl) or Urine output (ml/day)	1.2-1.9	2-3.4	3.5-4.9 or <500	>5 or <200

PREDILIC DATA SHEET

17. Adverse effects- 1)Yes 2)No

Day	Extrapyramidal 17A. 1)Yes 2)No	QT prolonged- 17B 1)Yes 2)No	Other- 17C. 1)Yes 2)No	Day	Extra pyramidal	Other- Specify
1				8		
2		[redacted]		9		
3		[redacted]		10		
4				11		
5		[redacted]		12		
6		[redacted]		13		
7		[redacted]		14		

18.Complications 1)Yes 2)No

19.Nosocomial infection- Specify	1)Yes 2)No	23. Invasive procedure related- Specify	1)Yes 2)No
	18A. Blood stream		22A. Bleeding
	18B. Urinary tract		22B. Pneumothorax
	18C. Pneumonia		
	18D. Soft tissue infection		
20.Accidental Extubation	1)Yes 2)No	24. Acute kidney injury	1)Yes 2)No
21. Failed Extubation	1)Yes 2)No	25. Bed sores	1)Yes 2)No
22.Arrhythmias	1)Yes 2)No		

Outcomes:

23. Delirium: 1)Yes 2)No

24. Ventilator-free days:

25. Day of onset of delirium:

26. Length of ICU stay:

27. Total days with delirium:

28: Length of hospital-stay:

29. Days of Ventilation:

30. Outcome at 28 days: 1)Alive and well

2)Death

3)Lost too follow up

Delirium Risk Factors:

31. Days with hypnatremia:

32. Days with uremia:

33. Days with acidosis:

34. Days with procedure:

35. Days with risk factor for delirium:

36. Days with fever:

37. Average SOFA score:

Contact Information:

No.	Age	Sex	Day in Hosp	Diagnosis	Infection	Caridac	Renal disease	Poisoning/ toxin	Malignancy	Respiratory	Gastrointestinal	Hepatic	Metabolic	Autoimmune
1	68	1	2	lymphoma pneumonia MODS	1	0	0	0	1	1	0	1	0	0
2	41	1	1	influenza a ards von willebran	1	0	0	0	0	0	0	0	0	0
3	37	0	10	sle jejunal perforation	1	1	0	0	0	1	1	0	1	1
4	26	1	2	right heart failure PAH	0	1	1	0	0	1	0	1	1	0
6	62	1	2	autoimmune hemolytic anemia MI	1	1	1	0	0	1	0	1	1	1
7	65	1	2	cholnagitis	1	0	1	0	0	1	0	1	0	0
8	49	1	1	OP poisoning	0	0	0	1	0	1	0	0	0	0
9	55	0	1	acute gastroeneteritis	1	0	1	0	0	0	1	0	1	0
10	43	0	1	pneumonia ards	1	0	1	0	0	1	0	0	1	0
11	28	1	1	oduvanthalai poisoning	0	0	0	1	0	1	0	0	0	0
12	39	1	1	melioidosis dka	1	0	0	0	0	1	0	0	1	0
13	37	1	2	hypokalemic periodic paralysis	0	0	0	0	0	1	0	0	1	0
14	29	1	1	MSSA sepsis multiple abscesse	1	0	1	0	0	1	0	0	1	0
15	43	1	4	pulmonary tb	1	0	0	0	0	0	1	0	0	0
16	28	0	1	left leg dvt femur fracture	0	1	0	0	0	1	0	0	0	0
17	20	1	1	op poisoning	0	0	0	1	0	1	0	0	0	0
18	18	1	1	AGE, myocarditis	1	1	1	0	0	1	1	0	0	0
19	41	0	1	haemotoxic snake bit	0	0	1	1	0	0	0	0	0	0
20	52	1	1	pneumonia CCF	1	1	1	0	0	1	0	0	0	0
21	20	1	1	snake bite anaphylaxis	0	0	0	1	0	1	0	0	0	0
22	31	0	1	disseminated tb	1	1	0	0	0	1	0	0	0	0
23	29	0	1	urosepsis sle	1	0	1	0	0	0	0	0	0	0

Serial no.	comorb	Diabetes	Hypertension	ckd	Malignancy	Auto immune	cardiac	chronic resp	apache ii	sofa	Resp failure	type 1 rf	type 2 rf	shock	Vaso pressor
1	1	1	1	0	1	0	0	0	14	8	1	1	0	0	0
2	1	0	0	0	0	0	0	0	9	3	1	1	0	0	0
3	1	1	0	0	0	1	0	0	11	5	1	0	1	1	1
4	0	0	0	0	0		0	0	17	7	1	1	0	1	1
6	1	1	1	0	0	0	0	1	14	4	1	1	0	0	0
7	0	0	0	0	0	0	0	0	23	12	1	1	0	1	1
8	0	0	0	0	0	0	0	0	19	7	1	0	1	1	1
9	1	0	1	0	0	0	0	0	19	6	0			1	1
10	1	1	1	0	0	0	0	0	15	4	1	1	0	0	0
11	0	0	0	0	0	0	0	0	14	4	1	1	0	0	0
12	1	1	0	0	0	0	0	0	16	8	1	1	0	1	1
13	0	1	0	0	0	0	0	0	6	3	1	1	0	0	0
14	0	0	0	0	0	0	0	0	15	5	1	1	0	1	1
15	1	1	0	0	0	0	0	0	12	6	1	1	0	1	1
16	1	1	0	0	0	0	0	0	8	2	1	1	0	0	0
17	0	0	0	0	0	0	0	0	11	3	1	1	0	0	0
18	0	0	0	0	0	0	0	0	11	8	1	1	0	1	1
19	0	0	0	0	0	0	0	0	25	10	1	1	0	1	1
20	1	0	1	0	0	0	1	0	8	7	1	1	1	1	1
21	0	0	0	0	0	0	0	0	9	2	1	1	0	0	0
22	0	0	0	0	0	0	0	0	15	3	1	1	0	1	1
23	1	0	0	0	0	1	0	0	21	7	0			1	1

Serial no.	Vent	Inv vent	NIV	Hb	TC	DC neutro	DC lymph	Plt	creat	urea	TB	BD	prot	alb	SGT	SGPT	Alk phos
1	1	0	1	7.4	8600	94	4	69000	1.2	53	7.1	6.5	5.5	1.8	50	48	438
2	1	0	1	7.5	14300	82	12	438000	0.6	44	0.3	0.3	5.7	2.8	41	189	88
3	1	1	0	6.4	4300			22000	0.58	34	2	1.8	5.6	2	93	48	244
4	1	0	1	12.8	17400	96	3	3400000	2.03	87	2.9	1.4	6.4	3.9	152	122	66
6	1	0	1	6.1	13500			317000	1.29	42	3.2	1.5	7.2	3.8	46	181	96
7	0			6.2	39900	76		16000	1.75	64	3.6	2.9	6.6	2.8	136	64	84
8	1	1	0	18.9	19700	81	15	195000	1.26	20	0.2	0.1	7.5	3.9	53	26	107
9	0			13.1	17000			290000	2.02	41	0.6	0.3	5.5	2.4	28	18	68
10	1	0	1	8.1	13600	95		149000	1.75	38	0.21	0.12	7.1	2.8	21	16	84
11	1	0	1	16.2	21700	93	2	340000	1.86	35	0.89	0.41	9.3	4.7	209	99	174
12	1	0	1	14.4	5800	87	8	35000	0.66	36	1.08	0.85	6.1	1.7	61	32	151
13	1	0	1	13.71	12600	91	6	312000	0.94	30	0.42	0.19	6.2	3	44	34	68
14	1	1	0	14.8	26200	81	2	259000	1.89	133	1.82	1.41	6.8	1.7	41	37	200
15	1	1	0	8.2	25200	81	11	89000	1	28	0.56	0.34	4.3	2.2	21	15	189
16	1	0	1	10.7	12200	81	13	228000	0.27	15	0.72	0.44	6.2	2.9	52	51	123
17	1	1	0	10.9	18700	86	7	237000	0.38	9	0.55	0.18	6.3	2.7	16	7	68
18	1	0	1	14.6	15600	81	10	307000	1.39	21	1.33	1.04	6	3.1	80	29	72
19	1	1	0	14.3	25800	75	16	168000	1.28	34	0.9	0.22	7.4	3.9	50	18	23
20	1	1	0	10.4	10100	89	6	172000	0.75	31	3.35	1.7	8.3	3.9	25	11	131
21	1	1	0	17.3	24400	76	16	377000	0.65	19	0.68	0.24	5.8	3.5	18	13	62
22	1	0	1	6.4	3100	79	8	22000	0.54	23	1	0.51	4.4	2	104	65	91
23	0			8.5	2100	12	40	236000	3.31	69	0.26	0.15	6	3.1	13	14	96

Serial no.	Benzo	Midaz	Loraz	opioid	fenta	morph	tram	sedat	prop	keta	dexmed	antipsy	halo	atyp
1	0	0	0	0	0	0	0	1	0	0	1	0	0	0
2	0	0	0	0	0	0	0	1	0	0	1	0	0	0
3	1	1	0	0	0	0	0	1	0	1	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0
6	0	0	0	0	0	0	0	1	0	0	1	0	0	0
7	0	0	0	0	0	0	0	0	0	0	0	0	0	0
8	1	1	0	1	1	0	0	0	0	0	0	0	0	0
9	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	1	1	0	0	0	0	0	1	0	0	1	0	0	0
11	1	1	0	0	0	0	0	1	1	1	0	0	0	0
12	0	0	0	0	0	0	0	1	0	0	1	0	0	0
13	1	0	0	0	0	0	0	1	0	0	1	0	0	0
14	1	1	0	1	0	1	1	1	0	0	1	0	0	0
15	0	0	0	1	1	0	0	0	0	0	0	0	0	0
16	1	1	0	1	1	0	0	1	0	0	1	1	1	0
17	0	0	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0	0	0
19	1	1	0	1	0	0	0	1	1	1	1	0	0	0
20	1	1	0	1	1	0	0	0	0	0	0	1	1	1
21	1	1	0	1	1	0	0	0	0	0	0	0	0	0
22	1	0	1	1	1	0	0	1	0	0	1	1	0	1
23	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Serial no.	adv	compl	delirium	vent free	del day	icu stay	hosp stay	vent dur	mortality dis	mort 28	drug
1	0	0	1	3	2	11			0	0	0
2	0	0	0	25		4	16	3	1	1	0
3	0	0	0	0		1		0	0	0	0
4	0	0	0	26		2	11	2	1	1	1
6	0	0	0	25		4	8	3	1	1	1
7	0	0	0	28		3	13	0	1	1	0
8	0	1	1	9	1	20	41	19	1	1	1
9	0	0	0	28		3	11	0	1	1	0
10	0	0	0	26		3	8	2	1	1	1
11	0	0		1		7			0	0	1
12	0		1				14		1	1	0
13	0	0	0	26		3	11	2	1	1	0
14	1	0	1		1	16	55		1	1	1
15	0	1	1		2	5	70		1	1	1
16	0	0	0	28		4	26		1	1	1
17	0	0	0	26		7	16	2	1	1	0
18	0	0	0	27		4	6	1	1	1	0
19	1	1		23		8	12	4	1		1
20	0	1	1	19	1	9	19	9	1	1	0
21	0	0	0	25		3	6	3	1		0
22	1	0	0	28		13	60		1	1	1
23	0	0	0	28		3	15		1	1	0

S.NO	Age	Sex	Day in hosp	Diagnosis	Infection	Caridac	Renal disease	Poison/ toxin	Malignancy	Respir	Gastrointestinal	Hepatic	Metabolic	Auto immune
24	28	1	1	neurotoic snake bite	0	0	0	1	0	1	0	0	0	0
25	47	1	1	alprazolam overdose	0	0	0	1	0	0	0	0	0	0
26	45	1	2	op pyrethroid poisoning	0	0	0	1	0	0	0	0	0	0
27	23	1	2	OP poisoning	0	0	0	1	0	1	0	0	0	0
28	62	1	1	salmonella gastroeneteritis	1	0	1	0	0	0	1	0	0	0
29	77	1	2	OP poisoning multi infarct st	0	0	0	1	0	1	0	0	0	0
30	26	0	2	T cell lymphblastic leukemia	0	0	0	0	1	1	0	0	0	0
31	77	1		celulitis ards	1	0	1	0	0	1	0	0	0	0
32	20	1	1	OP poisoning aspiration pneumo	1	0	0	1	0	1	0	0	0	0
33	76	0	1	tb spondylitis nstemi aki	1	1	1	0	0	1	1	1	0	0
34	30	1	1	OP poisoning	0	0	0	1	0	0	0	0	0	0
35	66	1	1	enetric fever	1	0	0	0	0	0	1	0	0	0
36	28	0	2	scrub ards myocarditis	1	1	0	0	0	1	0	0	0	0
37	37	0	1	OP poisoning	0	0	0	1	0	1	0	0	0	0
38	19	1	1	OP opinion Ecoli bacteremia	1	0	0	1	0	1	0	0	0	0
39	19	0	1	OP poisoning	0	0	0	1	0	1	0	0	0	0
40	41	0	1	OP poisoning	0	0	0	1	0	0	0	0	0	0
41	41	0	1	pyelonephritis	1	0	0	0	0	1	0	0	0	0
42	58	0	1		1	0	0	0	0	1	0	0	0	0
43	23	1	4	P poisoning aspiration pneumon	1	0	0	1	0	1	0	0	0	0
44	46	1	1	retropharyngeal abscess	1	0	1	0	0	1	0	0	1	0
45	46	0	1	afi/ards	1	0	0	0	0	1	0	0	0	0
46	58	1	1	pulmonary embolism	0	0	0	0	0	1	0	0	0	0

Serial no.	comorb	Diabetes	Hypertension	ckd	Malignancy	Auto immune	cardiac	chronic resp	apache ii	sofa	rf	type 1 rf	type 2 rf	shock	Vasopressor
24	0	0	0	0	0	0	0	0	4	0	1	1	0	0	0
25	0	0	0	0	0	0	0	0	7	2	1	0	1	0	0
26	1	1	0	0	0	0	0	0	6	3	1	1	0	0	0
27	0	0	0	0	0	0	0	0	11	2	1	1	0	0	0
28	0	1	1	0	0	0	0	0	16	6	1	1	0	1	1
29	1	0	0	0	0	0	1	0	11	1	1	0	1	0	0
30	0	0	0	0	0	0	0	0	4	1	0			0	0
31	1	0	1	0	0	0	0	1	20	7	1	1	0	1	1
32	0	0	0	0	0	0	0	0	5	5	1	1	0	0	0
33	1	1	1	0	0	1	1	0	17	9	0			1	1
34	0	0	0	0	0	0	0	0	8	2	1	1	0	0	0
35	1	1	1	0	0	0	0	0	8	1	0			0	0
36	0	0	0	0	0	0	0	0	9	5	1	1	0	0	0
37	0	0	0	0	0	0	0	0	4	0	1	0	1	0	0
38	0	0	0	0	0	0	0	0	2	0	1	1	0	0	0
39	0	0	0	0	0	0	0	0	6	2	1	1	0	0	0
40	1	1	0	0	0	0	0	0	16	8	1	1	0	1	1
41	1	1	1	0	0	0	0	0	8	3	1	1	0	0	0
42	0	1	0	0	0	0	0	0	7	3	1	1	0	0	0
43	0	0	0	0	0	0	0	0	13	4	1	1	0	0	0
44					0	0					1	1	0	1	1
45	0	0	0	0	0	0	0	0	25	9	1	1	0	1	1
46						0	0	0			1	1	0	0	0

Serial no.	Vent	Inv vent	NIV	Hb	TC	DC neutro	DC lymph	Plt	creat	urea	TB	BD	prot	alb	SGT	SGPT	Alk phos
24	1	1	0	17.4	13300	95	4	304000	0.81	22	1.04	0.25	7.1	4.1	24	18	66
25	1	1	0	11.9	11000	71	21	377000	1.34	30	0.54	0.21	6	3.9	29	20	60
26	1	1	0	10.7	14300	80	14	316000	0.73	16	0.35	0.19	8.7	4.7	28	23	65
27	0			16	18400	96	1	220000	1.65	32	0.73	0.13	6.6	3.7	24	10	52
28	0			13.9	4500	83	13	115000	1.76		0.67	0.24	6.07	3.63	86	46	32
29	1	1	0	13.1	11300	91	2	170000	1.71	39	0.4	0.19	7.9	4.3	33	7	107
30	0			10.9	7700	61	29	530000	1.76	23	0.29	0.11	6.6	3.6	27	56	113
31	1	1	1	13.4	13200	91	7	184000	1.76	48	1.69	1.19	6.3	3.2	63	45	87
32	1	1	0	14.5	18500	88	2	219000	0.82	26	2.08	0.56	7.7	4.4	20	11	68
33	0			11.1	10100	76	14	264000	2.15	50	2.53	2.3	7.4	2.5	89	48	109
34	1	1	0	12.7	22900	90	6	279000	0.82	21	0.45	0.21	7.5	5.1	30	56	72
35	0			10.7	9500	85	9	285000	0.9	34	0.7	0.33	6.8	3.5	11	7	68
36	1	1	0	9.7	10000	67	31	42000	1.09	66	0.77	0.46	5.2	2.3	142	77	214
37	1	1	0	13.2	13100	82	12	172000	0.64	25	0.93	0.35	6.9	4.5	24	10	88
38	1	1	0	11.1	7200	81	13	171000	0.69	19	0.68	0.23	6.3	3.4	28	18	90
39	1	1	0	11.8	10400	82	11	264000	0.52	29							
40	1	1	0	12	16200	90	5	291000	1.06	28	0.47	0.18	6.1	3.6	31	11	67
41	1	0	1	7.7	19700	87	6	200000	1.15	28	0.75	0.39	7.1	3	15	12	146
42	1	0	1	9.1	4500	75	14	144000	0.72	29	0.4	0.21	7.1	3.8	40	36	100
43	1	1	0	15.4	8200	92	6	118000	0.45	36	0.91	0.46	5.9	2.9	220	434	109
44	1		1	10	11900	84	11	134000	2.45	113	1.23	1.08	5.4	1.6	195	94	501
45	1	1	0	13	20300	40	10	305000	1.35	73	0.51	0.3	7.5	2.9	36	28	258
46	0			14.9	12500	64	26	249000	1.59	57							

Serial no.	Benzo	Midaz	Loraz	opioid	fenta	morph	tram	sedat	prop	keta	dexmed	antipsy	halo	atyp
24	1	1	0	1	1	0	0	0	0	1	0	0	0	0
25	1	1	0	1	1	0	0	0	0	0	0	0	0	0
26	1	0	0	1	0	0	0	0	0	0	0	1	1	0
27	1	0	1	0	0	0	0	0	0	0	0	1	1	0
28	0	0	0	0	0	0	0	0	0	1	0	0	0	0
29	1	1	1	1	1	0	0	1	0	0	1	0	0	0
30	0	0	0	1	1	0	0	0	0	0	0	0	0	0
31	1	1	0	0	0	0	0	1	0	0	1	0	0	0
32	1	1	0	1	1	0	0	0	0	0	0	0	0	0
33	1	0	0	1	1	0	1	0	0	0	0	0	0	0
34	1	1	0	1	1	0	0	0	0	0	0	0	0	0
35	0	0	0	0	0	0	0	1	0	0	1	0	0	0
36	1	1	0	1	1	1	0	0	0	0	0	0	0	0
37	1	1	0	1	1	0	0	0	0	0	0	0	0	0
38	1	1	0	1	1	0	0	0	0	0	0	0	0	0
39	1	1	0	1	1	0	0	1	1	0	0	0	0	0
40	1	1	0	1	1	0	0	1	0	1	0	0	0	0
41	0	0	0	0	0	0	1	1	0	0	1	0	0	0
42	0	0	0	0	0	0	0	1	0	0	1	0	0	0
43	1	1	0	1	1	0	0	1	1	0	0	0	0	0
44	0	0	0	0	0	0	0	0	0	0	0	0	0	0
45	1	1	0	1	1	0	0	1	0	1	0	0	0	0
46	1	1	1	1	1	1	1	1	1	1	1	1	1	1

Serial no.	adv	compl	delirium	vent free	del day	icu stay	hosp stay	vent dur	mortality dis	mort 28	drug
24	0	0	0	25		4	6	3	1	1	1
25	0	0	0	27		4	6	1	1	1	0
26	0	0	1		1	8	14	5	1	1	1
27	0	0	1	28		3	7		1	1	1
28	0	0	0	28		2	7		1	1	1
29	0	1	1	12	1	14	22	16	1	1	0
30	0	0	0	28		6	13		1	1	0
31	0	0	1		4	7	14		1	1	1
32	0	0	0	24		6	8	4	1	1	0
33	1	0	1	24	1	4	24	4	1		0
34	0	0	1	25		4	9	3	1		1
35	0	0	0	28		4	8		1	1	1
36	0	0	0	24		5	8	4	1	1	0
37	0	1	1			23	25		1	1	0
38	0	0	1	25		4	9	3	1	1	0
39	0	0	1		3	12	21		1	1	1
40	0	0	1	21		7	11	7	1	1	1
41	0	0	0	27		6	10	1	1	1	0
42	0		0			6	10		1	1	1
43	0		1		1	17			1	1	0
44	0		1		1	6			0	0	0
45									0	0	1
46			0								0