PRESCRIPTION PATTERN AND PHARMACOECONOMIC ANALYSIS OF SEDATIVES USED IN PATIENTS ON MECHANICAL VENTILATION IN ADULT ICU

THESIS

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DOCTOR OF MEDICINE (MD)

(PHARMACOLOGY)

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AIIMS, JODHPUR **Dr. ABISHA T**

DECLARATION

I hereby declare that thesis entitled "**Prescription pattern and pharmacoeconomic analysis of sedatives used in patients on mechanical ventilation in adult ICU"** embodies the original work carried out by me.

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CERTIFICATE

This is to certify that the thesis titled **"Prescription pattern and pharmacoeconomic analysis of sedatives used in patients on mechanical ventilation in adult ICU"** is the bonafide work of **Dr. Abisha T** carried out under our guidance and supervision, in the Department of Pharmacology and Department of Anesthesia and Critical care at AIIMS, Jodhpur.

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The work done by Dr. Abisha T is satisfactory for its submission in partial fulfilment of the requirement for the Degree of Doctor of Medicine (Pharmacology) by the institute.

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Dr. Abisha T

DEDICATED TO MY HUSBAND,
PARENTS
AND
DEPARTMENT OF PHARMACOLOGY
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LIST OF ABBREVIATIONS

ANOVA	:	Analysis Of Variance
ARDS	:	Acute Respiratory Distress Syndrome
ATC	:	Anatomical Therapeutic Chemical
cAMP	:	Cyclic adenosine monophosphate
CKD	:	Chronic Kidney Disease
CLD	:	Chronic Liver Disease
CMA	:	Cost Minimization Analysis
CNS	:	Central Nervous System
COPD	:	Chronic Obstructive Pulmonary Disease
CYP	:	Cytochrome
DDD	:	Defined Daily Dose
DBP	:	Diastolic Blood Pressure
GABA	:	Gamma Amino Butyric Acid
GBS	:	Guillain-Barre Syndrome
GCS	:	Glasgow Coma Scale
GDP	:	Guanosine Diphosphate
GFR	:	Glomerular Filtration Rate
GTP	:	Guanosine Diphosphate
HR	:	Heart Rate
ICER	:	Incremental Cost-Effectiveness Ratio
ICU	:	Intensive Care Unit
IM	:	Intramuscular
IV	:	Intravenous
NMDA	:	N-methyl D-aspartate
OP	:	Organophosphorus
RASS	:	Richmond Agitation and Sedation Scale

SAS	:	Sedation Agitation Scale
SBP	:	Systolic Blood Pressure
SCCM	:	Society of Critical Care Medicine
SGOT	:	Serum glutamic oxaloacetic transaminase
SGPT	:	Serum glutamic pyruvic transaminase
SpO_2	:	Peripheral capillary oxygen saturation
STROBE	:	Strengthening the Reporting of Observational Studies in Epidemiology
UGT	:	Uridine 5'-Diphosphate – Glucuronosyl Transferase
WBC	:	White Blood Cells
WHO	:	World Health Organization

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INTRODUCTION

Mechanical ventilation is short-term life support that is in practice for a various spectrum of indications which extend from scheduled surgical procedures to acute organ failure (1). The foremost indications include coma, Chronic Obstructive Pulmonary Disease (COPD), Acute Respiratory Distress Syndrome (ARDS), postoperative complications, trauma, sepsis, and pneumonia (2). Post-intubation pain and anxiety in patients on mechanical ventilation in the intensive care unit (ICU) may cause agitation, increased oxygen consumption, tachycardia, hypercoagulability, hypermetabolism, and immunosuppression (3). These probable complications can be best prevented by the usage of sedatives along with other drugs.

Sedatives are pharmacological agents used to facilitate tolerance to the artificial airway, reduce irritability or agitation while doing a medical procedure, and reduce pain and anxiety in critically-ill patients who are on mechanical ventilation in the ICU (3). On the whole, it decreases the activity, moderates excitement, and calms the recipient (4). A wide variety of pharmacological agents are now available for sedation.

Some of the commonly used sedatives in critically-ill patients on mechanical ventilation include alpha-adrenergic receptor agonists, benzodiazepines, general anaesthetic agents, and opioids (5). These drugs are either used alone or in combination. The choice of agent will be based on many factors, including the relative needs, co-morbidities, tolerance profile, and cost (6).

Alpha-adrenergic receptor agonists are used as sedatives and adjuncts to anaesthetic agents (7). Dexmedetomidine is a centrally acting selective α_2 adrenergic receptor agonist which has both sedative and analgesic effects. Compared to other sedatives, it does not have a respiratory depressant effect and is associated with less delirium. It is widely used as a short-term sedative in perioperative patients (8).

Benzodiazepines are potent sedative, hypnotic, anxiolytic, and they can also induce anterograde amnesia. Among the benzodiazepines, the widely used agent in mechanically ventilated patients is midazolam. Midazolam is a shorter-acting benzodiazepine that can be given orally, intravenously, and intramuscularly. Conventionally, it was used as a first-line agent for sedation in the ICU. But due to the increased incidence of delirium and prolonged ICU stay, alternative agents are preferred now (9).

The general anaesthetic agent frequently used as a sedative in the ICU is propofol. Propofol is used for induction and maintenance of general anaesthesia, sedation in critically ill patients in the ICU, effective control seizures in status epilepticus, and patients undergoing minor procedures (4,10). It has a rapid onset and offset of action and is well tolerated (9).

Opioids are potent analgesic and sedative agents. Among them, fentanyl is a potent synthetic opioid commonly used in intubated and critically-ill patients in the ICU. It is often used as a sedative of choice in renal failure patients, as its elimination is mainly through the liver (11).

Sedation strategy decides the effectiveness of the therapy. Till now, no sedatives are superior in efficacy and in reducing adverse clinical outcomes (12). The commonly employed sedation strategy in critically ill, mechanically ventilated patients in the ICU is a continuous infusion of sedatives. Others include no sedation, daily interruption, and nursing-directed algorithms using validated sedation scales (9).

Maintaining the patient at an adequate level of sedation to avoid potential adverse effects is crucial and remains a challenge for clinicians (13,14). Earlier it was believed that deep sedation was the better option for these patients. Since the last decade, due to the reduction in 90-day mortality, decrease in extubation time, development of new ventilators, and recognition of incidence of delirium in over-sedated patients, the Society of Critical Care Medicine (SCCM) has recommended light sedation in critically-ill, mechanically ventilated patients (15,16).

Both under-sedation and over-sedation have adverse effects on these patients. Under-sedation can lead to agitated patients who are more vulnerable to self-extubation and have compromised long-term psychological recovery. On the other hand, over-sedation may cause increased intensive care and duration of hospital stay, poor long-term recovery, and increased mortality (5). In order to minimize the varying degree of sedation in these patients, sedation scales are used (17).

The utilization of sedatives varies in different parts of the world and within different regions of the countries, including India. Analyzing the prescription pattern helps avoid the irrational prescription, which puts up to the unnecessary cost for the treatment, improves the quality of health, expands the accessibility, and assures the sustainability of the resources available for health care (18).

Therefore, drug utilization patterns and pharmacoeconomic evaluations are essential not only for assessing the rationality of the drug used but also for the cost analysis of the medical care provided. Daily ICU cost for mechanically ventilated patients is 20% to 44% higher when compared to non-ventilated patients (19).

Cost minimization analysis is one of the methods of pharmacoeconomic evaluation which identifies the treatment/intervention with the lowest cost. In this, the health outcomes of the pharmaceutical products compared have similar efficacy. Therefore, based on the net cost-saving, therapy with lower cost can be chosen over others (18).

There is a paucity of information regarding the utilization pattern of sedatives in adult ICU in patients on mechanical ventilation and their pharmacoeconomic evaluation in India. Hence, our study aimed to analyze the prescription pattern and pharmacoeconomics of sedatives used in patients on mechanical ventilation in adult ICU.

REVIEW OF LITERATURE

Sedation is the medically induced temporary depression of consciousness that relieves pain or discomfort caused to the patient (20). It facilitates tolerance to the artificial airway, reduces irritability or agitation while doing a medical procedure, and reduces pain and anxiety in critically ill patients on mechanical ventilation (3). Pain and anxiety in these patients give rise to a prominent sympathetic stress response, leading to physical and psychological stress (21). This, in turn, may lead to severe agitation, prolonged ICU stay, increased morbidity, and mortality.

Therefore, sedation is considered a prerequisite for the care of these patients in the ICU to keep them calm and co-operative with normal alertness (8,22). Studies propose that no sedative drug is superior to others (22). The choice of the sedative agent varies based on the patient's prerequisite and the clinician's choice.

The widely used classes of sedatives in patients on mechanical ventilation in the ICU are alpha$_2$ adrenergic receptor agonists, benzodiazepines, general anaesthetic agents, and opioids, as shown in **Table 1**.

Table 1: Commonly used sedatives (12,21,23)

Class of drug	**Name of sedatives**
Alpha$_2$ agonists	Dexmedetomidine, Clonidine
Benzodiazepines	Midazolam, Lorazepam
General anaesthetic agents	Propofol, Ketamine, Isoflurane, Sevoflurane
Opioids	Fentanyl, Hydromorphone, Morphine, Remifentanil

ALPHA$_2$ ADRENERGIC RECEPTOR AGONIST:

The α_2-adrenoceptor agonists treat medical diseases like hypertension, pain, anxiety, and attention-deficit hyperactivity disorder. Nowadays, they are used as a sedative and an adjunct to anaesthetic agents to reduce the dose of the latter (7). The α_2-adrenoceptors are G-protein coupled receptors with subtypes of α_{2A}, α_{2B}, and α_{2C}. The α_{2A} and α_{2C} subtypes are found mainly in the central nervous system (CNS). Stimulation of these receptor subtypes is responsible for sedation and analgesia (24). Dexmedetomidine and clonidine are the α_2 agonists which are widely used as sedatives.

Dexmedetomidine:

It is a potent and selective α_2-adrenoceptor agonist used as a sedative, anxiolytic, and analgesic in critically-ill adult patients. It is widely used for short-term sedation of mechanically ventilated patients in the ICU and during surgical and other procedures (25).

Dexmedetomidine or 4-[(1S)-1-(2,3-dimethyl phenyl) ethyl]-1H- imidazole, with molecular formula $C_{13}H_{16}N_2$, is a dextro-enantiomer of medetomidine, which is used as a sedative and an analgesic in veterinary medicine (26). The chemical structure of dexmedetomidine is shown in **Figure 1.**

Mechanism of action:

Dexmedetomidine is a specific and selective α_{2A}-adrenoceptor agonist compared to clonidine (non-selective α_2-adrenoceptor agonist) (24). On binding and activation of the presynaptic α_2-adrenoceptors, it inhibits the release of norepinephrine and terminates the propagation of pain signals (27). On activation of the postsynaptic α_2-adrenoceptors in CNS, it inhibits the sympathetic activity and thus decreases the heart rate and blood pressure. It causes sedation by interaction with Locus coeruleus. Combined effects produce analgesia, sedation, and anxiolysis (28). The mechanism of action of dexmedetomidine is shown in **Figure 2.**

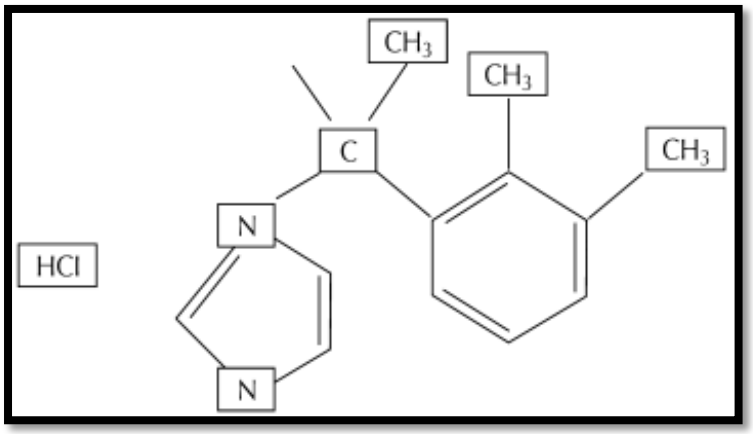


Figure 1: Chemical structure of Dexmedetomidine

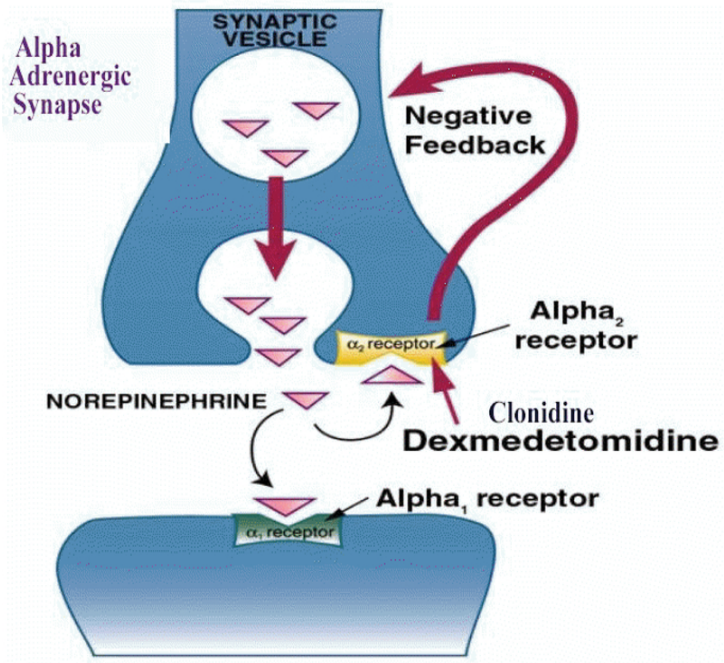


Figure 2: Mechanism of action of Dexmedetomidine

Pharmacokinetics:

Dexmedetomidine is a highly protein-bound (94%) drug. It can cross the placental and blood-brain barrier. It undergoes nearly complete biotransformation by direct glucuronidation and cytochrome P450 metabolism in the liver. The glucuronide and methyl conjugates are excreted in urine (28).

Adverse effects, drug interactions, and contraindications:

It includes bradycardia and hypotension, attributed to the inhibition of sympathetic activity by activation of postsynaptic α_2-adrenoceptors. Nausea and dry mouth are also commonly seen (27). Dexmedetomidine inhibits CYP2D6 and CYP2DA4 enzymes. Therefore, the concomitant use of drugs like tramadol, which are metabolized by these enzymes, should be avoided. Dexmedetomidine should be used with caution in patients with hypotension, bradycardia, and heart failure (29).

Dose and route of administration:

The recommended loading dose is 1 μg/kg given over 10 min, followed by infusion at a rate of 0.2–0.7 μg/kg/h. It can be administered via intravenous (IV), intramuscular (IM), buccal, transdermal, and intranasal routes. IV route is the most preferred route (30).

Clonidine:

It is the prototypical non-selective α_2-adrenoceptor agonist. It is widely used as an anti-hypertensive and in withdrawal syndromes of alcohol, nicotine, and opioid addiction. It decreases norepinephrine release and increases parasympathetic activity. The sedative effect is due to its action on Locus coeruleus.

Sudden withdrawal of clonidine causes life-threatening rebound hypertension and tachycardia (31). Hemodynamic stability is better observed with dexmedetomidine when compared to clonidine (32). Therefore, dexmedetomidine is preferred over clonidine for sedation in the ICU.

BENZODIAZEPINES:

Benzodiazepines are positive allosteric modulators on Gamma-Aminobutyric acid-A (GABA-A) receptors. It is used for various indications such as anxiety, muscle relaxation, epilepsy, and insomnia. They are also used as a sedative in the ICU and intra-operatively due to their anxiolytic and amnesic properties. Benzodiazepines bind to the GABA-A receptor and cause a conformational change in the chloride channel, which in turn leads to hyperpolarization of cells accounting for GABA's inhibitory effect throughout the CNS (33). Midazolam and lorazepam are the commonly used benzodiazepines as sedatives in critically-ill patients in the ICU.

Midazolam:

Midazolam or midazolam hydrochloride with molecular formula $C_{18}H_{13}ClFN_3$ is a short-acting hypnotic-sedative drug with anxiolytic, muscle relaxant, anticonvulsant, sedative, hypnotic, and amnesic properties (34). The chemical structure of midazolam is shown in **Figure 3**.

Mechanism of action:

It acts by selectively binding to GABA-A receptors, which mediate inhibitory synaptic transmission throughout the CNS by increasing the frequency of chloride channel opening. This causes sedation, skeletal muscle relaxation, induces sleep, anaesthesia, and amnesia (34). The mechanism of action of midazolam is shown in **Figure 4.**

Pharmacokinetics:

It is well absorbed orally, usually giving a peak plasma concentration in about 1 hour. Sedation is achieved within 3 to 5 minutes post IV injection in adult and paediatric patients. They bind strongly to plasma protein (97%) and have high lipid solubility. It can cross both the placental and blood-brain barriers. The volume of distribution is 1 to 3.1 L/kg when administered intravenously. They are all metabolized in the liver and gut by CYP3A4 to their active pharmacologic metabolite and also undergo N-glucuronidation via UGT1A4 and are excreted in urine (34).

Adverse effects, drug interactions, and contraindications:

The main side effects of benzodiazepines are bradycardia, hypotension, confusion, tremors, amnesia, and impaired coordination. Drug interaction of midazolam on concomitant use with CYP3A4 inhibitors, inducers, and substrates of CYP are predictable (4). Contraindications include hypotension, shock, and acute angle-closure glaucoma (35).

Dose and route of administration:

The sedative dose of midazolam is 0.01 to 0.05 mg/kg through the IV route. Midazolam can be administered through oral, IV, IM, and rectal routes (4).

Lorazepam:

Lorazepam is widely used as a sedative as well as an anxiolytic. It has a rapid onset of action (1-3 minutes) when administered intravenously. It is also being used in the treatment of status epilepticus. It acts through the same mechanism as that of midazolam. Its half-life is 14 hours (36).

Lorazepam is used in the ICU for long-term sedation as it is more potent and has a longer duration of action (37). However, it can cause a delay in extubation, incidence of delirium, and increase in length of the ICU stay even with a short duration of infusion (38,39). The dose of lorazepam should be tapered every third day by 0.5mg to avoid withdrawal symptoms (40). Whereas midazolam is short-acting and has lesser side effects compared to lorazepam. Hence, midazolam is preferred over lorazepam.

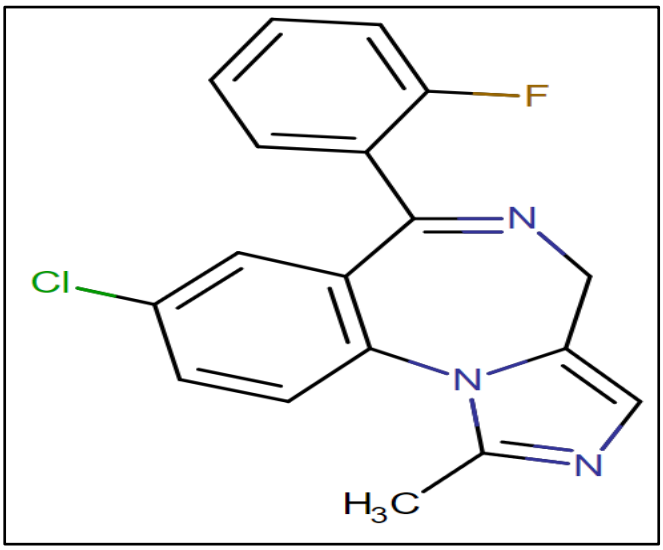


Figure 3: Chemical structure of Midazolam

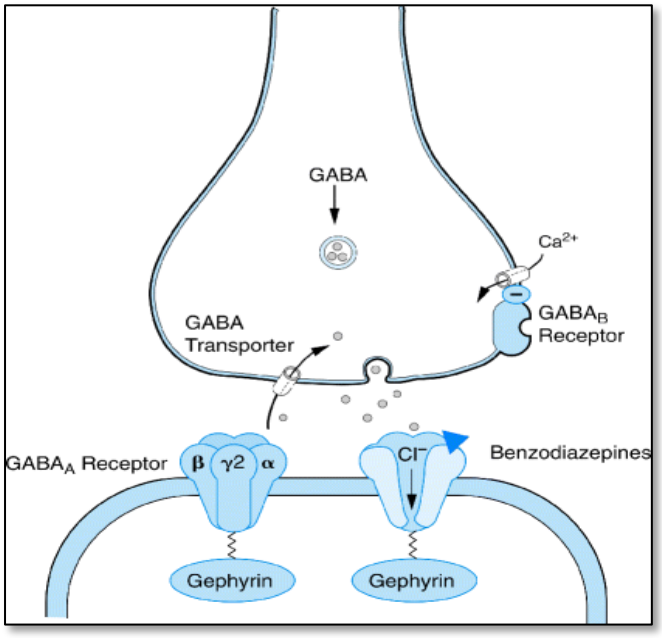


Figure 4: Mechanism of action of Midazolam

GENERAL ANAESTHETIC AGENTS:

The general anaesthetic agent which is frequently used as a sedative in the ICU is propofol. Other agents such as ketamine, isoflurane, and sevoflurane are used as an adjunct therapy for sedation (21). These agents mainly act by activating GABA-A receptors leading to the post-synaptic hyperpolarization of the cell membrane and finally causing inhibition of the neuronal activity (41).

Propofol:

Propofol or 2,6-Diisopropyl phenol with molecular formula $C_{12}H_{18}O$ is used for induction and maintenance of general anaesthesia, sedation in critically-ill patients in the ICU, and patients undergoing procedures like gastrointestinal endoscopy procedures and during transvaginal oocyte retrieval (4). It effectively controls seizures in status epilepticus (10). It is generally used in low doses to achieve sedation which has an intact respiratory and cardiac function with diminished cognitive function (42). The chemical structure of propofol is shown in **Figure 5.**

Mechanism of action:

Propofol entails a positive modulation of the inhibitory function of GABA through GABA-A receptors. Therefore, the channels are activated for a longer time, directed towards an increase in chloride conductance across the neuron resulting in hyperpolarization of the cell membrane (43). The mechanism of action of propofol is shown in **Figure 6.**

Pharmacokinetics:

It has rapid distribution and thereby rapid onset of action. The volume of distribution is 60 L/kg. It is 95 – 99% protein bound. Duration of action is 5-10 min (44). It has very high clearance. It is metabolized in the liver by conjugation to sulphate and glucuronide to less-active metabolites that are renally excreted.

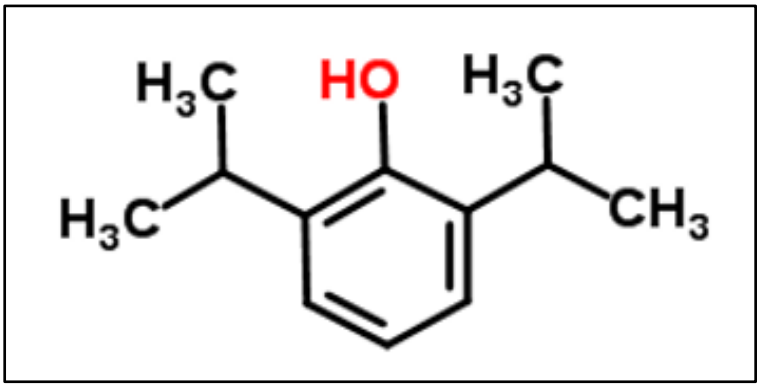


Figure 5: Chemical structure of Propofol

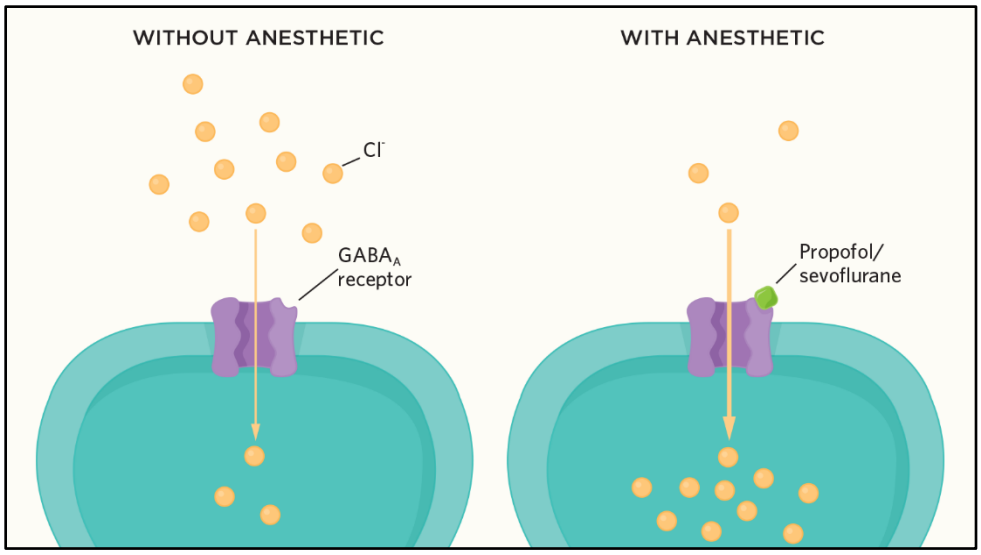


Figure 6: Mechanism of action of Propofol

Adverse effects, drug interactions, and contraindications:

It includes light-headedness, headache, reduced intracranial and intraocular pressures, dose-dependent hypotension, respiratory depression, and allergic reactions. It may also cause propofol infusion syndrome on long-term use, resulting in death (45). CYP2B6 inhibitors like clopidogrel may reduce propofol metabolism and cause toxicity. Propofol is contraindicated in hypotensive patients and patients with known hypersensitivity (43).

Dose and route of administration:

The required initiation dose is a slow IV injection of 0.5 mg/kg followed by a maintenance infusion of 6 to 9 mg/kg/h (46). The optimum dose for sedation is about 6.5 mg/kg.

Ketamine:

Ketamine is an IV anaesthetic agent which can be used for various indications such as sedation, catalepsy, analgesia, and bronchodilation. It is highly lipid-soluble. It mainly acts by non-competitive antagonism of the N-methyl D-aspartate (NMDA) receptor. It increases the heart rate, blood pressure, and cardiac output by stimulating the cardiovascular system, and so it is not indicated in patients with hypertension and raised intraocular pressure (47).

Volatile agents:

The widely used volatile anaesthetic agents as a sedative are isoflurane and sevoflurane. Isoflurane is a fluorinated ether used for induction and maintenance of general anaesthesia and as muscle relaxant. It is also used to treat status asthmaticus due to its remarkable broncho-dilatory activity and as an adjunct for sedation in critically-ill patients. It acts through the same mechanism as that of propofol. In addition, it inhibits glutamate-mediated excitatory transmission by increasing glutamate re-uptake and potentiates the glycine receptor activity (48).

Sevoflurane is a halogenated inhalational anaesthetic agent used for induction and maintenance of general anaesthesia, analgesia, and sedation. It acts by enhancing the inhibitory post-synaptic channel activity and inhibiting the excitatory synaptic

activity in CNS. It produces a dose-dependent decrease in blood pressure and cardiac output by reducing vascular resistance. It also increases the intracranial tension. Hence, continuous monitoring of vitals is mandatory (49).

Because of cardiovascular instability, general anaesthetics other than propofol are used as an adjunct therapy for sedation.

OPIOIDS:

Opioids are widely used as analgosedative in the ICU. Fentanyl, morphine, hydromorphone, and remifentanil are the widely used opioids. Analgosedation can be defined as either analgesia-first sedation, i.e., use of analgesic before sedative to reach the sedative goal, or analgesia-based sedation, i.e., use of analgesic instead of sedative to reach the sedative goal (16). This practice of analgosedation provides light sedation while managing the pain. The advantage of this therapy includes a reduction in the duration of mechanical ventilation, a decrease in length of ICU stay, and pain alleviation (50). Opioids bind to opioid receptors, closing N-type voltage-gated calcium channels and opening inward rectifying potassium channels. This leads to hyperpolarization and reduced neuronal excitability (51).

Fentanyl:

Fentanyl or N-phenyl-N-[1-(2-phenylethyl) piperidin-4-yl] propanamide with molecular formula $C_{22}H_{28}N_2O$ is a synthetic opioid (52). It is a potent analgesic commonly used in chronic pain. It is used as a sedative in mechanically ventilated patients and as a pre-medication in procedures, causing discomfort. It can also be used for the treatment of epilepsy (11). The chemical structure of fentanyl is shown in **Figure 7**.

Mechanism of action:

Fentanyl binds to the opioid receptors, mainly the mu-receptor. As these receptors are coupled to G-proteins, activation causes GTP to be exchanged for GDP, which in turn down regulates adenyl cyclase. As a result, cAMP decreases, leading to reduced cAMP dependant influx of calcium ions into the cell, causing hyperpolarization of the cell and inhibition of nerve activity (52). The mechanism of action of fentanyl is shown in **Figure 8.**

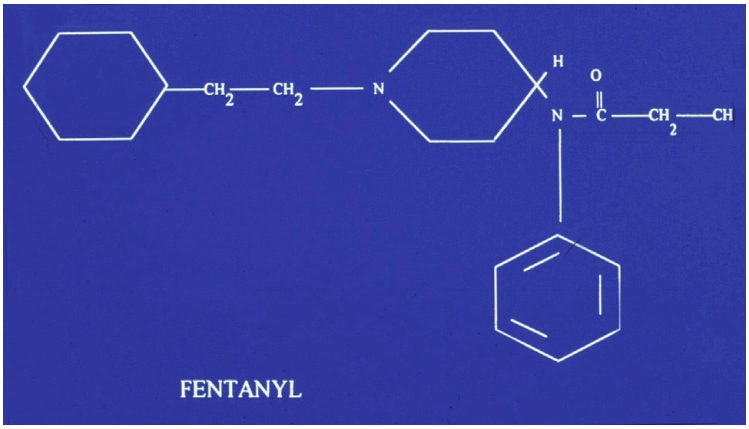


Figure 7: Chemical structure of Fentanyl

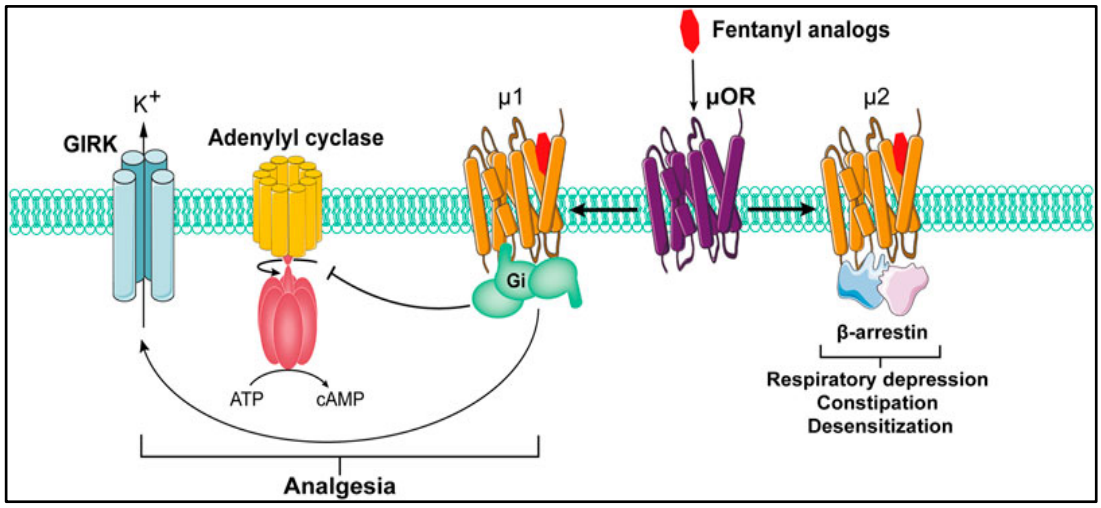


Figure 8: Mechanism of action of Fentanyl

Pharmacokinetics:

The IV volume of distribution of fentanyl is 4L/kg and is 80-85% protein bound. It can cross the blood-brain and placental barrier. It is highly lipid-soluble, and its half-life is 7 hours. The total plasma clearance is 0.5L/hr/kg. It is 99% N-dealkylated to nor-fentanyl by CYP3A4 and is eliminated through urine and faeces (52).

Adverse effects, drug interactions, and contraindications:

It includes bradycardia, hypotension, delayed respiratory depression, confusion, narcotic delirium, constipation, coma, and even death (11). Fentanyl on concomitant use with CYP3A4 inhibitors will increase the plasma concentration of fentanyl, which increases the adverse drug reactions and might lead to fatal respiratory arrest (53). It is contraindicated in asthma, COPD, liver failure, and known hypersensitivity (11).

Dose and route of administration:

The loading dose of fentanyl is 25 to 100 mcg, and the maintenance dose range from 50 to 700 mcg/hour infusion (54). It can be administered by various routes, which include IV, IM, transdermal, intranasal, buccal, sublingual, and intrathecal routes (55).

Remifentanil:

Remifentanil is a potent, ultra-short acting synthetic opioid agonist used as an analgesic and an adjunct to anaesthetic agents for induction and maintenance. Its half-life is 1-20 minutes. The mechanism of action is similar to that of fentanyl. The adverse effects include bradycardia, hypotension, and serotonin syndrome (56).

Morphine:

Morphine is indicated for the management of chronic and severe pain. But it has a high chance of developing dependence, drug abuse, and addiction. Its half-life is 1.5–4.5 hours after IV or IM administration (57). It acts as an agonist of mu and kappa opioid receptors, which causes hyperpolarization of interneurons and decreases neurotransmitter release (58).

Hydromorphone:

Hydromorphone is a semi-synthetic opioid that selectively binds to the mu-opioid receptor and leads to hyperpolarization and reduced excitation. The plasma half-life is 2-3 hours (59). It is mainly used for relieving moderate to severe pain like cancer pain. The adverse effects are similar to that of morphine (60).

Fentanyl has faster induction and recovery over morphine and hydromorphone due to its faster redistribution, shorter duration of action, and elimination half-life of 4 hours (61). The rapid offset of effect with remifentanil resulted in more incidence of pain, leading to the requirement of change in the regimen (62). Hence, fentanyl is considered the preferred sedative of choice over other opioids.

Maintaining the patient at an adequate level of sedation to avoid potential adverse effects is crucial and remains a challenge for clinicians (13,14). Earlier, it was believed that deep sedation was the better option for critically ill patients on mechanical ventilation. Since the last decade, due to reduced 90-day mortality, decreased extubation time, development of new ventilators, and recognition of incidence of delirium in over-sedated patients, SCCM recommends light sedation in critically-ill, mechanically ventilated patients (15,16).

Both under-sedation and over-sedation have adverse effects in these patients. Under-sedation can lead to agitated patients who are more vulnerable to self-extubation and have compromised long-term psychological recovery. On the other hand, over-sedation may cause increased intensive care and duration of hospital stay, poor long-term recovery, and increased mortality (5).

In order to minimize the varying degree of sedation in these patients, sedation scales are used. For better utilization, the sedation scales should be simple to use and should have potent psychometric properties, in particular feasibility, validity, and reliability (14). The widely used sedation scales are Richmond Agitation Sedation Scale (RASS), Riker Sedation-Agitation Scale (SAS), and Ramsay Sedation Scale (17).

RASS is a 10 point scale that consists of the score, the term given to each score, the description of each score, and the procedure to perform (63). SAS is a 7 point scale

containing the score, the term given to each score, and the description of each score. These scales are found to satisfy the criteria for better utilization of the sedation scale, and hence both the scales were utilized to assess the sedation level in our study.

Studies on sedation of mechanically ventilated patients in the ICU:

A randomized, double-blind, controlled, multicentric trial was conducted by *Muellejans et al* (2003) at 21 centers to compare the efficacy and safety of fentanyl with remifentanil for ICU sedation. They concluded that analgesia-based sedation with remifentanil provided effective sedation and rapid extubation without the need for propofol in most patients. But Remifentanil resulted in the rapid offset of effect, leading to increased incidence of pain. Thus, there was a need for proactive pain management with remifentanil (62).

A multicentric trial was conducted by *Riker et al* (2009) in Portland to compare the efficacy and safety of dexmedetomidine vs. midazolam on prolonged sedation for patients on mechanical ventilator for more than 24 hours. The median time to extubation was lesser (1.9 days) in dexmedetomidine-treated patients when compared to midazolam-treated patients (5.6 days). The study showed no difference between dexmedetomidine and midazolam in time at the targeted sedation level. Dexmedetomidine developed less tachycardia and hypertension, but bradycardia was observed significantly (64).

A prospective, longitudinal, multicentric, observational cohort study was conducted by *Shehabi et al* (2013) in 11 hospitals in Malaysia to estimate the depth of sedation, extubation time, and long-term mortality in critically-ill mechanically ventilated patients. There was an increased prescription of midazolam when compared to that of propofol. They concluded that irrespective of the sedative used, early deep sedation was associated with delayed extubation and higher mortality (65).

A prospective, randomized clinical study was conducted by *Shah et al* (2014) in India to assess the efficacy and safety of dexmedetomidine in post-operative ICU sedation compared to propofol. The depth of sedation, changes in cardiovascular and respiratory parameters were found to be similar with both the sedatives. Due to lack of respiratory depression, dexmedetomidine is advantageous in patients at myocardial ischemia risk. They concluded that dexmedetomidine appears to be a safe and

acceptable ICU sedative agent when both the clinician's and patient's perspectives were considered (66).

A single-center, prospective, randomized, open-label trial was conducted by *Zhou et al* (2014) in China to assess the safety, efficacy, and cost of propofol, midazolam, and their sequential use in mechanically ventilated patients for long-term use. Propofol for long-term sedation was related to faster recovery. Sequential use was related to less cost and low adverse events compared to propofol alone. They concluded that sequential use of midazolam and propofol was a safe and effective sedation protocol, with higher clinical effectiveness and better cost-benefit ratio than the use of midazolam or propofol alone, for long-term sedation in critically-ill mechanically ventilated patients (67).

A randomized, open-label trial in 40 adults was conducted by *Gupta et al* (2015) in India to compare the efficacy of dexmedetomidine and midazolam in terms of cardiovascular changes, sedation properties, ventilation, and safety to facilitate extubation. They concluded that dexmedetomidine has clinically relevant benefits compared with midazolam in facilitating extubation due to its shorter time to extubation, more hemodynamic stability, easy arousability, and lack of respiratory depression (68).

A study was conducted by *Hayashida et al* (2016) in Japan to detail the current sedative utilization pattern in patients on mechanical ventilation in the ICU and correlate with their clinical outcomes. They concluded that propofol was the most frequently used sedative drug, followed by benzodiazepines, barbiturates, and dexmedetomidine. The mortality rate was lower, and ventilator weaning was earlier among patients who received only propofol (69).

A retrospective study was conducted by *Nunes et al* (2018) in Sweden to find out whether different sedation regimens influence the course and duration of the weaning process from 15 ICUs in patients mechanically ventilated for ≥24 hours. Patients sedated with dexmedetomidine were arousable compared to patients sedated with propofol and/ midazolam which contributed to the shortening of weaning time. Dexmedetomidine has better health-related outcomes like early recovery from weaning and quality of life than other sedatives (70).

A multinational, open-label randomized controlled trial was conducted by *Shehabi et al* (2019) in 8 countries to explore the effect of dexmedetomidine as the sole agent for patients on ventilatory support requiring early sedation. The trial concluded that among patients undergoing mechanical ventilation in the ICU, those who received early dexmedetomidine for sedation required additional sedatives to achieve the prescribed level of sedation. More adverse events were reported in the dexmedetomidine group than in the usual-care group (71).

A prospective, multicentric cohort study was conducted by *Aragon et al* (2019) in the United States of America to analyze the association between medications, sedation status, and clinical outcomes. The more cumulative dose of benzodiazepine was associated with 41% higher mortality. They concluded that deep sedation with benzodiazepines, opioids, and antipsychotics was associated with less ventilator-, ICU-, and hospital-free days (72).

A cohort study was conducted by *Klompas et al* (2020) in Boston to find out the relation between the sedative used and the ventilator-associated events, length of stay, and mortality in mechanically ventilated patients. They concluded that dexmedetomidine was associated with lesser extubation time than benzodiazepines and propofol. There was no significant difference in length of stay and mortality between the groups (73).

PHARMACOECONOMICS:

Pharmacoeconomics is a scientific discipline under health economics that compares the value of one pharmaceutical product or treatment mix to another. It compares the costs, clinical, and humanistic outcomes of different therapies. Studying the utilization pattern of drugs plays a vital role in clinical practice to facilitate rational drug use. World Health Organization (WHO) recommends Anatomical Therapeutic Chemical/Defined Daily Dose (ATC/DDD) as the international standard for drug utilization monitoring and research (74).

Anatomical Therapeutic Chemical (ATC):

ATC is the classification system that groups the active medical substance according to the organ or system they act on and based on their therapeutic, pharmacological, and chemical properties. ATC code varies with the route of administration and for the combination products of the same medicinal substance.

Defined Daily Dose (DDD):

DDD is the assumed average maintenance dose per day for a drug used for its main indication in adults (75). It does not necessarily reflect the recommended or prescribed daily dose. The data presented in DDD only gives a rough estimate of consumption and not an exact picture of actual use.

The ATC/DDD system represents a stable drug utilization metric to enable comparisons of drug use between countries, regions, or health care settings. It is also used to examine the trends in drug use over time. Drug utilization is usually presented as DDD per 1000 inhabitants per day, DDD per inhabitant per year, or DDD per 100 bed days (76).

As this study encompasses patients from the ICU, estimation of DDD per 100 bed days has been used. DDD/100 bed days is estimated as (Utilization in DDDs/Number of occupied bed days) x 100. In this, a bed day is defined as the day during which the patient stays overnight in the hospital (77).

The major four types of pharmacoeconomic analysis include

1. Cost minimization analysis,
2. Cost effectiveness analysis,
3. Cost benefit analysis and
4. Cost utility analysis.

1. Cost minimization analysis:

It compares and determines the more advantageous strategy based on cost in interventions with similar outcomes. It shows the cost saving of one intervention over the other (78).

2. Cost effectiveness analysis:

It compares the interventions in monetary terms per physical unit of improvement in clinical outcome. It helps to make individual patient treatment decisions (78).

$$\text{Cost effectiveness ratio} = \frac{\text{Net cost of intervention}}{\text{Net change in health effect}}$$

3. Cost benefit analysis:

It translates the outcome of interest into monetary terms, and thereby it helps in deciding the resource allocation (78).

$$\text{Cost benefit} = (\text{Net benefit}) - (\text{Net cost})$$

4. Cost utility analysis:

It compares the interventions in monetary terms, adjusted for quality. Its main aim is to improve the quality of life (78).

$$\text{CUA} = \frac{\text{Cost}}{\text{Quality-Adjusted Life Years}}$$

According to WHO's world health statistics 2012, approximately 30% of the population in rural India did not go for any treatment because of financial constraints. Increasing the public health care funding would not necessarily help the quality of healthcare delivery until there are strict pharmacoeconomic guidelines (79).

Studies on pharmacoeconomics of sedation of mechanically ventilated patients in the ICU:

A cost-effectiveness study was conducted by *Hohl et al* (2008) in Canada to analyze the incremental cost-effectiveness of propofol or midazolam in adults for procedural sedation in an emergency. The ICER (Incremental cost effectiveness ratio) of propofol was -$597.03 showing a saving of $597.03 per additional sedation performed. They concluded that the use of propofol is cost-saving compared to midazolam in the emergency department for procedural sedation (80).

A double-blinded, randomized, multi-centric cost minimization analysis was conducted by *Dasta et al* (2010) in 8 centers to compare the ICU costs and assess the factors influencing the cost in mechanically ventilated patients receiving dexmedetomidine or midazolam through continuous infusion. They concluded that significantly lesser ICU cost was seen with continuous dexmedetomidine sedation when compared with midazolam based on the ICU stay cost and decreased ventilator cost (81).

A cost-effectiveness study was conducted by *Bioc et al* (2014) in Boston to assess the cost-effectiveness between benzodiazepine-based and non-benzodiazepine-based sedation in critically-ill mechanically ventilated patients. The use of propofol or dexmedetomidine was cost-effective compared to benzodiazepines with a favorable cost-effectiveness ratio. They concluded that the use of non-benzodiazepine sedatives, in spite of their greater drug acquisition cost, will be helpful to give efficient care (82).

A cost-minimization analysis study was conducted by *Aggarwal et al* (2020) in the United States to determine the length of stay and cost in mechanically ventilated patients receiving sedatives. Dexmedetomidine was associated with a saving of $5958 compared with propofol and $6487 per patient compared with midazolam. They concluded that on comparison of dexmedetomidine with other sedatives for short-term sedation in patients on mechanical ventilation, the reduced cost was found with dexmedetomidine (83).

This study was undertaken because the information is scarce regarding the commonly used sedatives in India compared to their cost and utilization pattern in adults in the ICU.

AIM AND OBJECTIVES

AIM:

To analyze the prescription pattern and pharmacoeconomics of sedatives used in patients on mechanical ventilation in adult ICU.

OBJECTIVES:

A. Primary objective

To analyze the prescription pattern of sedatives used in patients on mechanical ventilation in adult ICU.

B. Secondary objectives

1. To analyze the cost of sedatives used in patients on mechanical ventilation in adult ICU.
2. To analyze the incidence of excessive and insufficient sedation.

MATERIALS AND METHODS

1. Study setting

This study was conducted in the Department of Pharmacology in collaboration with the Department of Anaesthesia and Critical care at the All India Institute of Medical Sciences, Jodhpur.

2. Study Design

Exploratory prospective observational study.

3. Study Participants

Mechanically ventilated adult patients of either sex who were started on sedatives as per eligibility criteria from adult ICU were enrolled for this study.

Inclusion criteria:

1. Age > 18 years.
2. Patients who were on mechanical ventilator atleast for 24 hours.

Exclusion criteria:

1. Post cardiac surgery patients.
2. Comatose patients (GCS score ≤ 8).
3. Patients with End-Stage Renal Disease (GFR <15mL/min/1.73m^2).
4. Patients with decompensated heart failure/liver dysfunction.

Sample size:

In accordance with the eligibility criteria, 131 mechanically ventilated patients who were admitted in adult ICU from 14th October 2020 (after ethical approval) to 30th September 2021 were enrolled in our study.

METHOD:

The study was started after getting approval from the Institutional Ethics Committee (IEC), AIIMS Jodhpur. Patients admitted to the adult ICU at AIIMS Jodhpur were screened. Mechanically ventilated patients who were started on sedatives and appropriate as per eligibility criteria were selected. After explaining the details of the study to the patient's attendant, informed written consent was obtained, and the patients were enrolled in our study.

Demographic and clinical details:

The basic demographic details of the study participants such as age, gender, locality, and occupation were recorded in the case record form. The reason for ICU admission and co-morbidities such as diabetes mellitus, hypertension, hypothyroidism, COPD, and seizures were also noted. Personal history comprising smoking, alcohol, and tobacco chewing was taken down. General physical examination, which includes anaemia, cyanosis, and jaundice at the time of admission was done. Baseline investigations such as complete blood count, blood sugar level, liver function test, renal function test, and arterial blood gas analysis of the patient after ICU admission were noted. Details of other medications given to the patient on the first day of ICU admission were noted. Vitals such as pulse rate, blood pressure, and SpO_2 at baseline, 2, 4, 8, and 24 hours were recorded. Data of utilization pattern of sedatives, including indication, class, dose, and duration during the initial 24 hours, were recorded. The level of sedation was assessed using RASS and SAS sedation scales at baseline, 2, 4, 8, and 24 hours. The cost of the sedative given for 24 hours was estimated. The duration of ICU stay and outcome of the patient after the initial 24 hours of mechanical ventilation were noted.

Defined daily dose (DDD):

WHO has defined the DDD as the assumed average maintenance dose per day for a drug used for its main indication in adults (84). The WHO DDD of fentanyl, dexmedetomidine, propofol, and midazolam were noted according to the ATC code. The median DDD of the patients receiving various sedatives was calculated. Using this, DDD/100 bed days was estimated. Then the ratio of DDD of the patient and WHO DDD was estimated.

$$\text{DDD/100 bed days} = \frac{\text{Utilization in DDDs}}{\text{Number of occupied bed days}} \times 100$$

Pharmacoeconomic analysis:

Pharmacoeconomic analysis was done by using Cost Minimization Analysis (CMA). CMA is used to measure and compare the costs of different interventions/therapies (85). It was done by comparing the cost of the sedatives given to patients on mechanical ventilation in the adult ICU for initial 24 hours. It was expressed as the average cost per patient per day in different sedative groups.

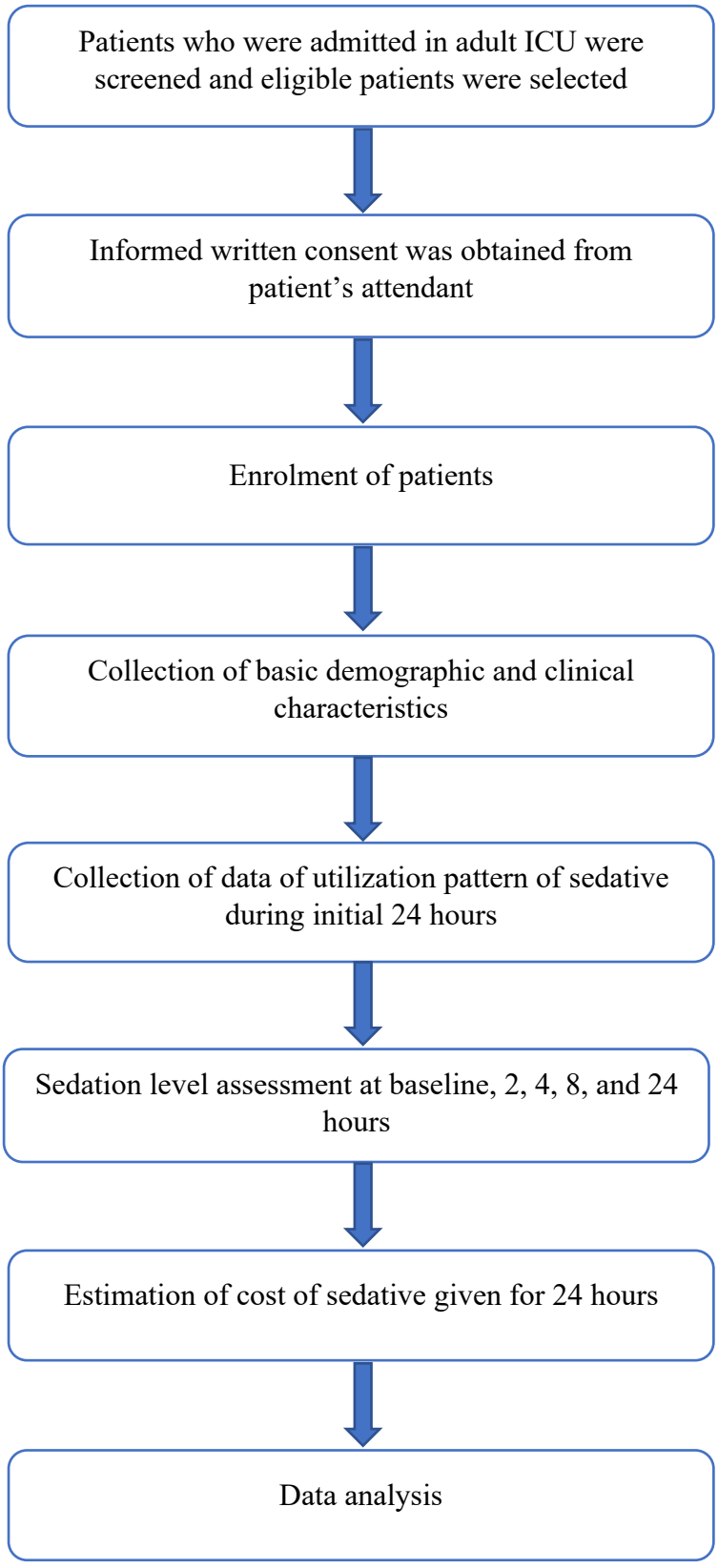
Sedation score assessment:

Sedative agents and sedation levels vary with the medical condition of the patient and their treatment needs (86). The depth of sedation was assessed at baseline, 2, 4, 8, and 24 hours using RASS and SAS. A sedation score of 0 and 4 in RASS and SAS were considered ideal for adequate sedation, respectively. The incidence of excessive and insufficient sedation was also assessed. A score above ideal (+1 to +4 in RASS and 5 to 7 in SAS) was considered insufficiently sedated, and a score below ideal (-1 to -5 in RASS and 1 to 3 in SAS) was considered as excessively sedated.

Statistical analysis:

Data were entered in Microsoft Excel and analyzed using SPSS version 21 (IBM SPSS statistics, Somers NY, USA). The distribution of data was analyzed using the Shapiro-Wilk test and was found to be normally distributed. Continuous variables were expressed as mean ± standard deviation, and categorical variables were expressed as number and percentage. DDD of patients receiving various sedatives and length of ICU stay was expressed in terms of the median (interquartile range). Comparison of change in vitals at baseline and 24 hours was done by paired t-test. Comparison of change in vitals between the sedative groups and between the groups based on age and reason for ICU admission was done by one-way ANOVA and unpaired t-test, respectively. Comparison of the sedation of level between the groups and within the group at various time points was done by Kaplan Meier analysis and Pearson Chi-square test, respectively. Comparison of cost between the groups was done by the linear regression model. A p-value of <0.05 was considered to be significant.

STUDY FLOW CHART:



RESULTS

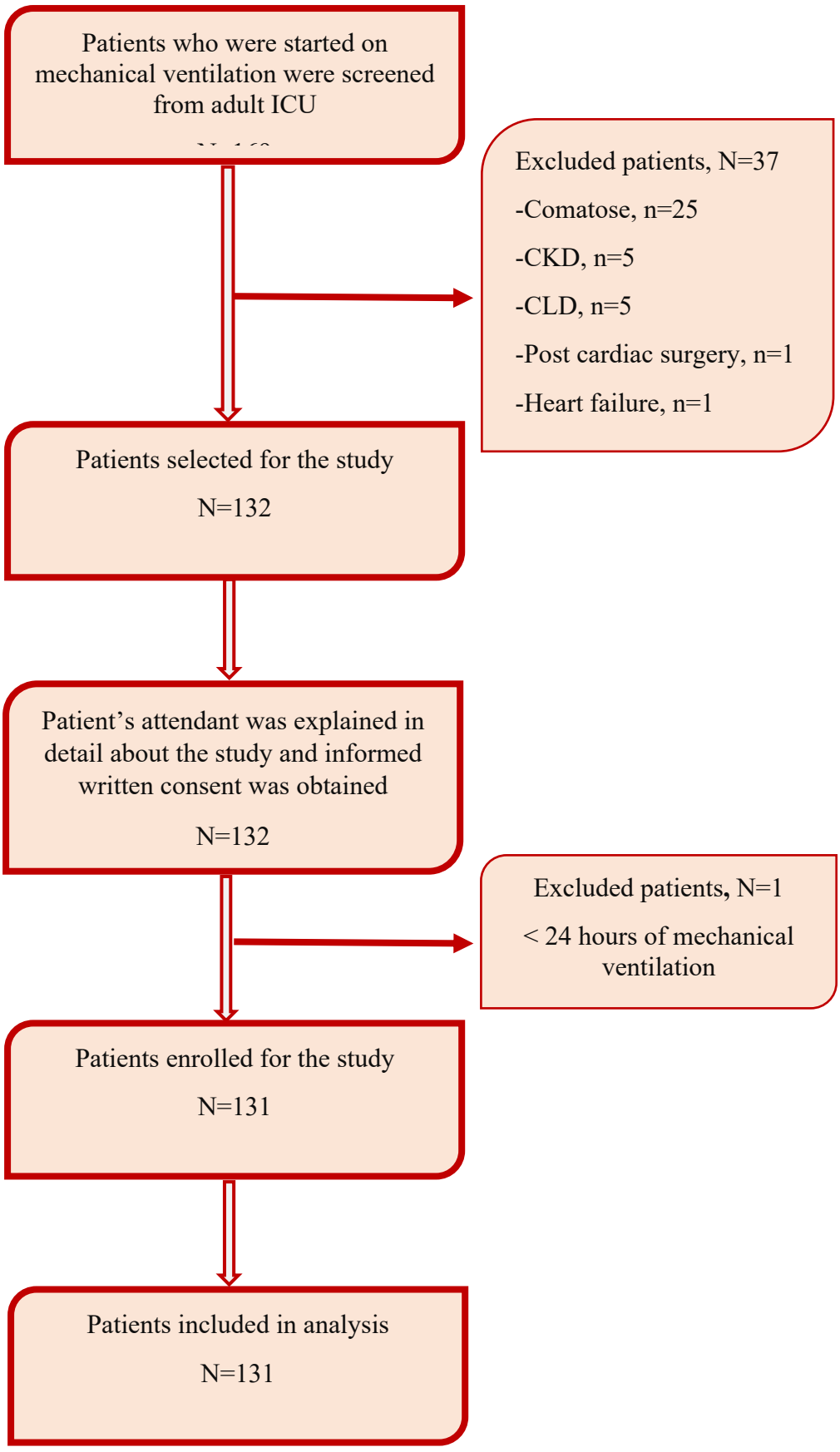


Figure 9: STROBE flow chart

In our study, among the 169 patients screened from adult ICU, a total of 131 patients were enrolled and included for analysis. The STOBE flow chart of our study is displayed in **Figure 9**. The total number of males in our study was 90 (68.7%), and females was 41 (31.3%). The proportion of gender distribution in the study participants is shown in **Figure 10**. The average age among the males was 52.7±16.9 and among the females was 52.6±16.8. Out of 131 patients, 49 (37.4%) were unemployed, 33 (25.2%) were skilled workers, 23 (17.6%) were semi-skilled workers, 12 (9.2%) were in arithmetic skill jobs, 6 (4.6%) were unskilled workers, 4 (3.1%) were semi-professional, and 4 (3.1%) were professional workers.

The reason for ICU admission among the study participants is displayed in **Figure 11**. These include patients who were admitted in ICU for post-surgical observation 40 (30.5%) which covers decompressive craniotomies, exploratory laparotomy, etc.; CNS complications 33 (25.2%) patients comprising of hemiplegia, subarachnoid hemorrhage, Guillain-Barre syndrome (GBS), etc.; respiratory complications 23 (17.6%) patients which adds pneumonia, ARDS, COPD, etc.; infectious disease 8 (6.1%) patients who comprise complicated malaria, sepsis, mucormycosis, etc.; abdominal complications 7 (5.3%) patients including pancreatitis, gastroenteritis, alcoholic liver disease, etc.; orthopedic complications 7 (5.3%) patients taking into consideration pelvic fracture, multiple fractures, etc.; cardiovascular complications 5 (3.8%) patients which covers aortic dissection, pericardial effusion, etc.; malignancy 4 (3.1%) patients who comprise Hodgkin's lymphoma, hepatocellular carcinoma, etc.; and organophosphorus poisoning 4 (3.1%) patients.

Amongst the total patients, 55 (41.9%) patients were found to have co-morbidities. In particular, 39 (29.8%) patients were hypertensive, 30 (20.9%) patients were diabetic, 4 (3.1%) of them had COPD, 3 (2.3%) patients had hypothyroidism, and 3 (2.3%) patients had epilepsy. Amidst, patients having a history of smoking, alcoholism, tobacco chewing, and opium addiction were 45 (34.4%), 41 (31.3%), 17 (13%), and 7 (5.3%), respectively. On general physical examination, 81 (61.8%) patients were found to have anaemia, and 9 (6.9%) patients were found to have jaundice. The basic demographic and clinical characteristics of the study participants are shown in **Table 2**.

Table 2: Basic demographic and clinical characteristics of the study participants

Variable		Number (%)	Mean±SD
Age	All		52.6±16.8
	Male		52.7±16.9
	Female		52.6±16.8
Gender	All	131 (100)	
	Male	90 (68.7)	
	Female	41 (31.3)	
***Occupation**	Professional	4 (3.1)	
	Semi-professional	4 (3.1)	
	Arithmetic skill job	12 (9.2)	
	Skilled worker	33 (25.2)	
	Semi-skilled worker	23 (17.6)	
	Unskilled worker	6 (4.6)	
	Unemployed	49 (37.4)	
Reason for ICU admission	Post-surgical	40 (30.5)	
	CNS complications	33 (25.2)	
	Respiratory complications	23 (17.6)	
	Infectious disease	8 (6.1)	
	Abdominal complications	7 (5.3)	
	Orthopedic complications	7 (5.3)	
	Cardiovascular complications	5 (3.8)	
	Malignancy	4 (3.1)	
	OP poisoning	4 (3.1)	
Comorbidities	Hypertension	39 (29.8)	
	Diabetes	30 (20.9)	
	COPD	4 (3.1)	
	Hypothyroidism	3 (2.3)	
	Epilepsy	3 (2.3)	
Personal history	Smoking	45 (34.4)	
	Alcohol	41 (31.3)	
	Tobacco chewing	17 (13)	
	Opium addict	7 (5.3)	
General examination	Anaemia	81 (61.8)	
	Jaundice	9 (6.9)	
	Cyanosis	0	

*According to Modified Kuppusamy Scale

CNS- Central Nervous System, COPD- Chronic Obstructive Pulmonary Disease, ICU- Intensive Care Unit, OP- Organophosphorus, SD- Standard Deviation

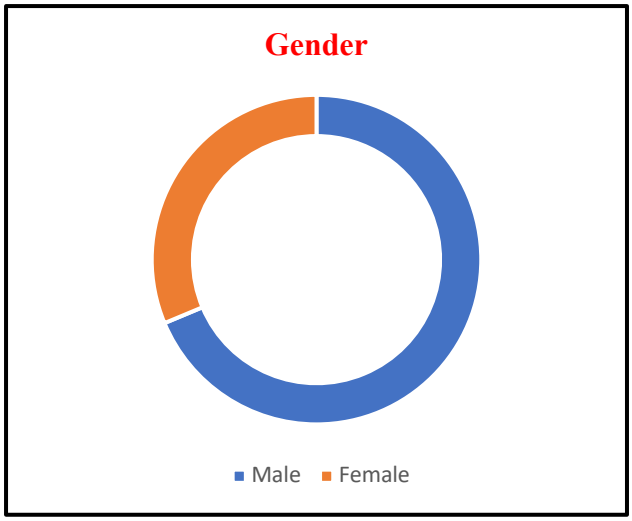


Figure 10: Proportion of gender distribution in the study participants

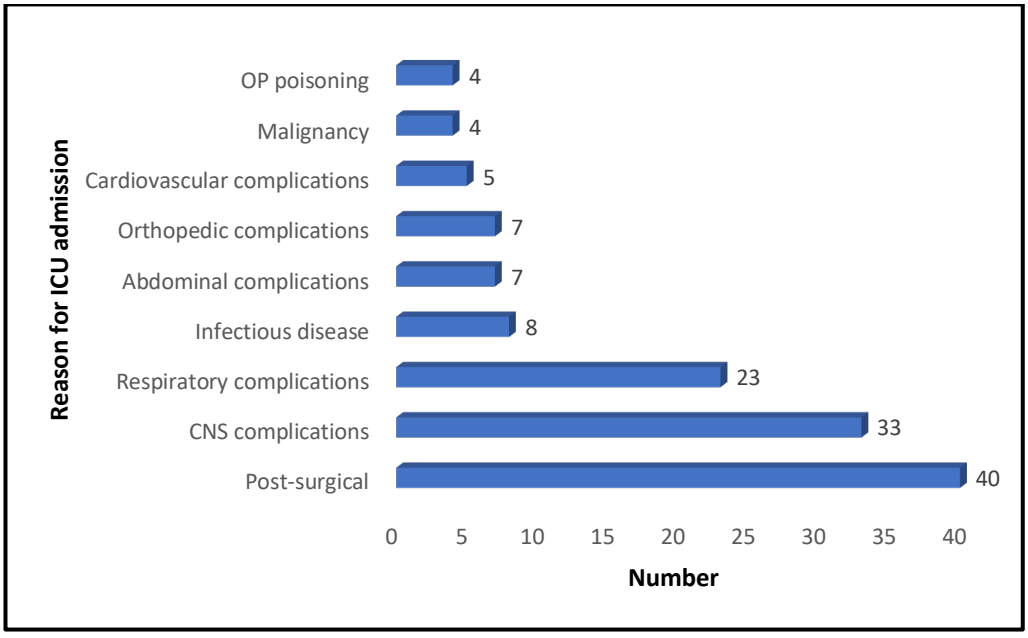


Figure 11: Reason for ICU admission among the study participants

Complete blood count showed hemoglobin 10.85±2.85 g/dl, hematocrit 33.78±9.28 %, white blood cells (WBC) count 24.05±68.42s cells/ml, and platelets 213.19±115.55 x 10^6/ml. The random blood sugar level was 145.12±52.7 mg/dl. Liver function test showed total bilirubin 1.09±1.29 mg/dl, direct bilirubin 0.92±6.20 mg/dl, Serum Glutamate-Pyruvate Transaminase (SGPT) 140.02±578.22 U/L, Serum Glutamate Oxaloacetate Transaminase (SGOT) 158.63±590.09 U/L, total protein 6.68±7.89 g/dl, serum albumin 3.17±0.95 g/dl, and serum globulin 2.79±0.65 g/dl. Renal function test showed urea 50.76±48.99 mg/dl and creatinine 1.91±6.55 mg/dl. Arterial blood gas test showed pH 7.35±0.11, pO2 124.08±87.2, pCO2 44.5±28.86, sodium 141.59±7.24 mmol/L, potassium 3.81±0.76 mmol/L, chloride 104.04±12.8 mmol/L, and calcium 1.71±8.12 mmol/L. The baseline investigations of the study participants have been tabulated in **Table 3**.

Table 3: Baseline investigations of the study participants

Baseline investigations	Mean ± SD
Hemoglobin (g/dl)	10.85±2.85
Hematocrit (%)	33.78±9.28
WBC count (cells/ml)	24.05±68.42
Platelets (10^6/ml)	213.19±115.55
Random blood sugar level (mg/dl)	145.12±52.7
Total bilirubin (mg/dl)	1.09±1.29
Direct bilirubin (mg/dl)	0.92±6.20
SGPT (U/L)	140.02±578.22
SGOT (U/L)	158.63±590.09
Total protein (g/dl)	6.68±7.89
Serum albumin (g/dl)	3.17±0.95
Serum globulin (g/dl)	2.79±0.65
Urea(mg/dl)	50.76±48.99
Creatinine (mg/dl)	1.91±6.55
pH	7.35±0.11

pO2	124.08±87.2
pCO2	44.5±28.86
Sodium (mmol/L)	141.59±7.24
Potassium (mmol/L)	3.81±0.76
Chloride (mmol/L)	104.04±12.8
Calcium (mmol/L)	1.71±8.12

pCO2- partial pressure of carbon dioxide, pH- potential of hydrogen, pO2- partial pressure of oxygen, SGOT- Serum glutamic oxaloacetic transaminase, SGPT- Serum glutamic pyruvic transaminase, WBC- White blood cells

Out of 131 patients, 92 (70.2%) patients were given a sedative as monotherapy (i.e., either fentanyl alone, dexmedetomidine alone, midazolam alone, or propofol alone), 37 (28.2%) patients were given dual therapy, and 2 (1.5%) patients were given triple therapy. The utilization pattern of different sedative drugs according to the type of therapy, i.e., monotherapy, dual therapy, and triple therapy, has been shown in **Figure 12**.

The number of patients receiving various sedatives among the study participants has been displayed in **Figure 13**. The most commonly used sedative was fentanyl 63.4% as monotherapy. Other drugs given as monotherapy were dexmedetomidine 3.8%, propofol 1.5%, and midazolam 1.5%. In combination therapy, commonly prescribed dual therapy was the combination of fentanyl and dexmedetomidine 17.6%, followed by the combination of fentanyl and midazolam 4.6%. Other dual therapies given include the combination of fentanyl and propofol 3.1%, the combination of dexmedetomidine and propofol 1.5%, the combination of midazolam and dexmedetomidine 0.75%, the combination of midazolam and propofol 0.75%. A combination of fentanyl, dexmedetomidine and midazolam 0.75%, and a combination of fentanyl, propofol and dexmedetomidine 0.75% were given as triple therapy. The pattern of sedative therapy of the study participants receiving various sedatives has been shown in **Table 4.**

Table 4: Pattern of sedative therapy of the study participants receiving various sedatives

Pattern of sedative therapy	Number (%)	Sedative group	Number (%)
Monotherapy	92 (70.2)	Fentanyl	83 (63.4)
		Dexmedetomidine	5 (3.8)
		Propofol	2 (1.5)
		Midazolam	2 (1.5)
Dual therapy	37 (28.3)	Fentanyl and Dexmedetomidine	23 (17.6)
		Fentanyl and Midazolam	6 (4.6)
		Fentanyl and Propofol	4 (3.1)
		Dexmedetomidine and Propofol	2 (1.5)
		Dexmedetomidine and Midazolam	1 (0.75)
		Midazolam and Propofol	1 (0.75)
Triple therapy	2 (1.5)	Fentanyl, Dexmedetomidine and Midazolam	1 (0.75)
		Fentanyl, Dexmedetomidine and Propofol	1 (0.75)

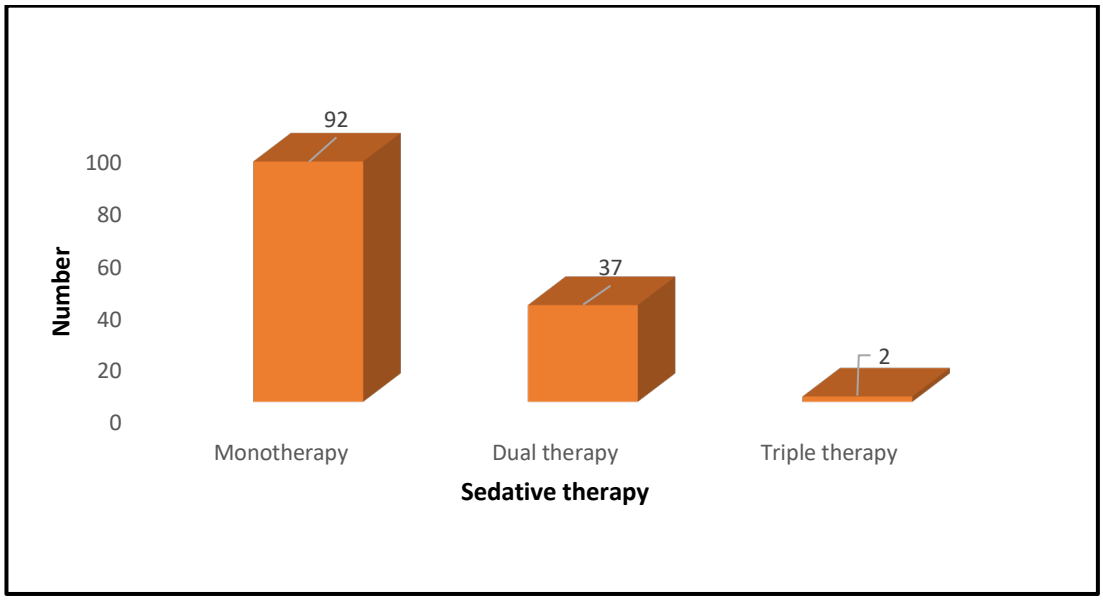


Figure 12: Pattern of sedative therapy among the study participants

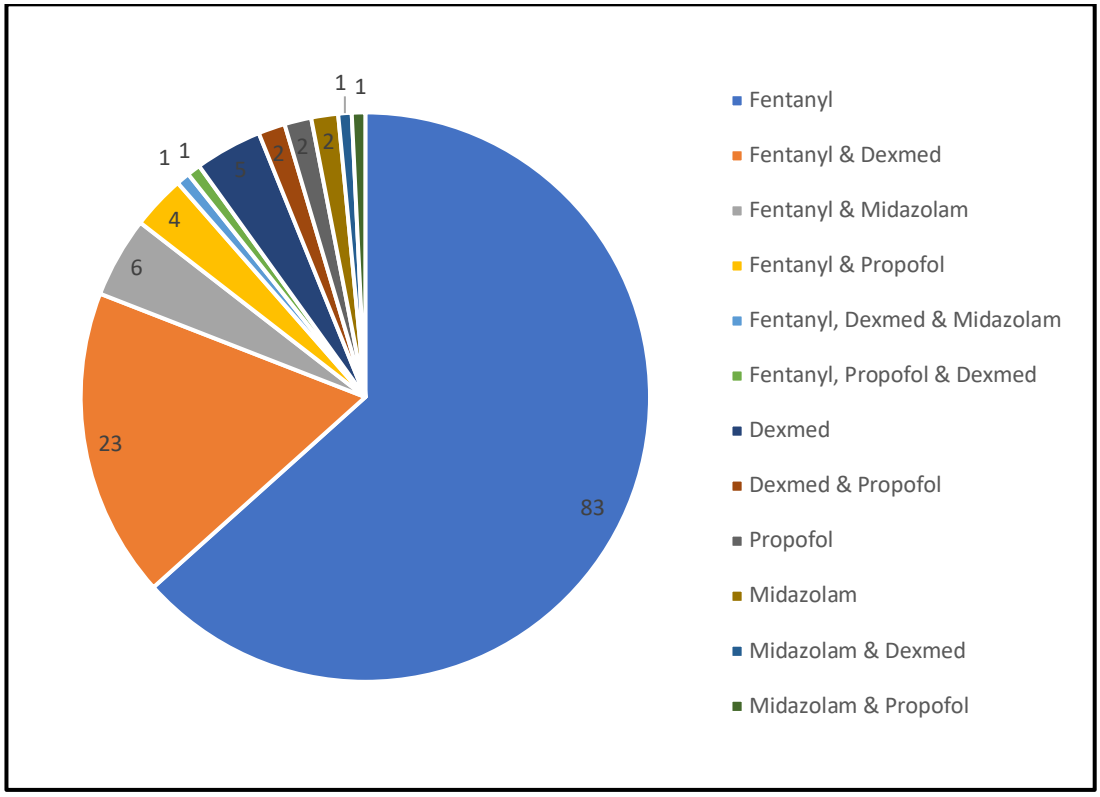


Figure 13: Number of patients receiving various sedatives among the study participants

The commonly given sedative group among the study participants ≤60 years of age is fentanyl alone 48 (60%), followed by combination of fentanyl and dexmedetomidine 16 (20%). Similarly, the commonly given sedative group among the study participants >60 years of age is fentanyl alone 35 (68.63%), followed by the combination of fentanyl and dexmedetomidine 7 (13.73%). The pattern of sedative therapy based on the age of the study participants has been shown in **Table 5**.

Table 5: Pattern of sedative therapy based on the age of the study participants

Age (number)	Sedative group	Number (%)
≤60 years (80)	Fentanyl	48 (60)
	Fentanyl and Dexmedetomidine	16 (20)
	Fentanyl and Midazolam	5 (6.25)
	Fentanyl and Propofol	3 (3.75)
	Dexmedetomidine	2 (2.5)
	Dexmedetomidine and Propofol	2 (2.5)
	Fentanyl, Dexmedetomidine and Propofol	1 (1.25)
	Midazolam	1 (1.25)
	Dexmedetomidine and Midazolam	1 (1.25)
	Midazolam and Propofol	1 (1.25)
>60 years (51)	Fentanyl	35 (68.63)
	Fentanyl and Dexmedetomidine	7 (13.73)
	Dexmedetomidine	3 (5.88)
	Propofol	2 (3.92)
	Fentanyl and Midazolam	1 (1.96)
	Fentanyl and Propofol	1 (1.96)
	Midazolam	1 (1.96)
	Fentanyl, Dexmedetomidine and Midazolam	1 (1.96)

The pattern of sedative therapy based on the reason for ICU admission among the study participants has been tabulated in **Table 6**. It is found that among all the patients, fentanyl alone is the most commonly used sedative group, followed by the combination of fentanyl and dexmedetomidine.

Table 6: Pattern of sedative therapy based on the reason for ICU admission among the study participants

Reason for ICU admission (Number)	Sedative group	Number (%)
Post-surgical (40)	Fentanyl	30 (75)
	Fentanyl and Dexmedetomidine	4 (10)
	Fentanyl and Midazolam	1 (2.5)
	Fentanyl and Propofol	1 (2.5)
	Dexmedetomidine	1 (2.5)
	Dexmedetomidine and Propofol	1 (2.5)
	Propofol	1 (2.5)
	Fentanyl, Dexmedetomidine and Midazolam	1 (2.5)
CNS complications (33)	Fentanyl	21 (63.6)
	Fentanyl and Dexmedetomidine	5 (15.2)
	Fentanyl and Midazolam	2 (6.1)
	Dexmedetomidine	2 (6.1)
	Fentanyl and Propofol	1 (3)
	Midazolam	1 (3)
	Midazolam and Propofol	1 (3)
Respiratory complications (23)	Fentanyl	13 (56.5)
	Fentanyl and Dexmedetomidine	4 (17.5)
	Fentanyl and Midazolam	2 (8.7)
	Dexmedetomidine	2 (8.7)
	Midazolam	1 (4.3)
	Fentanyl, Dexmedetomidine and Propofol	1 (4.3)

Infectious disease (8)	Fentanyl	4 (50)
	Fentanyl and Dexmedetomidine	3 (37.5)
	Fentanyl and Propofol	1 (12.5)
Abdominal complications (7)	Fentanyl	3 (42.9)
	Fentanyl and Dexmedetomidine	3 (42.9)
	Propofol	1 (14.2)
Orthopedic complications (7)	Fentanyl	3 (42.9)
	Fentanyl and Dexmedetomidine	3 (42.9)
	Fentanyl and Midazolam	1 (14.2)
Cardiovascular complications (5)	Fentanyl	4 (80)
	Fentanyl and Dexmedetomidine	1 (20)
Malignancy (4)	Fentanyl	4 (100)
OP poisoning (4)	Fentanyl	1 (25)
	Fentanyl and propofol	1 (25)
	Dexmedetomidine and Propofol	1 (25)
	Dexmedetomidine and Midazolam	1 (25)

CNS- Central Nervous System, OP- Organophosphorus

Comparison of heart rate (HR), SpO2, systolic blood pressure (SBP), and diastolic blood pressure (DBP) at baseline and 24 hours of sedation in the study participants receiving various sedatives have been displayed in **Table 7 and Table 8**. The difference of mean HR at baseline and 24 hours was statistically significant in the combination of fentanyl and dexmedetomidine and the combination of fentanyl and propofol groups (p=0.045 and p=0.029, respectively). Whereas the difference was not significant in other groups. There was no significant difference in SpO2 levels in any of the sedative groups at baseline and 24 hours.

The difference of mean SBP at baseline and 24 hours was statistically significant in the combination of fentanyl and dexmedetomidine group (p=0.019). But the difference of mean DBP at baseline and 24 hours was statistically significant in fentanyl alone and the combination of fentanyl and midazolam groups (p=0.000 and p=0.046, respectively). Whereas the difference was not significant in other groups. The change in vitals was not statistically significant between the commonly given sedative groups.

Table 7: Comparison of HR and SpO2 at baseline and 24 hours of sedation in the study participants receiving various sedatives

Vitals / Sedatives	HR (/min)			SpO2 (%)		
	Baseline	**24 hours**	**p-value**	**Baseline**	**24 hours**	**p-value**
Fentanyl	99.76 ± 28.04	94.95 ± 25.26	0.057	97.67 ± 4.13	98.12 ± 1.93	0.343
Fentanyl and Dexmedetomidine	110.48 ± 22.06	100.30 ± 20.89	0.045*	96.17 ± 4.94	97.35 ± 2.82	0.311
Fentanyl and Midazolam	110.17 ± 22.52	102.17 ± 37.34	0.369	96.17 ± 2.22	97.17 ± 2.63	0.363
Fentanyl and Propofol	107.50 ± 9.25	95.25 ± 13.35	0.029*	99.25 ± 0.95	98.75 ± 1.25	0.495
Dexmedetomidine	110.40 ± 21.55	86.40 ± 10.99	0.102	95.00 ± 2.44	97.40 ± 2.96	0.186

*p < 0.05

Table 8: Comparison of SBP and DBP at baseline and 24 hours of sedation in the study participants receiving various sedatives

Vitals / Sedatives	SBP (mm/Hg)			DBP (mm/Hg)		
	Baseline	**24 hours**	**p-value**	**Baseline**	**24 hours**	**p-value**
Fentanyl	122.93 ± 25.69	117.39 ± 24.13	0.092	69.92 ± 13.69	63.39 ± 11.78	0.000*
Fentanyl and Dexmedetomidine	114.91 ± 26.60	132.13 ± 25.96	0.019*	69.30 ± 18.81	67.00 ± 16.03	0.576
Fentanyl and Midazolam	119.33 ± 15.42	131.50 ± 25.52	0.237	74.00 ± 7.23	65.33 ± 10.76	0.046*
Fentanyl and Propofol	137.50 ± 37.93	117.00 ± 18.70	0.497	77.25 ± 20.99	59.50 ± 8.66	0.088
Dexmedetomidine	131.40 ± 16.34	120.40 ± 18.63	0.214	66.20 ± 6.30	68.20 ± 9.01	0.587

*p < 0.05

Comparison of vitals in ≤60 years and >60 years of age groups on fentanyl alone and combination of fentanyl and dexmedetomidine at baseline and at 24 hours has been displayed in **Table 9**. There was no significant difference in vitals among ≤60 years of age patients between the groups. Among >60 years of age patients, SBP at 24 hours in the combination of fentanyl and dexmedetomidine group was significantly high as compared to fentanyl alone group, whereas SpO_2 in the combination of fentanyl and dexmedetomidine group was significantly less as compared to fentanyl alone group.

In the fentanyl alone group among ≤60 years of age patients, HR and DBP were significantly decreased at 24 hours as compared to baseline. However, only a significant reduction of DBP was seen among >60 years of age patients at 24 hours as compared to baseline. In combination of fentanyl and dexmedetomidine group among ≤60 years of age patients, HR was significantly decreased, whereas SBP was significantly increased at 24 hours as compared to baseline. However, there was no significant change in vitals seen in the combination of fentanyl and dexmedetomidine group among >60 years of age patients at 24 hours as compared to baseline.

In the fentanyl alone group, HR at baseline among >60 years of age patients was significantly less when compared to ≤60 years of age patients. Whereas in the combination of fentanyl and dexmedetomidine group, SpO_2 at 24 hours among >60 years of age patients was significantly less when compared to ≤60 years of age patients.

Table 9: Comparison of vitals in ≤60 years and >60 years of age groups on fentanyl alone and combination of fentanyl and dexmedetomidine at baseline and 24 hours

		≤60 years		>60 years	
		Fentanyl	**Fentanyl and Dexmedetomidine**	**Fentanyl**	**Fentanyl and Dexmedetomidine**
HR	**0 hr**	104.92 ± 27.651	113.75 ± 22.305	92.69 ± 27.391[#]	103.00 ± 21.134
	24 hr	97.50 ± 25.579[$]	99.94 ± 19.948[$]	91.46 ± 24.759	101.14 ± 24.606
SBP	**0 hr**	121.77 ± 24.525	110.63 ± 26.399	124.51 ± 27.493	124.71 ± 26.291
	24 hr	118.88 ± 18.686	129.94 ± 28.841[$]	115.34 ± 30.244	137.14 ± 18.721*
DBP	**0 hr**	70.31 ± 14.781	69.31 ± 20.244	69.37 ± 12.248	69.29 ± 16.530
	24 hr	63.83 ± 10.612[$]	66.38 ± 17.158	62.77 ± 13.364[$]	68.43 ± 14.270
SpO_2	**0 hr**	97.54 ± 4.197	96.88 ± 4.395	97.86 ± 4.095	94.57 ± 6.079
	24 hr	98.40 ± 1.783	98.31 ± 2.089	97.74 ± 2.091	95.14 ± 3.185*[#]

*$p<0.05$, comparison between fentanyl alone and combination of fentanyl and dexmedetomidine groups

[$]$p<0.05$, comparison between baseline and 24 hours

[#]$p<0.05$, comparison between ≤60 years and >60 years of age

Based on the reason for ICU admission, we have broadly classified the patients into post-surgical and non-surgical groups. Comparison of vitals in post-surgical and non-surgical groups on fentanyl alone and combination of fentanyl and dexmedetomidine at baseline and 24 hours has been shown in **Table 10**. Among post-surgical patients, in the combination of fentanyl and dexmedetomidine group, SpO2 at baseline was significantly higher when compared to fentanyl alone. Whereas among non-surgical patients, there was no significant difference between these groups.

In the fentanyl alone group among post-surgical patients, SBP and DBP were significantly decreased at 24 hours as compared to baseline. However, only a significant reduction of DBP was seen among non-surgical patients at 24 hours as compared to baseline. In combination of fentanyl and dexmedetomidine group among post-surgical patients, no significant change in vitals was seen between baseline and 24 hours. However, SBP was significantly increased among non-surgical patients at 24 hours as compared to baseline.

In the fentanyl alone group, HR and SpO_2 at baseline among non-surgical patients were significantly less when compared to post-surgical patients. Whereas in the combination of fentanyl and dexmedetomidine group, DBP at 24 hours was significantly high, and SpO_2 at baseline was significantly less among non-surgical patients than post-surgical patients.

Table 10: Comparison of vitals in post-surgical and non-surgical groups on fentanyl alone and combination of fentanyl and dexmedetomidine at baseline and 24 hours

		Post-surgical		Non-surgical	
		Fentanyl	**Fentanyl and Dexmedetomidine**	**Fentanyl**	**Fentanyl and Dexmedetomidine**
HR	**0 hr**	107.97 ± 30.906	125.50 ± 18.806	95.11 ± 25.422[#]	107.32 ± 21.797
	24 hr	101.57 ± 26.320	107.00 ± 21.071	91.21 ± 24.095	98.89 ± 21.160
SBP	**0 hr**	125.53 ± 29.230	130.00 ± 29.956	121.45 ± 23.625	111.74 ± 25.575
	24 hr	113.07 ± 18.430[$]	123.00 ± 19.339	119.83 ± 26.688	134.05 ± 27.190[$]
DBP	**0 hr**	69.80 ± 14.691	64.75 ± 22.336	69.98 ± 13.248	70.26 ± 18.544
	24 hr	60.17 ± 9.560[$]	53.25 ± 6.702	65.21 ± 12.596[$]	69.89 ± 16.000[#]
SpO_2	**0 hr**	98.90 ± 1.863	100.00 ± 0.000*	96.98 ± 4.862[#]	95.37 ± 5.090[#]
	24 hr	98.40 ± 1.850	97.00 ± 3.830	97.96 ± 1.980	97.42 ± 2.694

*$p<0.05$, comparison between fentanyl alone and combination of fentanyl and dexmedetomidine groups

[$]$p<0.05$, comparison between baseline and 24 hours

[#]$p<0.05$, comparison between post-surgical and non-surgical patients

Utilization of the various sedative agents based on their median DDD prescribed, DDD/100 bed days, and their ratio has been presented in **Table 11**. It showed that the DDD of fentanyl given in the study participants (5.05mg (3.46)) was higher compared to its WHO DDD, followed by dexmedetomidine (3.3mg (7.7)) and midazolam (45.5mg (143.25)). On the other hand, the DDD of propofol given in the study participants (1.23g (0.82)) was lower when compared to its WHO DDD.

Table 11: Defined daily dose of the patients receiving various sedatives

Drug name	ATC code	WHO DDD	DDD of patient Median (IQR)	DDD/100 bed days	Ratio
Fentanyl*	N02AB03	1.2mg	5.05mg (3.46)	505mg	4.2
Dexmedetomidine	N05CM18	1mg	3.3mg (7.7)	330mg	3.3
Propofol	N01AX10	14g	1.23g (0.82)	123g	0.08
Midazolam	N05CD08	15mg	45.5mg (143.25)	4550mg	3.03

ATC- Anatomical Therapeutic Chemical, DDD- Defined Daily Dose

*DDD has not been established for intravenous fentanyl as the doses vary substantially. Therefore, we have taken the transdermal DDD value.

The cumulative proportion of the study participants experiencing various levels of sedation as per the sedation scale over 24 hours of sedation in terms of adequate, insufficient, and excessive sedation among the commonly given sedative groups has been displayed in **Table 12 and Figure 14**. The proportion of patients who were adequately sedated were 74.8%, 43.5%, 54%, 43.75%, and 75% in fentanyl alone, the combination of fentanyl and dexmedetomidine, the combination of fentanyl and midazolam, the combination of fentanyl and propofol, and dexmedetomidine alone groups respectively.

The proportion of patients who were insufficiently sedated were 19.5%, 56.5%, 37.5%, 56.25%, and 20% in fentanyl alone, the combination of fentanyl and dexmedetomidine, the combination of fentanyl and midazolam, the combination of fentanyl and propofol, and dexmedetomidine alone groups respectively. Whereas the proportion of patients who were excessively sedated were 5.7%, 8.5%, and 5% in fentanyl alone, the combination of fentanyl and midazolam, and dexmedetomidine alone groups, respectively. Excessive sedation was not found in the combination of fentanyl and dexmedetomidine and the combination of fentanyl and propofol groups.

Table 12: Cumulative proportion of the study participants experiencing various levels of sedation as per sedation scale over 24 hours of sedation with various sedatives

Sedative / Sedation level (%)	Fentanyl	Fentanyl and Dexmedetomidine	Fentanyl and Midazolam	Fentanyl and Propofol	Dexmedetomidine
Adequate	74.8	43.5	54	43.75	75
Insufficient	19.5	56.5	37.5	56.25	20
Excessive	5.7	0	8.5	0	5

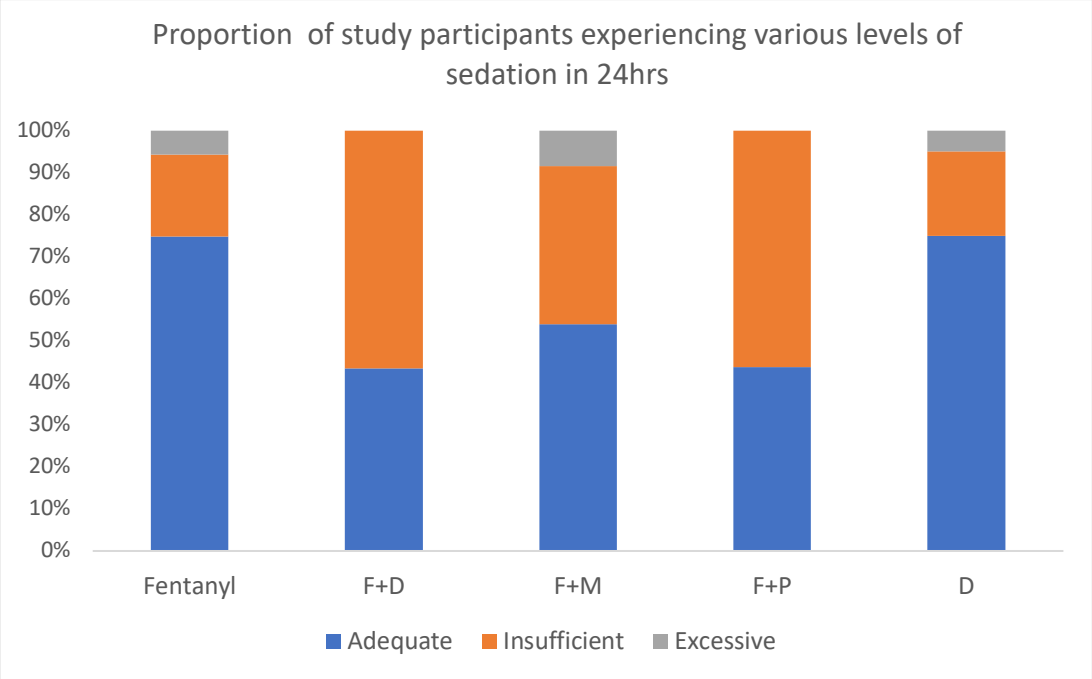


Figure 14: Cumulative proportion of the study participants experiencing various levels of sedation as per sedation scale over 24 hours of sedation with various sedatives

Comparison of sedation level using RASS and SAS scale over 24 hours between the commonly given sedative groups applying Kaplan Meier plot has been displayed in **Figure 15 and Figure 16**. There was no significant difference between these groups (p value=0.163). Hence, all the treatment groups had a similar level of sedation.

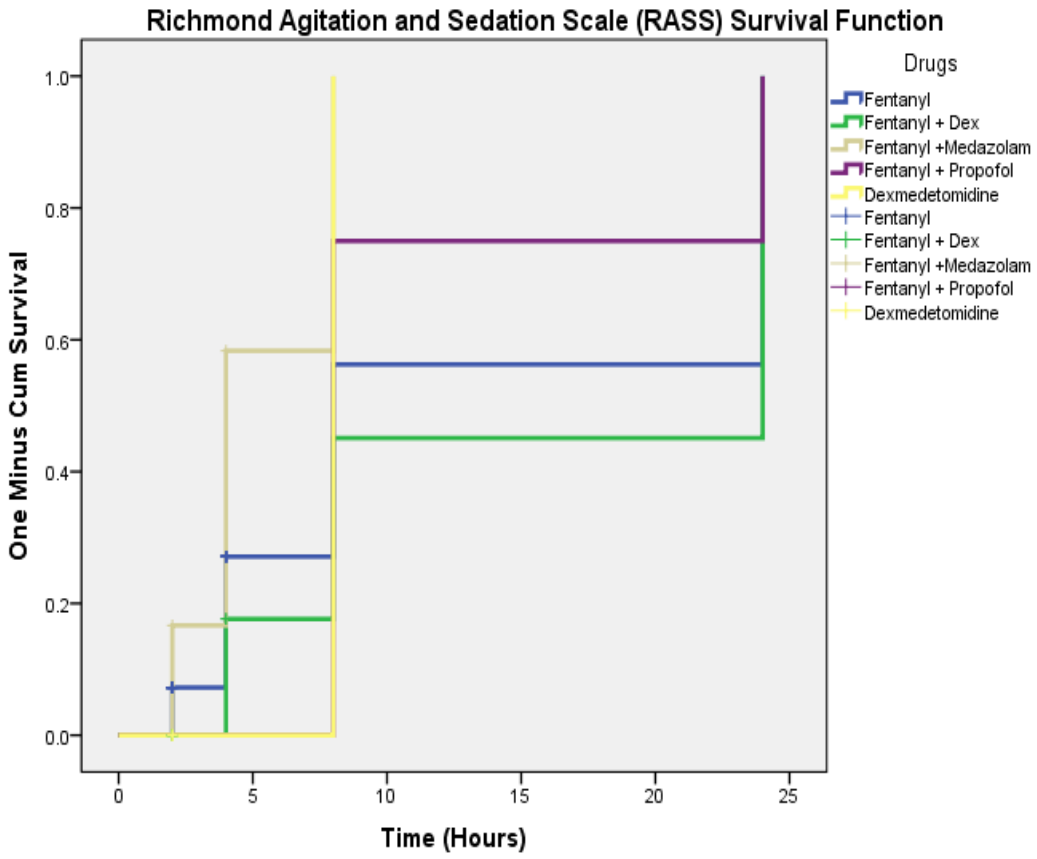


Figure 15: Comparison of sedation level using RASS scale over 24 hours between the commonly given sedative groups applying Kaplan Meier plot

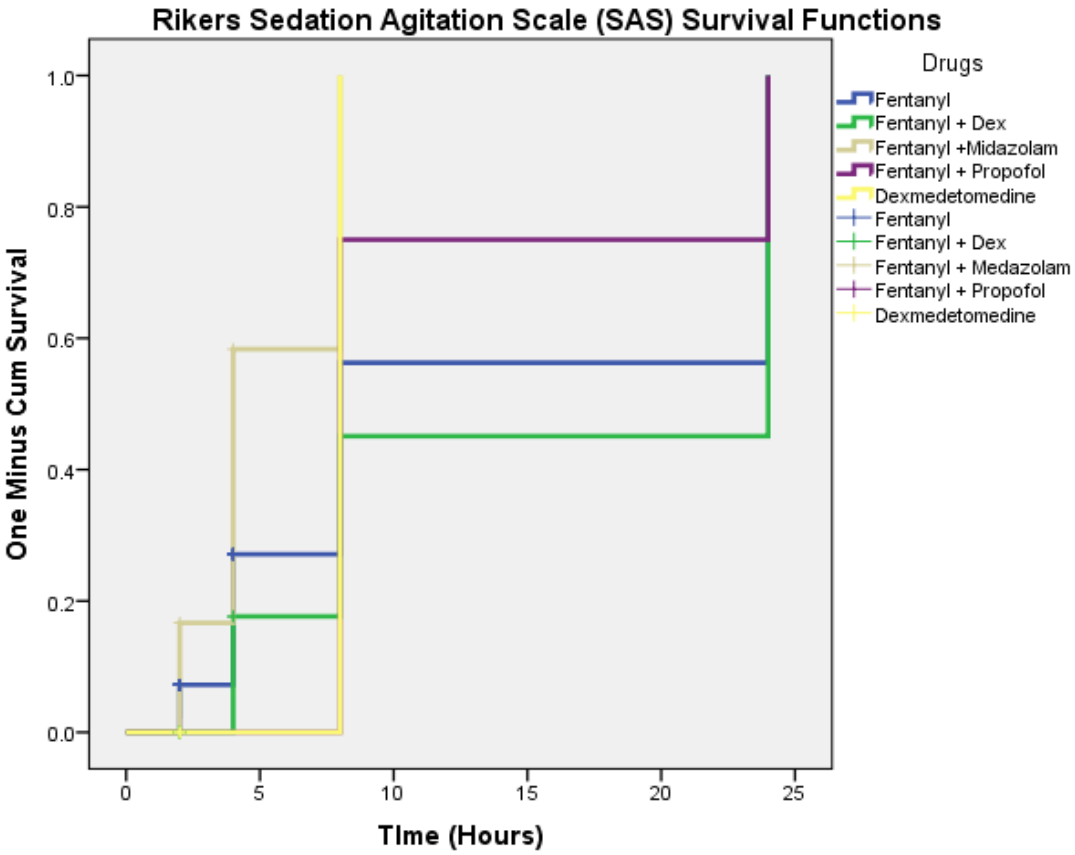


Figure 16: Comparison of sedation level using SAS scale over 24 hours between the commonly given sedative groups applying Kaplan Meier plot

Comparison of sedation level using RASS and SAS scale over 24 hours between ≤60 years and >60 years of age groups receiving fentanyl alone and combination of fentanyl and dexmedetomidine as sedative applying Kaplan Meier plot has been displayed in **Figure 17 and Figure 18**. There was no significant difference between the groups (p value=0.454). Hence, both the treatment groups had a similar level of sedation in ≤60 years and >60 years of age groups.

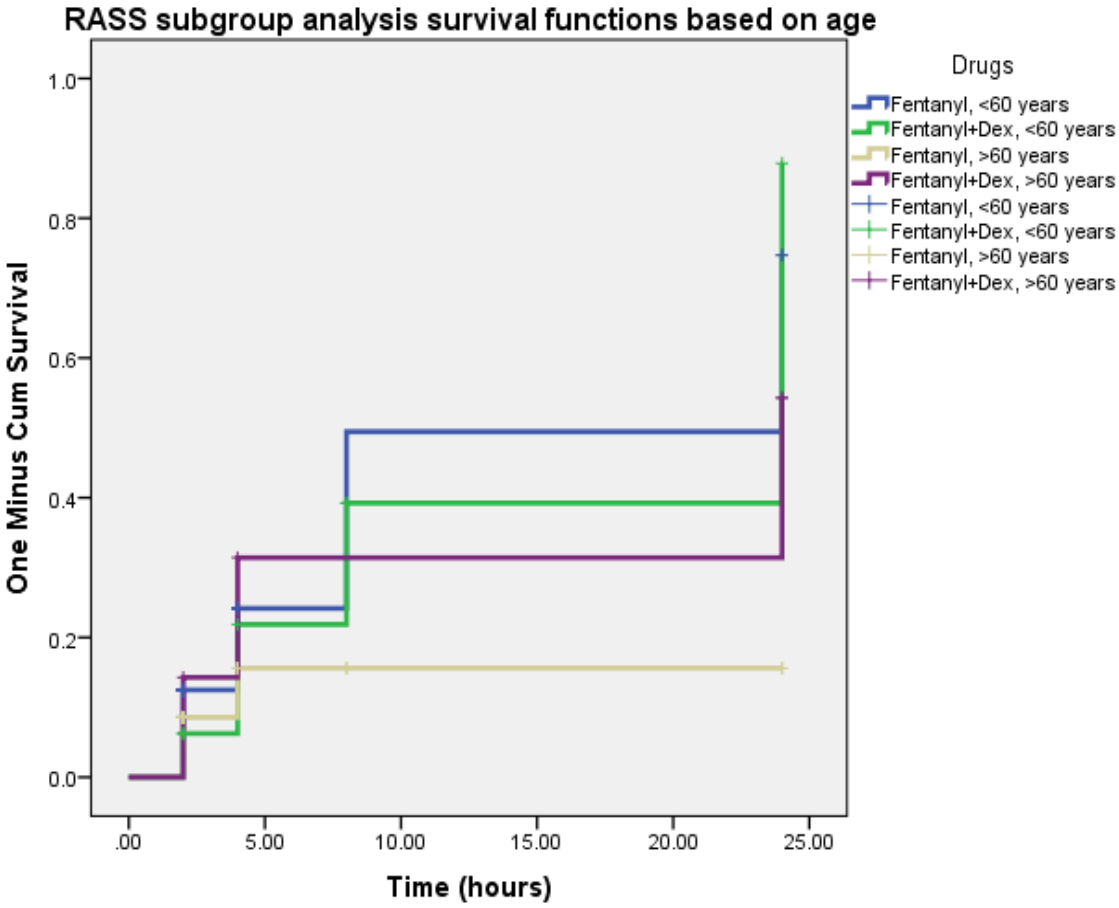


Figure 17: Comparison of sedation level using RASS scale over 24 hours between ≤60 years and >60 years of age groups on fentanyl alone and combination of fentanyl and dexmedetomidine as sedative applying Kaplan Meier plot

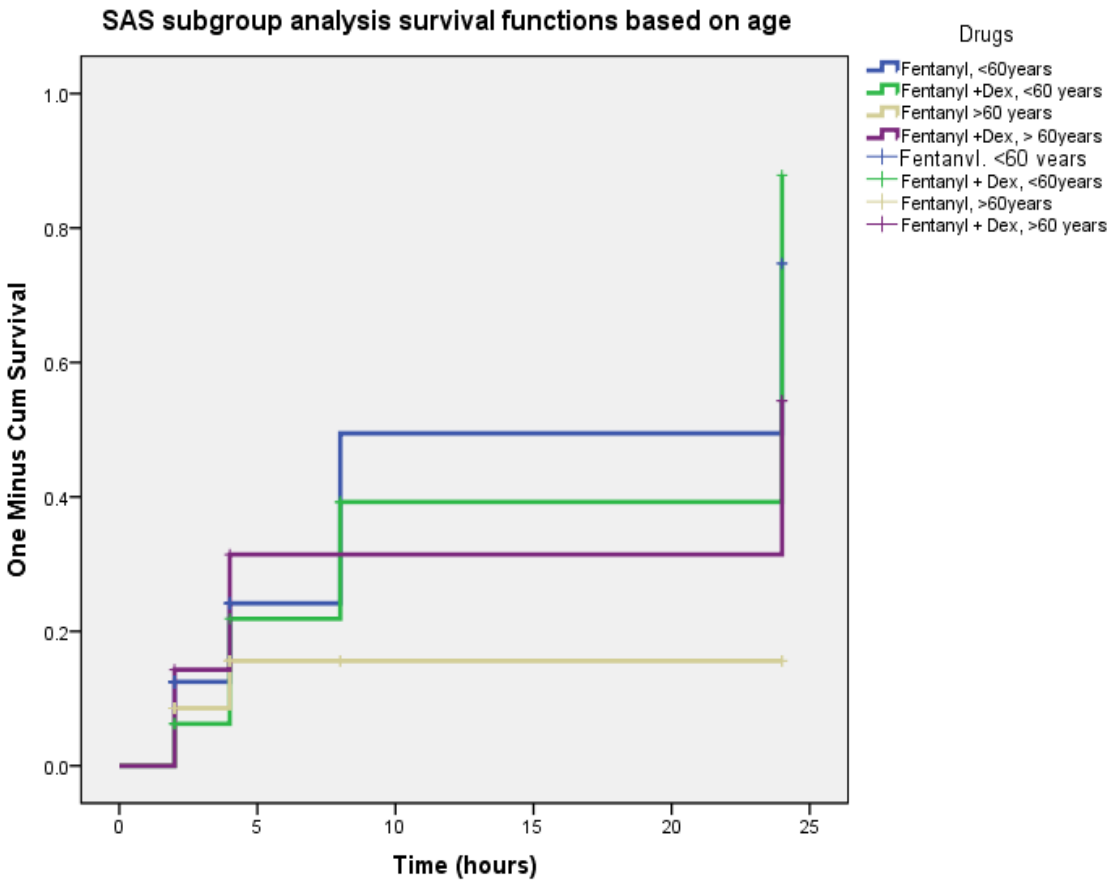


Figure 18: Comparison of sedation level using SAS scale over 24 hours between ≤60 years and >60 years of age groups on fentanyl alone and combination of fentanyl and dexmedetomidine as sedative applying Kaplan Meier plot

Comparison of sedation level using RASS and SAS scale over 24 hours between post-surgical and non-surgical groups on fentanyl alone and combination of fentanyl and dexmedetomidine as sedative applying Kaplan Meier plot has been displayed on **Figure 19 and Figure 20**. There was no significant difference between the groups (p value=0.806). Hence, both the treatment groups had a similar level of sedation in post-surgical and non-surgical groups.

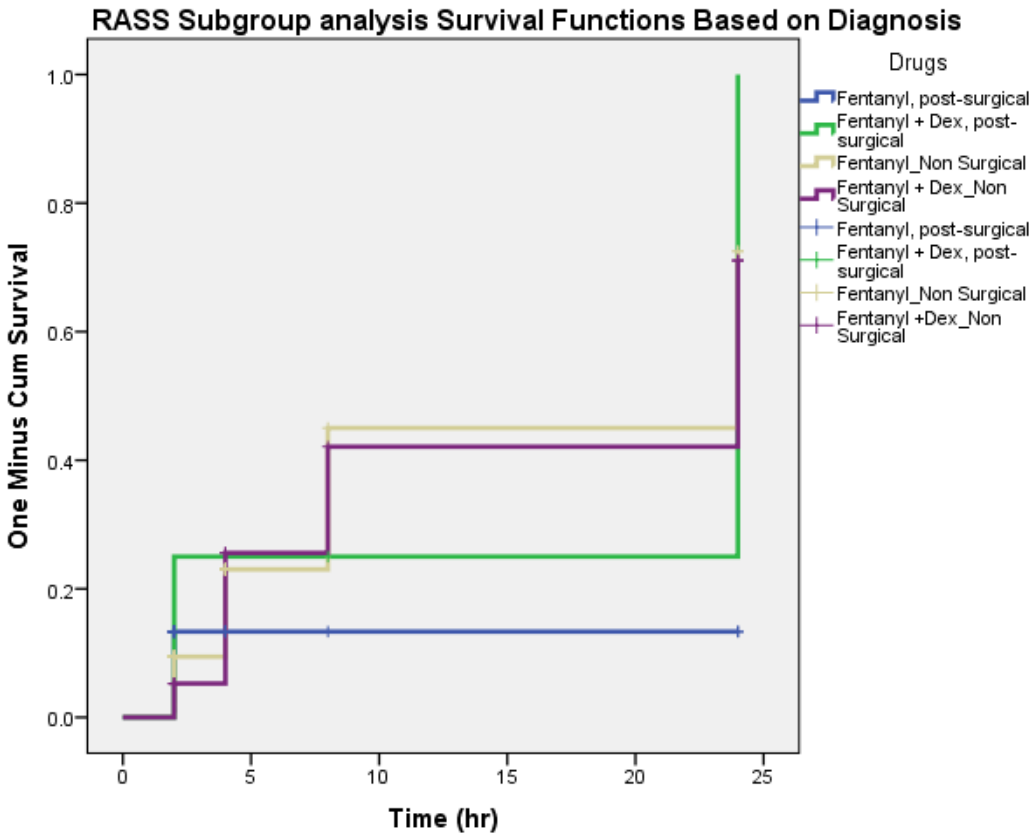


Figure 19: Comparison of sedation level using RASS scale over 24 hours between post-surgical and non-surgical groups on fentanyl alone and combination of fentanyl and dexmedetomidine as sedative applying Kaplan Meier plot

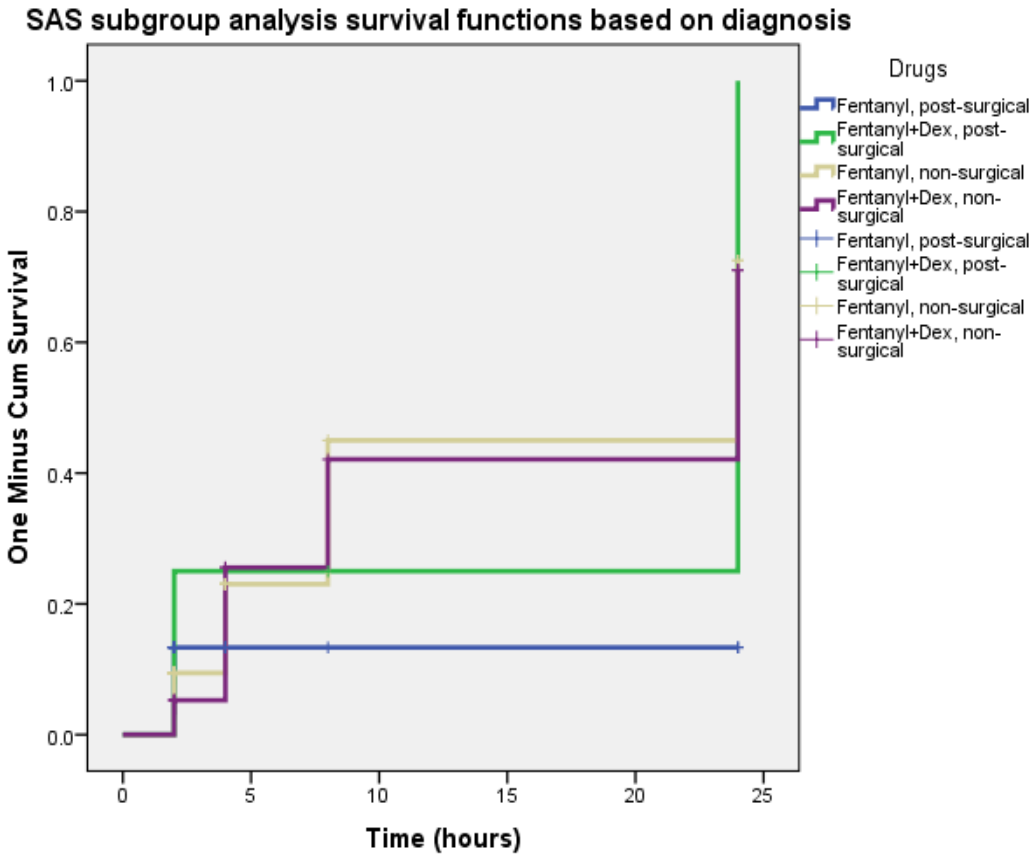


Figure 20: Comparison of sedation level using SAS scale over 24 hours between post-surgical and non-surgical groups on fentanyl alone and combination of fentanyl and dexmedetomidine as sedative applying Kaplan Meier plot

Sedation levels of the study participants among the commonly given sedative groups were compared with RASS and SAS scales at 2, 4, 8, and 24 hours. At 2 hours of sedation, in fentanyl alone and dexmedetomidine alone groups, patients achieved statistically significant adequate sedation ($p = 0.001$) within the group when compared to inadequate sedation. At 4 hours of sedation, in fentanyl alone, the combination of fentanyl and midazolam, and dexmedetomidine alone groups, patients achieved statistically significant adequate sedation ($p = 0.001$) within the group when compared to inadequate sedation. At 8 hours of sedation, no statistical significance ($p = 0.273$) was found within the groups. At 24 hours of sedation, in fentanyl alone, the combination of fentanyl and propofol and dexmedetomidine alone groups, patients achieved statistically significant adequate sedation ($p = 0.004$) within the group when compared to inadequate sedation. Comparison of sedation levels in terms of adequate or inadequate sedation (insufficient or excessive) at various time points has been tabulated in **Table 13**.

Table 13: Comparison of sedation level in terms of adequate sedation or inadequate sedation (insufficient or excessive) at various time points

Time (hour)	Sedative	Sedation level		p-value
		Adequate (%)	Inadequate (%)	
2	Fentanyl	55 (66.3)	28 (33.7)	0.001*
	Fentanyl and Dexmedetomidine	6 (26.1)	17 (73.9)	
	Fentanyl and Midazolam	2 (33.3)	4 (66.7)	
	Fentanyl and Propofol	0 (0)	4 (100)	
	Dexmedetomidine	3 (60)	2 (40)	
4	Fentanyl	65 (78.3)	18 (21.7)	0.001*
	Fentanyl and Dexmedetomidine	11 (47.8)	12 (52.2)	
	Fentanyl and Midazolam	5 (83.3)	1 (16.7)	
	Fentanyl and Propofol	0 (0)	4 (100)	
	Dexmedetomidine	3 (60)	2 (40)	
8	Fentanyl	61 (73.5)	22 (26.5)	0.273
	Fentanyl and Dexmedetomidine	12 (52.2)	11 (47.8)	
	Fentanyl and Midazolam	3 (50)	3 (50)	
	Fentanyl and Propofol	3 (75)	1 (25)	
	Dexmedetomidine	4 (80)	1 (20)	
24	Fentanyl	67 (80.7)	16 (19.3)	0.004*
	Fentanyl and Dexmedetomidine	11 (47.8)	12 (52.2)	
	Fentanyl and Midazolam	3 (50)	3 (50)	
	Fentanyl and Propofol	4 (100)	0 (0)	
	Dexmedetomidine	5 (100)	0 (0)	

*$p < 0.05$

Length of ICU stay and proportion of mortality in the ICU in study participants receiving various sedatives have been shown in **Table 14**. Among the commonly given sedative groups, the median length of ICU stay was 9 (10.5) days in the fentanyl alone group, 9 (9) days in the combination of fentanyl and dexmedetomidine group, 8.5 (3.25) days in the combination of fentanyl and midazolam group, 16 (4.25) days in the combination of fentanyl and propofol group, and 18 (14) days in dexmedetomidine alone group.

The proportion of mortality in the ICU in fentanyl alone, the combination of fentanyl and dexmedetomidine, the combination of fentanyl and midazolam, dexmedetomidine alone, and the combination of fentanyl and propofol groups were 48.19%, 47.83%, 16.67%, 60%, and 0% respectively.

Table 14: Length of ICU stay and proportion of mortality in the ICU in study participants receiving various sedatives

Pattern	Sedative	ICU stay (days) (Median (IQR))	Mortality (%)
Monotherapy	Fentanyl	9 (10.5)	40 (48.19)
	Dexmedetomidine	18 (14)	3 (60)
	Propofol	28.5 (14.5)	1 (50)
	Midazolam	12 (5)	2 (100)
Dual therapy	Fentanyl and Dexmedetomidine	9 (9)	11 (47.83)
	Fentanyl and Midazolam	8.5 (3.25)	1 (16.67)
	Fentanyl and Propofol	16 (4.25)	0
	Dexmedetomidine and Propofol	17.5 (2.5)	0
	Dexmedetomidine and Midazolam	20	0
	Midazolam and Propofol	17	0
Triple therapy	Fentanyl, Dexmedetomidine and Midazolam	21	0
	Fentanyl, Dexmedetomidine and Propofol	18	0

The frequency and proportion of adverse events, which includes hypotension, bradycardia, constipation, tachycardia, hypertension, skin reaction, and raised intracranial tension were 5 (27.8%), 4 (22.2%), 3 (16.7%), 2 (11.1%), 2 (11.1%), 1 (5.6%), and 1 (5.6%) respectively and has been displayed in **Table 15**.

Table 15: Frequency and proportion of adverse events among the study participants

Events	Number of events (% of events)
Hypotension	5 (27.8)
Bradycardia	4 (22.2)
Constipation	3 (16.7)
Tachycardia	2 (11.1)
Hypertension	2 (11.1)
Skin reaction	1 (5.6)
Raised intracranial tension	1 (5.6)

Other classes of drugs prescribed along with sedatives in these patients mainly constitute antibiotics (86.3%), proton pump inhibitors (86.3%), anti-pyretic (52.7%), anti-coagulants (29.8%), anti-emetics (25.9%), and steroids (21.4%). It also consists of anti-epileptics, vitamins, anti-hypertensive, anti-platelet, analgesic, noradrenaline, hypolipidemic, mannitol, laxative, potassium chloride, nebulization, diuretics, fluids, calcium gluconate, anti-fungal, atropine, anti-viral, thyroid drugs, sodium bicarbonate, magnesium sulphate, nitro-glycerine, and anti-Parkinson drugs.

Cost minimization analysis was done in patient groups receiving various sedatives and has been tabulated in **Table 16**. The average drug acquisition cost per patient per day of fentanyl alone, the combination of fentanyl and dexmedetomidine, the combination of fentanyl and midazolam, the combination of fentanyl and propofol, and dexmedetomidine alone groups were Rs.563.8 (ranging between Rs.245 and Rs.980), Rs.2016.74 (ranging between Rs.1055 and Rs.4220), Rs.889.83 (ranging between Rs.799 and Rs.1055), Rs. 1720 (ranging between Rs.1523 and Rs.1917) and

Rs.2106 (ranging between Rs.1620 and Rs.2430) respectively. It was found that the average drug acquisition cost spent by a patient per day was lower with the use of fentanyl alone, followed by the combination of fentanyl and midazolam. On the other hand, it was higher with the use of dexmedetomidine alone.

Table 16: Average (Range) costs in the study participants receiving various sedatives

Sedative	Average cost/ patient/day (Range) (Rs.)
Fentanyl	563.8 (245 - 980)
Fentanyl and Dexmedetomidine	2016.74 (1055 - 4220)
Fentanyl and Midazolam	889.83 (799 - 1055)
Fentanyl and Propofol	1720 (1523 - 1917)
Dexmedetomidine	2106 (1620 - 2430)

The difference in average cost between the groups was statistically significant (p-value = 0.008). However, no significant difference was found when the patients were adjusted with age and gender. This implies that the patient's age and gender do not play any role in the average cost of sedative.

DISCUSSION

Mechanical ventilation is short-term life support that is in practice for a various spectrum of indications (1). Post-intubation pain and anxiety in patients on mechanical ventilation in the ICU may cause agitation, increased oxygen consumption, tachycardia, hypercoagulability, hypermetabolism, and immunosuppression (3). The usage of sedatives can best prevent these probable complications along with other drugs. Sedatives are pharmacological agents used to facilitate tolerance to the artificial airway, reduce irritability or agitation while doing a medical procedure and reduce pain and anxiety in critically ill patients on mechanical ventilation in the ICU (3).

Some of the commonly used sedatives include alpha-adrenergic receptor agonist (e.g., dexmedetomidine), benzodiazepines (e.g., midazolam), general anaesthetic agents (e.g., propofol), and opioids (e.g., fentanyl) (5). Maintaining a balance between the adequate level of sedation to avoid potential adverse effects is crucial and remains a challenge for clinicians (13,14). Proper observation of the level of sedation is necessary for the care of mechanically ventilated patients in the ICU (87). Sedation strategy decides the effectiveness of the therapy. The use of sedatives in the appropriate dose for the appropriate duration can influence the daily ICU cost. The present study found the prescription pattern of sedatives given in adult patients on mechanical ventilation in the adult ICU and the pharmacoeconomics of sedatives given.

In our study, a total of 169 patients who were on mechanical ventilation were screened from the adult ICU, out of which 131 patients were enrolled and included in the analysis. The proportion of males was higher than females, with an average age of 53 years. Most of them were admitted to the ICU for post-surgical observation, followed by patients with other medical complications.

Studying the utilization pattern of drugs plays an essential role in clinical practice to facilitate rational drug use. Our study found that 70% of the study participants were given a sedative as monotherapy. Among which, fentanyl alone (63%) had been given most commonly, followed by dexmedetomidine alone (4%).

The study conducted by *Soliman et al* also showed that fentanyl (33%) and morphine (33%) were commonly administered over other agents as a continuous intravenous infusion in the ICU, with a significant difference among the European countries (6). *Jung et al* studied the annual trend in the use of sedatives in elderly

patients who were on mechanical ventilation in the ICU. They observed that, in 2012, midazolam was used in 63.5% of patients, and fentanyl was used in 10.7% of patients. But by 2016, the use of midazolam decreased to 60.6%, and fentanyl increased to 12.3%. Hence, there was an increase in the use of opioids as compared to benzodiazepines for sedation every year, considering analgesia-based sedation (88).

However, *Watling et al* observed that benzodiazepines (lorazepam 67% and midazolam 22%) was given as the first-line sedative of choice in ventilated patients in the ICU, and opioids (morphine 17% and fentanyl 12%) was given as add-on therapy (89). *Hayashida et al* also observed that the use of propofol and benzodiazepines were common (41.7% and 30.9%, respectively) during the initial 24 hours of mechanical ventilation in patients in the ICU. Whereas the use of fentanyl and dexmedetomidine was only 7.4% and 0.2%, respectively, in these patients (69).

In our study, the combination of two sedatives was given in 28% of the study participants, where the combination of fentanyl and dexmedetomidine (18%) was given commonly, followed by the combination of fentanyl and midazolam (5%), and the combination of fentanyl and propofol (3%).

But the study conducted by *Hayashida et al* observed that the combination of fentanyl and dexmedetomidine was not given during the initial 24 hours of mechanical ventilation in patients in the ICU. Instead, the combination of fentanyl and propofol (7.2%) and the combination of fentanyl and benzodiazepine (6.7%) were administered to these patients (69). Similarly, *Watling et al* and *Soliman et al* reported that the commonly given sedative combination therapy was fentanyl – midazolam combination in the ICU. Around 46% of the patients receiving combination therapy were administered this combination of sedatives (6,89).

In our study, most of the patients on mechanical ventilation admitted in the ICU were for post-surgical observation and with CNS complications. We observed that fentanyl was the commonly given sedative for these patients either alone or in combination. Similarly, a study conducted by *Paul et al* observed that fentanyl was the drug of choice for sedation in these patients in the ICU (90).

The ATC/DDD system represents a stable drug utilization metric to enable comparisons of drug use between countries, regions, or health care settings. On comparison of the utilization of various sedative agents based on the DDD of WHO and that of the study participants, the results of our study indicate that the median DDD of fentanyl (5.05mg), dexmedetomidine (3.3mg), and midazolam (45.5mg) in the study participants were higher than the DDD defined by the WHO (1.2mg, 1mg, and 15mg respectively) with the ratio of 4.2, 3.3, and 3.03 respectively. Whereas the median DDD of propofol (1.23g) in the study participants was lower than the WHO DDD (14g) with a ratio of 0.08. The dosing of the sedative was adjusted according to the patient's sedation level.

In our study, on comparing the vitals at baseline and 24 hours among the commonly given sedative groups, it was found that there was a significant decrease in DBP in fentanyl alone and the combination of fentanyl and midazolam groups. In subgroup analysis, there was a significant reduction in DBP in the fentanyl alone group in ≤60 years of age patients as compared to >60 years of age patients. A study conducted by *Watanabe et al* also observed a decrease in DBP after administration of midazolam as a sedative (91). The reduction in blood pressure observed with fentanyl and midazolam was due to the blocking effect of the sympathetic nervous system (92,93).

There was a significant decrease in HR in the fentanyl and propofol combination group in our study. A study conducted by *Aken et al* also observed a significant reduction in HR after administration of fentanyl along with propofol for sedation (94). This decrease in HR was due to the inhibition of sympathetic nerve activity by propofol (95,96).

In our study, there was a significant decrease in HR and an increase in SBP in the fentanyl and dexmedetomidine combination group. In subgroup analysis, there was a significant increase in SBP in the fentanyl and dexmedetomidine combination group in non-surgical patients as compared to post-surgical patients. A study conducted by *Shah et al* also showed a rise in blood pressure followed by a reflex decrease in HR after administration of dexmedetomidine for sedation (66). The increase in blood pressure was due to the peripheral α_2-adrenoceptor mediated arterial vasoconstriction,

and the decrease in HR was due to the baroreflex mediated parasympathetic activation in response to increased blood pressure by dexmedetomidine (97,98).

In our study, the percentage of study participants who achieved adequate sedation over 24 hours was 75% in both fentanyl and dexmedetomidine groups when given as monotherapy. Adequate sedation was also achieved in combination therapy accounting for 54% in the fentanyl and midazolam combination group and 44% in both fentanyl and dexmedetomidine combination group, and fentanyl and propofol combination group.

A study conducted by *Shehabi et al* in critically-ill patients in the ICU also observed that in the dexmedetomidine group, 56.6% of patients achieved adequate sedation when compared to the usual care group (71). Similarly, *Richman et al* observed that 54% of patients receiving the combination of fentanyl and midazolam sedation achieved adequate sedation (99). But *MacLaren et al* observed that 76% of patients receiving propofol and 64% of patients receiving midazolam attained adequate sedation over 24 hours (100).

However, there was no significant difference in sedation levels between the sedative groups. *Riker et al*, *Gupta et al* and *Jakob et al* also reported no significant difference between the dexmedetomidine, propofol, and midazolam groups to attain adequate sedation in the ICU (64,68,101). Further subgroup analysis based on the patient's age and the reason for ICU admission in fentanyl alone and the combination of fentanyl and dexmedetomidine groups also showed a similar level of sedation between the groups.

In our study, among all the study participants, hypotension was the predominant adverse event noted, followed by bradycardia. Other adverse events noted were tachycardia, hypertension, skin reactions, constipation, and raised intracranial tension. *Aggarwal et al* also observed that hypotension was the predominant adverse event found with the administration of dexmedetomidine and propofol as a sedative in the ICU. Other adverse events observed were hypertension, bradycardia, infection, and delirium (83). *Park et al* and *Riker et al* also found the occurrence of hypotension, bradycardia, hypertension, and tachycardia in critically-ill patients receiving fentanyl, midazolam, and dexmedetomidine as a sedative in the ICU (64,102).

Pharmacoeconomics is a scientific discipline under health economics that compares the value of one pharmaceutical product or treatment mix to another (79). In our study, pharmacoeconomic evaluation was done using Cost Minimization Analysis (CMA), as drug procurement and hospital expenses are the same for all patients in our center. Since there was no difference in the sedation level between these sedative groups, the denominator would be zero in Incremental Cost Effectiveness Ratio estimation. Besides, we have not studied the long-term assessment of adverse events and their management. Thus, cost-effectiveness analysis could not be performed (81). Therefore, CMA was the most appropriate analysis in our study as it compares and determines the more advantageous strategy based on the cost in interventions with similar outcomes (78). In our study, CMA was done by comparing the drug acquisition cost of the sedatives given in patients on mechanical ventilation in the adult ICU for initial 24 hours.

According to the results of our study, the average drug acquisition cost per patient per day was lower in the fentanyl group (Rs.564) and higher in the dexmedetomidine group (Rs.2106). There was a significant difference in cost between the commonly given sedative groups. Fentanyl was found to be more cost-saving when compared to other sedatives. However, the age and gender of the study participants did not play any role in the drug acquisition cost.

In earlier studies, the administration of dexmedetomidine was not economically compared with that of fentanyl. However, cost minimization analysis done by *Dasta et al*, which includes ICU and adverse drug reaction management costs, showed that dexmedetomidine-based sedation was significantly less costly as compared to that of midazolam (81). Similarly, *Aggarwal et al* concluded that the cost minimization analysis of sedatives, which includes ICU cost, showed that dexmedetomidine-based sedation was associated with reduced cost as compared to midazolam and propofol (83).

Strengths of the study:

Our study comprehensively analyzed the prescription pattern of sedatives given in the adult ICU at our center. We compared the level of sedation of various sedatives over 24 hours and observed the hemodynamic changes during sedation along with subgroup analysis based on age and reason for ICU admission. Despite the covid crisis, adequate sample size was obtained for our study in a short duration.

Limitations of the study:

This is an exploratory prospective observational study. The shorter timeline of the study was due to the Covid crisis. The study participants were observed only for 24 hours, and for pharmacoeconomic analysis, only the drug acquisition cost of sedatives was estimated and compared.

Future implications:

Fentanyl can be given as the sedative of choice, either alone or in combination in mechanically ventilated patients in the adult ICU. It has fewer hemodynamic changes and adverse events. However, continuous monitoring is essential. Further studies need to be done to analyze the efficacy and safety of sedative therapy in the ICU with more sample size and to be observed for more than 24 hours. In addition, pharmacoeconomic studies of sedatives given in mechanically ventilated patients in the ICU in India need to be done in the future.

CONCLUSION

1. Sedatives are agents that are used to facilitate tolerance to artificial airway, reduce irritability or agitation, reduce pain and anxiety in critically-ill and mechanically ventilated patients.
2. Commonly used sedative agents are alpha-adrenergic receptor agonists (e.g., dexmedetomidine), benzodiazepines (e.g., midazolam), general anaesthetic agents (e.g., propofol), and opioids (e.g., fentanyl).
3. This study was carried out in the Department of Pharmacology in collaboration with the Department of Anaesthesiology and Critical care of the All India Institute of Medical Science, Jodhpur.
4. After getting approval from the Institutional Ethics Committee, the patients on mechanical ventilation atleast for 24 hours in the adult ICU were included in the study.
5. Baseline demographic details, clinical characteristics, and baseline investigations were recorded for all the patients.
6. The commonly given five sedative groups in our study were fentanyl alone; the combination of fentanyl and dexmedetomidine; the combination of fentanyl and midazolam; dexmedetomidine alone; and the combination of fentanyl and propofol.
7. Sedative as monotherapy was commonly given in mechanically ventilated patients in the ICU. They include fentanyl (most common), followed by dexmedetomidine, propofol, and midazolam.
8. Sedatives given as combination therapy were the combination of fentanyl and dexmedetomidine (most common), followed by the combination of fentanyl and midazolam; the combination of fentanyl and propofol; the combination of dexmedetomidine and propofol; the combination of dexmedetomidine and midazolam; the combination of midazolam and propofol; the combination of fentanyl, dexmedetomidine and midazolam; and fentanyl, dexmedetomidine, and propofol.
9. In our study, comparing the patient DDD with WHO DDD, we found that DDD of fentanyl, dexmedetomidine, and midazolam was given to our patients was higher than that of WHO DDD.

10. The change in vitals was compared at baseline and 24 hours and found that there was a significant decrease in DBP in fentanyl alone; and combination of fentanyl and midazolam group, the significant reduction in HR in the combination of fentanyl and dexmedetomidine group; and combination of fentanyl and propofol group along with a significant increase in SBP in the combination of fentanyl and dexmedetomidine group.
11. In subgroup analysis, there was a significant reduction in DBP in fentanyl alone group in ≤60 years of age patients as compared to >60 years of age patients and the significant increase in SBP in fentanyl and dexmedetomidine combination group in non-surgical patients as compared to post-surgical patients.
12. Richmond Agitation Sedation Scale and Riker Sedation-Agitation Scale were used to assess the sedation level of patients.
13. The incidence of adequate, insufficient, and excessive sedation was calculated in commonly given sedative groups and found no significant difference between the sedative groups. Further subgroup analysis based on the patient's age and reason for ICU admission in fentanyl alone and the combination of fentanyl and dexmedetomidine groups also showed a similar level of sedation between the groups.
14. Cost minimization analysis was done for pharmacoeconomic evaluation of sedatives given in mechanically ventilated patients in the ICU.
15. The average drug acquisition cost per patient per day was significantly less for fentanyl (Rs.564) and high for dexmedetomidine (Rs.2106). Thus, fentanyl was found to be the cost-saving sedative of choice.
16. Further studies need to be done to analyze the efficacy and safety of sedative therapy in the ICU with more sample size and to be observed for more than 24 hours. In addition, pharmacoeconomic studies of sedatives given in mechanically ventilated patients in the ICU in India need to be done in the future.

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ANNEXURES

ANNEXURE: I

INSTITUTIONAL ETHICS COMMITTEE CERTIFICATE

अखिल भारतीय आयुर्विज्ञान संस्थान, जोधपुर
All India Institute of Medical Sciences, Jodhpur
संस्थागत नैतिकता समिति
Institutional Ethics Committee

No. AIIMS/IEC/2020/ 3229 **Date: 14/10/2020**

ETHICAL CLEARANCE CERTIFICATE

Certificate Reference Number: **AIIMS/IEC/2019-20/964**

Project title: **"Prescription pattern and pharmacoeconomic analysis of sedatives used in patients on mechanical ventilation in adult ICU."**

Nature of Project:	**Research Project**
Submitted as:	**M.D. Dissertation**
Student Name:	**Dr.T. Abisha**
Guide:	**Dr.Sneha Ambawani**
Co-Guide:	**Dr. Pradeep Kr. Bhatia, Dr. Pradeep Dwivedi & Dr. Shoban Babu Varthya**

Institutional Ethics Committee after thorough consideration accorded its approval on above project.

The investigator may therefore commence the research from the date of this certificate, using the reference number indicated above.

Please note that the AIIMS IEC must be informed immediately of:

- Any material change in the conditions or undertakings mentioned in the document.
- Any material breaches of ethical undertakings or events that impact upon the ethical conduct of the research.

The Principal Investigator must report to the AIIMS IEC in the prescribed format, where applicable, bi-annually, and at the end of the project, in respect of ethical compliance.

AIIMS IEC retains the right to withdraw or amend this if:

- Any unethical principle or practices are revealed or suspected
- Relevant information has been withheld or misrepresented

AIIMS IEC shall have an access to any information or data at any time during the course or after completion of the project.

Please Note that this approval will be rectified whenever it is possible to hold a meeting in person of the Institutional Ethics Committee. It is possible that the PI may be asked to give more clarifications or the Institutional Ethics Committee may withhold the project. The Institutional Ethics Committee is adopting this procedure due to COVID-19 (Corona Virus) situation.

If the Institutional Ethics Committee does not get back to you, this means your project has been cleared by the IEC.

On behalf of Ethics Committee, I wish you success in your research.

Dr. Praveen Sharma
Member Secretary
Member secretary
Institutional Ethics Committee
AIIMS,Jodhpur

Basni Phase-2, Jodhpur, Rajasthan-342005; **Website:** www.aiimsjodhpur.edu.in; **Phone:** 0291-2740741 Extn. 3109
E-mail : ethicscommittee@aiimsjodhpur.edu.in; ethicscommitteeaiimsjdh@gmail.com

ANNEXURE: II

PATIENT INFORMATION SHEET (English)

Part-1

1. Purpose of the study: To analyze the prescription pattern and pharmacoeconomics of sedatives used in patients on mechanical ventilation in adult ICU.

2. Study procedures to be followed: Patients on mechanical ventilation in adult ICU for 24 hours in AIIMS, Jodhpur shall be observed for –

a. Clinical History.
b. Prescription pattern of sedative used.
c. Vitals.
d. Laboratory Investigations.
e. Depth of sedation.
f. Cost of sedative used.

3. Benefits from the study: To analyze the prescription pattern and pharmacoeconomics of sedatives used in patients on mechanical ventilation in adult ICU.

4. Risks of the study: No risk involved.

5. Complications of the study: None

6. Confidentiality: Data collected from the patients shall not be shared with anyone except the study investigators.

7. Rights of participants: Patients would have the freedom to share their data and continue or leave the study if they desire.

Part-2

Patient's/ Patient's relative word

I have this patient information sheet, and I have understood the study procedures, benefits and harms involved. I have been given enough opportunities to ask questions regarding the study. I / my relative agree to participate in the study.

Patient's relative signature:

Date:

Part-3

Investigator's word

I have explained the purpose, procedures, benefits, and harms of the study in detail to the patient/ patient's relative. All information regarding the study has been disclosed, and enough opportunity for asking questions regarding the study was given to the patient/ patient's relative.

Principal investigator signature: Witness signature:

ANNEXURE: III

PATIENT INFORMATION SHEET (Hindi)

रोगी सूचना पत्र

भाग - 1

1. **अध्ययन का उद्देश्य: वयस्क आईसीयू में यांत्रिक वेंटिलेशन पर रोगियों में इस्तेमाल किए गए शामक (सीडेटिव) के प्रिस्क्रिप्शन पैटर्न और फार्माकोकॉनोमिक विश्लेषण।**

2. **अध्ययन की जाने वाली प्रक्रियाएं:** एम्स, जोधपुर में 24 घंटे तक वयस्क आईसीयू में यांत्रिक वेंटिलेशन पर मरीजों को देखा जाएगा।

a. नैदानिक इतिहास
b. प्रयुक्त शामक का प्रिस्क्रिप्शन पैटर्न
c. नब्ज
d. प्रयोगशाला जांच
e. शामक की गहराई (डेप्थ ऑफ सीडेटिव)
f. प्रयुक्त शामक की लागत

3. **अध्ययन से लाभ:** वयस्क आईसीयू में यांत्रिक वेंटिलेशन पर रोगियों में इस्तेमाल किए गए शामक (सीडेटिव) के प्रिस्क्रिप्शन पैटर्न और फार्माकोकॉनोमिक विश्लेषण।

4. **अध्ययन के जोखिम:** इसमें कोई जोखिम शामिल नहीं है।

5. **अध्ययन की जटिलताओं:** कोई नहीं

6. **गोपनीयता:** अध्ययन जांचकर्ताओं को छोड़कर रोगियों से एकत्र किया गया डेटा किसी के साथ साझा नहीं किया जाएगा।

7. **प्रतिभागियों के अधिकार:** मरीजों को अपने डेटा को साझा करने और यदि वे चाहें तो अध्ययन जारी रखने या छोड़ने की स्वतंत्रता होगी।

भाग 2

रोगी का / रोगी का रिश्तेदार शब्द

मेरे पास यह रोगी सूचना पत्र है और मैंने इसमें शामिल अध्ययन प्रक्रियाओं, लाभों और हानियों को समझा है। मुझे अध्ययन के संबंध में प्रश्न पूछने का पर्याप्त अवसर दिया गया है। मैं / मेरे रिश्तेदार अध्ययन में भाग लेने के लिए सहमत हैं।

रोगी के सापेक्ष हस्ताक्षर:

तारीख:

भाग- 3

अन्वेषक का शब्द

मैंने रोगी के / रोगी के रिश्तेदार के अध्ययन के उद्देश्य, प्रक्रिया, लाभ और हानि के बारे में विस्तार से बताया है। अध्ययन के बारे में सभी जानकारी का खुलासा किया गया है और रोगी / रोगी के रिश्तेदार को अध्ययन से संबंधित प्रश्न पूछने का पर्याप्त अवसर दिया गया है।

प्रधान जांचकर्ता हस्ताक्षर: साक्षी हस्ताक्षर:

ANNEXURE: IV

INFORMED CONSENT FORM (English)

All India Institute of Medical Sciences Jodhpur, Rajasthan

Title of the thesis**: To analyze the prescription pattern and pharmacoeconomics of sedatives used in patients on mechanical ventilation in adult ICU.**

Name of PG student: Dr. Abisha T Tel. No: +91 8890015420

Name of the Guide: Dr. Sneha R Ambwani

Patient/Volunteer Identification No.:

I, _____ R/o _____
give full, free, voluntary consent to be a part of the study **"To analyse the prescription pattern and pharmacoeconomics of sedatives used in patients on mechanical ventilation in adult ICU".** The procedure and nature of the study has been explained to me in my own language to my full satisfaction. I confirm that I have had the opportunity to ask questions.

I understand that my participation is voluntary, and I am aware of my right to opt-out of the study at any time without giving any reason.
I understand that the information collected about me and any of my medical records may be looked at by a responsible individual from AIIMS Jodhpur or from regulatory authorities. I give permission for these individuals to have access to my records.

Date: _____ _____
Place: _____ Signature/Left thumb impression
This is to certify that the above consent has been obtained in my presence.

Date: _____ _____
Place: _____ Signature of Principal Investigator

1. Witness 1

_____
Signature
Name: _____
Address: _____
_____

2. Witness 2

_____
Signature
Name: _____
Address: _____
_____

ANNEXURE: V

INFORMED CONSENT FORM (Hindi)

अखिल भारतीय आयुर्विज्ञान संस्थान

जोधपुर, राजस्थान

सूचित सहमति प्रपत्र

थीसिस का शीर्षक: **वयस्क आईसीयू में यांत्रिक वेंटिलेशन पर रोगियों में इस्तेमाल किए गए शामक (सीडेटिव) के प्रिस्क्रिप्शन पैटर्न और फार्माकोकॉनोमिक विश्लेषण।**

पीजी छात्रा का नाम: डॉ. अबिशा टी. दूरभाषा/मोबाईल नंबर: +91 8890015420

गाइड का नाम: डॉ. स्नेहा आर अंबवानी

रोगी / स्वयंसेवक पहचान संख्या:

मैं, _____ आर / ओ _____ पूर्ण, मुक्त, स्वैच्छिक सहमति "**वयस्क आईसीयू में यांत्रिक वेंटिलेशन पर रोगियों में इस्तेमाल किए गए शामक (सीडेटिव) के प्रिस्क्रिप्शन पैटर्न और फार्माकोकॉनोमिक विश्लेषण**" अध्ययन की प्रक्रिया और प्रकृति को मुझे अपनी भाषा में मेरी पूर्ण संतुष्टि के लिए समझाया गया है। मैं पुष्टि करता हूं कि मुझे सवाल पूछने का अवसर मिला है।

मैं समझता हूं कि मेरी भागीदारी स्वैच्छिक है और मुझे बिना कोई कारण बताए किसी भी समय अध्ययन से बाहर निकलने के अपने अधिकार के बारे में पता है।

मैं समझता हूं कि मेरे और मेरे किसी भी मेडिकल रिकॉर्ड के बारे में एकत्रित जानकारी को एम्स जोधपुर के जिम्मेदार व्यक्ति या नियामक अधिकारियों से देखा जा सकता है। मैं इन व्यक्तियों को अपने रिकॉर्ड तक पहुंचने की अनुमति देता हूं।

तारीख: _____ _____

स्थान: _____ हस्ताक्षर / बाएं अंगूठे का निशान

यह प्रमाणित करने के लिए कि मेरी उपस्थिति में उपरोक्त सहमति प्राप्त की गई है।

तारीख: _____ _____

स्थान: _____ प्रधान अन्वेषक के हस्ताक्षर

1.साक्षी 1	2. गवाह 2
_____	_____
हस्ताक्षर	हस्ताक्षर
नाम _____	नाम: _____
पता _____	पता: _____
_____	_____

ANNEXURE: VI

CASE RECORD FORM

Sr. No. AIIMS/JDH/____/____/_____ Date of admission:

Name: Age/Sex:

Address: Contact number:

Occupation:

DIAGNOSIS:

Co-morbidities:

	Duration	Treatment
Diabetes mellitus		
Hypertension		
Thyroid Disorder		
H/O chronic drug intake		
H/O surgery		
Others		

PERSONAL HISTORY: Smoker/ Alcoholic/ others

GENERAL PHYSICAL EXAMINATION:

Anaemia Cyanosis Jaundice

Pulse: /min BP: mm/Hg

Date & Indication for mechanical ventilation:

VITALS	0 hr	2hr	4hr	8hr	24hr
Heart rate					
BP					
SpO2					
Others					

INVESTIGATIONS	
CBC	
FBS	
HbA1c	
LFT	
RFT	
ABG	
Coagulation profile	
Others	

TREATMENT:

Drug	Dose	Duration	Reason

SEDATIVE HISTORY:

Drug	
Dose & rate of infusion	
Duration of infusion	
Indication	
Recovery time*	
Adverse events (if any) and treatment given	
Total Cost	
Others	

*Time from the cessation of sedation to wakefulness.

SEDATION ASSESSMENT:

	0hr	**2hr**	**4hr**	**8hr**	**24hr**
RASS					
SAS					

Sedation scales:

Richmond Agitation Sedation Scale (RASS)

+4	Combative	Overtly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive vigorous
0	Alert and calm	
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to voice (>10 seconds)
-2	Light sedation	Briefly awakens with eye contact to voice (<10seconds)
-3	Moderate sedation	Movement or eye-opening to voice (but no eye contact)
-4	Deep sedation	No response to voice, but movement or eye-opening to physical stimulation
-5	Unarousable	No response to voice or physical stimulation

Riker Sedation-Agitation Scale (SAS)

7	Dangerous Agitation	Dangerous Agitation Pulling at ET tube, trying to remove catheters, climbing over bedrail, striking at staff, thrashing side-to-side
6	Very Agitated	Very Agitated Requiring restraint and frequent verbal reminding of limits, biting ETT
5	Agitated	Agitated Anxious or physically agitated, calms to verbal instructions
4	Calm and Cooperative	Calm and Cooperative Calm, easily arousable, follows commands
3	Sedated	Sedated Difficult to arouse but awakens to verbal stimuli or gentle shaking, follow simple commands but drifts off again
2	Very Sedated	Very Sedated Arouses to physical stimuli but does not communicate or follow commands, may move spontaneously
1	Unarousable	Unarousable Minimal or no response to noxious stimuli, does not communicate or follow commands

Outcome: