UNIVERSITY OF INDONESIA

COMPARISON BETWEEN INTRAVENOUS MAGNESIUM SULFATE ADMINISTRATION WITH INTRAVENOUS DEXMEDETOMIDINE TO REDUCE CONSCIOUS RECOVERY AGITATION IN ADULT PATIENTS UNDERGOING OTORHINOLARYNGOLOGY SURGERY

RESEARCH PROPOSAL

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VERIFICATION PAGE

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TABLE OF CONTENTS

TABLE LIST

IMAGE LIST

LIST OF ATTACHMENTS

ABBREVIATION LIST

AV	Atrioventricular
EC50	Half maximum effective concentration
etCO2	*End-tidal carbon dioxide*
ECG	Electrocardiography
IM	Intramuscular
IV	Intravenously
IL-1	*Interleukin-1*
IL-6	*Interleukin-6*
LMA	*Laryngeal mask airway*
MRI	*Magnetic Resonance Imaging*
MAC	*Minimum alveolar concentration*
MgSO4	Magnesium sulfate
DRUGS	Narcotics, psychotropics, and other addictive substances
NMDA	*N-methyl-D-aspartate*
NaCl	Sodium chloride
PACU	*Post-anesthesia care unit*
DPO	Postoperative delirium
SASR	Richmond Sedation Agitation Scale
SSAR	Agitation Sedation Scale Riker
SPSS	*Statistical Package for Social Sciences*
TIVA	*Total Intravenous Anesthesia*
TNF-α	*Tumor necrosis factor alpha*

BAB 1
INTRODUCTION

1.1 Background

Conscious recovery agitation is a state that includes restless states, disorientation, excitation, aimless movements, inability to calm down, throwing tantrums, and confusion during initial recovery from general anesthesia. The incidence of conscious recuperation agitation varied from 0.25% to 90.5%. Some of the factors influencing incidence are age, assessment tools used, definition, anesthesia techniques, type of surgery, and assessment time of conscious recovery agitation during recovery.[1] The clinical consequences of conscious recovery agitation also vary. It is generally short-lived and resolves on its own, and the clinical consequences are often considered minimal. However, conscious recovery agitation can have significant clinical consequences, such as injury in patients suffering from conscious recovery agitation or injury to medical staff, falling out of bed, bleeding at the surgical site, detachment of an intravenous tube or catheter, accidental extubation, respiratory depression, and increased medical care costs.[2,3]

Agitation during recovery from general anesthesia is a potentially serious phenomenon that has not been as well studied in the adult population as it is in the pediatric population. In the adult population, the incidence rate can reach 21.3% to 45.9% globally and the number varies depending on several factors, one of which is the type of surgery. In patients with otorhinolaryngology surgery the incidence ranged from 22.2% in one study in Korea to 55.4% in one study in China, in elective craniotomy based on the study in China the incidence was up to 29%, and in cardiac surgery up to 48% in one study in Australia.[4–7] Agitation of conscious recovery in adult patients has also been studied in 1 study in Tasikmalaya, Indonesia which showed agitation of conscious recovery in outpatient surgical patients, with a cumulative amount of 25.5% with 14.9% caused by desflurane and 10.6% caused by sevoflurane.[8] Recognized risk factors that may trigger recovering agitation in adults include otorhinolaryngology, obesity, premediation with benzodiazepines, sevofluran anesthesia, endotracheal tubes, and a history of psychological illness.[2,9]

Dexmedetomidine, which is a highly selective α2-symtolytic, is an effective preventative agent of conscious recovery agitation. Several doses of dexmedetomidine have been studied and the results vary regarding the prevention of cough, postoperative pain, bradycardy, and hypotension but from the set of doses given they are equally beneficial in reducing the incidence of recovering agitation.[10–13] Dexmedetomidine has also been shown to be superior to propofol in terms of the prevention of recovering agitation and has a minimal risk of respiratory depression than fentanyl, so Dexmedetomidine is the best standard for recovering agitation.[14–16] This is the case with magnesium sulfate. Several published studies have shown that magnesium sulfate can improve postoperative analgesia, sedation, reduce postoperative agitation, and provide a good recovery after general anesthesia. In addition, magnesium sulfate in MgSO preparations4 20% has a more affordable price than dexmedetomidine. The availability of magnesium sulfate in Indonesia is also better and widespread because it is a national formulary drug. So magnesium sulfate is more cost effective when proven to be no more inferior in its effect in preventing agitation from recovering consciously. [1]

Based on this, the researcher is interested in researching the effectiveness of intravenous magnesium sulfate administration compared to intravenous dexmedetomidine to reduce conscious recovery agitation in patients at risk of recovering agitation, namely patients undergoing otorhinolaryngology surgery.

1.2 Problem Formulation

Conscious recovery agitation does not only occur in pediatric patients. Young adult patients aged <40 years and older adults who undergo general anesthesia also have a risk of recovering agitation, although the number is not as high as in pediatrics. This opportunity is magnified by the type of patient surgery along with other risk factors. Surgery that manipulates the head and neck area increases the risk of recovering agitation, one of which is surgery in otorhinolaryngology. The incidence of conscious recovery agitation that occurs in this patient can reach 1 in 5 patients who have surgery. When considering the incidence rate and the number of patients

carried out at RSCM, it can be said that the topic of conscious recovery agitation needs to be raised in adult patients.

There is no standard procedure for the prevention of conscious agitation at RSCM. Drugs commonly used in pediatric patients, such as propofol, do not have a meaningful effect in adult patients. In adult patients, according to the literature reference, it can be said that dexmedetomidine is the best standard for the prevention of agitation to recover consciousness. Although the effect of preventing agitation of conscious recovery is not superior to fentanyl, the side effects of respiratory depression are more common with fentanyl. Another therapeutic alternative is the use of magnesium sulfate as an anesthetic adjuvant. Its work as a sedative, analgesic, and neuroprotective agent is believed to be the main mechanism of magnesium to prevent agitation from regaining consciousness. However, there have not been many studies that compare the effectiveness of magnesium sulfate compared to the best standard for preventing agitation of regaining consciousness, namely dexmedetomidine, especially in the adult population in Indonesia.

1.3 Research Questions

Does the use of magnesium sulfate as an anesthetic adjuvant have a similar effect of preventing agitation of conscious recovery than dexmedetomidine in patients undergoing otorhinolaryngological surgery?

1.4 Research Hypothesis

The effectiveness of administering magnesium sulfate as an anesthetic adjuvant is no less good than Dexmedetomidine in the prevention of agitation of conscious recovery.

1.5 Research Objectives

1.5.1 General Purpose

Comparing the effectiveness of magnesium sulfate administration with dexmedetomidine on the incidence of conscious recovery agitation in patients undergoing otorhinolaryngology surgery.

1.5.2 Special Purpose

- Comparing the proportion of events of agitation recovering conscious in otorhinolaryngology surgical patients between patients receiving intravenous magnesium sulfate with intravenous dexmedetomidine
- To compare the amount of dosing of propofol as a heavy conscious recovering agitation rescue agent in patients receiving magnesium sulfate versus patients receiving propofol to determine the effectiveness of both agents in reducing the severity of recovering agitation in otorhinolaryngology surgery
- To know and compare the onset and duration of events of conscious recovery agitation in patients receiving magnesium sulfate with patients receiving dexmedetomidine in otorhinolaryngology surgery
- To compare changes in mean arterial pressure and pulse frequency in otorhinolaryngology surgery patients receiving intravenous magnesium sulfate with intravenous dexmedetomidine to find out how much the two agents have an impact on mean arterial pressure and pulse frequency
- Comparing the amount of administration of ephedrine as a significant salvage agent of hypotension and bradycardia in patients receiving magnesium sulfate with dexmedetomidine in otorhinolaryngology surgery
- Comparing the number of doses of fentanyl and the concentration of intraoperative sevoflurane used in patients receiving magnesium sulfate with dexmedetomidine in otorhinolaryngology surgery
- Comparing the 1-hour postoperative pain score of patients receiving magnesium sulfate versus patients receiving dexmedetomidine in otorhinolaryngology surgery

- To determine and compare the duration of extubation in patients receiving magnesium sulfate versus patients receiving dexmedetomidine in otorhinolaryngology surgery

1.6 Research Benefits

1.6.1 Scientific Benefits

1. This study can be used as a reference for new research that will be conducted on the use of magnesium sulfate in the prevention of conscious agitation when compared to other agents or in special populations.
2. Educational institutions can implement the use of magnesium sulfate to prevent agitation from regaining consciousness.
3. Researchers can increase knowledge about the effectiveness of magnesium sulfate in reducing the incidence of agitation and recovering consciousness

1.6.2 Clinical Benefits

1. This study could be the basis for magnesium sulfate to be routinely practiced in otorhinolaryngology surgery as an alternative to dexmedetomidine, especially in patients with a high risk of agitation regaining consciousness.
2. Patients complete the procedure in a more comfortable state because they are less restless and postoperative pain is reduced
3. This research can be used as a reference to make guidelines for the practice of preventing agitation from recovering consciousness

1.6.3 Benefits of Community Service

1. The results of this study are expected to contribute to reducing the morbidity rate of patients caused by conscious recovery agitation
2. This result has the potential to reduce the burden of hospital costs due to the severe side effects posed by the heavy conscious recovery agitation

BAB 2
LITERATURE REVIEW

2.1 Agitation regained consciousness

2.1.1 Definition of Conscious Recovery Agitation

Conscious recovery agitation is a phenomenon that occurs after general anesthesia, this process is characterized by a state of psychomotor excitation that is temporary and varies between individuals. Common symptoms include aimless movements, restlessness, and confusion. This process usually lasts for a short time, ranging from 2 to 5 minutes after the discontinuation of the inhaled anesthetic agent and lasting up to 15 minutes after extubation.[9] However, some cases can last up to 30-45 minutes after extubation.[17,18] During this agitation phase, the patient is often unresponsive to communication and has difficulty following verbal commands. [2,9]

It is important to distinguish between conscious recovery agitation and other types of perioperative delirium, such as delirium in the post-anesthesia care unit (PACU) or postoperative delirium (DPO). Conscious relapse agitation occurs when the patient transitions back to consciousness, whereas delirium is a reversible change in consciousness, with attention disorders and cognitive deficits. The incidents are also related to each other. In a prospective cohort study in China, geriatric patients reported that the incidence of delirium recovered, consciously increased the incidence of DPO. Despite the differences, some literature states that agitation regains consciousness and DPO in general are often considered similar in medical practice.[2,9,19–22]

In addition to the agitation of recovering consciousness in some literature, it is also known that there is a term delirium of recovering consciousness. Delirium recovering consciousness is a state of acute confusion that occurs during recovery from anesthesia. Patients with recovering delirium may experience disorientation, hallucinations, restlessness, and aimless hyperactive physical behavior just like recovering agitation, but some literature says recovering delirium is not equivalent to recovering agitation. Conscious recovered delirium can include hypoactive signs or mixed forms, without triggering agitation. However, the terminology of

conscious recovered agitation and conscious recovered delirium were used interchangeably in some studies. This is because the measuring instruments used in conscious recovery agitation and conscious recovery delirium are the same, for example the Riker sedation-agitation scale or the Richmond agitation-sedation scale.[9,19]

2.1.2 Mechanism of Agitation Recovered Consciousness

The etiology of conscious recuperation agitation is not yet fully understood. Increased postoperative pain sensation has been suspected as the cause. However, pain is not the only major cause because conscious recovery agitation can occur in patients undergoing MRI (*Magnetic Resonance Imaging*). There are triggers and there are those that increase the risk of recovering agitation which is multifactorial in nature.[2]

Inhalation anesthesia plays an important role in the occurrence of agitation and regaining consciousness. Inhaled anesthesia such as sevoflurane, isoflurane, and desflurane are suspected, especially in pediatric populations, to alter brain activity and disrupt the balance between excitation and synaptic inhibition of central nervous system neurons. In the adult population, the main conjecture is that during the excitation stage or "phase 2" of anesthesia recovery, hyperarousal appears in response to internal and external stimuli while consciousness is restored. For example, in surgery involving the oral cavity, the sensation of shortness of breath due to the placement of the casing in the oral cavity may contribute to the frequent occurrence of conscious recovery agitation in this group.[2,9]

Uninhibited sympathetic activation due to poorly handled nociception stimuli or the presence of an attached endotracheal catheter and tube can also trigger resuscitation agitation. Other studies have shown that conscious recovery agitation is more common in patients with higher inflammatory mediators (interleukin-6 [IL-6], tumor necrosis factor alpha [TNF-α], and T and B lymphocytes) as well as postoperative endogenous catecholamines, which indicate a neuroinflammatory contribution.[2,23]

The solubility of anesthesia gases affects the incidence of agitation to recover consciousness. Low-solubility inhalation agents will cause different levels of recovery in brain function due to differences in inhalation anesthesia clearance from the central nervous system. This results in hearing and movement being restored first, before cognitive function returns which leads to the agitation of regaining consciousness. In addition, increased concentrations of lactate and glucose in the parietal cortex due to sevoflurane anesthesia, and the occurrence of clinically unseen epileptogenic activity of sevoflurane have been proposed as triggers for recovering conscious agitation.[9]

2.1.3 Risk Factors Agitation Recovery

Identifying the causes and risk factors of conscious recovery agitation is important. As a clinician, risk factors need to be detected and addressed to reduce incidence and prevent adverse consequences. In recovering agitation, there are several differences in risk factors for the pediatric and adult populations.[9]

Broadly speaking, risk factors for agitation of conscious recovery in children are preschool age (2–5 years), no previous history of surgery, no previous hospitalization or intervention, poor adaptability, attention deficit disorder and hyperactivity, daily patient behavior, low psychological maturity, preoperative anxiety, parental anxiety, patient and parent interaction with medical personnel, lack of premediation (with midazolam), paradoxical reactions to midazolam recorded in the child's medical history, type of surgery, use of inhaled anesthesia with a low blood–gas partition coefficient (e.g., sevoflurane and desflurane), too rapid recovery (forcibly awakened), and postoperative pain.[9,19,20,24–26]

In the adult population, conscious recovery agitation is influenced by several risk factors including age, sex, obesity (body mass index ≥ 30 kg/m2), African ethnicity, number of intubation attempts, type of surgery, emergency surgery, anesthesia method (inhalation anesthesia), duration of surgery or anesthesia, pre-existing mental health problems (e.g., psychiatric problems or cognitive impairment), chronic lung disease, recent smoking, alcohol intoxication, acute withdrawal syndrome from drug abuse (narcotics, psychotropics, and other addictive substances), anticholinergics, doxapram, premediation with benzodiazepines,

repeated intubation attempts, urgency incontinence, postoperative pain, postoperative nausea and vomiting, and the presence of invasive instruments in the patient's body (e.g., urinary catheters, chest tubes, or tracheal tubes). [9,19,20,24,25,27]

A. Age

Young adult patients (<40 years) and geriatric patients (>64 years) had a higher incidence of recovering agitation or recovering delirium compared to middle-aged surgical patients. One of the causes geriatrics to have a higher incidence is hearing impairment which can increase the incidence of agitation to recover consciousness by up to 2.3 times. In addition, children have a higher risk of experiencing recovering agitation. In pediatric patients, younger age is associated with an increased risk of preoperative anxiety that can increase the incidence of recovering agitation. Age-related physiological changes may increase the sensitivity and toxicity of the drug in patients with advanced age compared to young adults. Complications caused by conscious recovery agitation can also have more serious consequences in elderly patients.[4,9,22,28–31]

B. Gender

In the child population, sex has nothing to do with the incidence of agitation. In contrast to the adult population, some studies have shown that male sex is associated with the incidence of agitation regaining consciousness. This may be due to lower pain tolerance in men after surgery. In addition, male sex is a risk factor for bladder discomfort associated with catheters and also smoking habits which are also closely related to the increased incidence of recovering agitation.[4,30]

C. Types of Surgery

The type of operation affects the incidence of recovering agitation. In children aged 3–7 years, ophthalmology and otorhinolaryngology procedures are related to the occurrence of recovering agitation. In particular, otorhinolaryngology procedures are an independent risk factor for conscious recovery agitation. Some also mention strabismus surgery and tonsillectomy identified as risk factors for agitation of conscious recovery in pediatric patients. In the adult population, spine surgery, musculoskeletal surgery, oral cavity surgery, otorhinolaryngology surgery, breast surgery, and abdominal surgery are

closely associated with an increased incidence of recovering agitation. The duration of the action also affects the incidence of recovering agitation. Longer duration of operation is associated with an increased incidence of recovering agitation. The use of chemicals during surgery also needs to be considered, there is one case report of alcohol use in the action of celiacus plexus block triggering agitation of conscious recovery in a 66-year-old geriatric patient. [4,9,19,28,31,32]

D. Anesthesia Techniques

It is still unclear whether intravenous anesthesia or inhalation has the same effect on the incidence of regaining consciousness. In both groups, children and adults, studies have shown mixed results. There are several studies that show no significant difference between inhaled and intravenous anesthesia on the incidence of recovering agitation. However, some show TIVA (*Total Intravenous Anesthesia*) has a lower incidence of conscious recovered agitation compared to inhalation.[33] Premediation of benzodiazepines has been reported to increase the incidence of recovering agitation in the adult population. Inhaled anesthesia such as halothan, isofluran, desfluran, and sevofluran can all be triggers for recovering agitation. However, conscious recovery agitation is more common with inhaled anesthesia that has low blood-gas solubility, such as sevoflurane and desflurane. In low-blood-gas solubility inhalation agents, sevoflurane triggers conscious recovery agitation more often than desflurane. Inhalation agents that have the potential to reduce the rate of conscious recovery agitation in the pediatric population are nitrous oxide (N_{2O}). [4,9,27,28,30]

In addition to inhalation anesthetic agents, anesthesia techniques also need to discuss the involvement of neuromuscular blocking agents and their reversals. Studies that discuss such agents are still few. One study showed rocuronium-sugammadex reduced the incidence, severity, and duration of conscious recovery agitation in patients undergoing closed reduction of nasal fractures compared to succinylcholine. It is suspected that due to increased lactate and potassium concentrations, incomplete neuromuscular blockade during surgery, increased intraocular pressure, and histamine release due to succinylcholine

administration may cause greater negative effects on recovering agitation, compared to the use of rocuronium-sugammadex.[9]

E. Pain

Pain is a major risk factor for conscious recovery agitation in both children and adults, although conscious recovery agitation has been reported to occur even in painless procedures and can occur regardless of pain intensity. An increased risk of agitation recovering consciousness is common in patients with severe postoperative pain. In adults, an increased risk of agitation occurs when the postoperative numerical pain assessment scale scores ≥ 5 points.[9,28,30]

F. Preoperative Anxiety

Several studies have found a link between preoperative anxiety levels and recovering agitation. Patients with severe preoperative anxiety have an increased risk of agitation regaining consciousness. An observational study with soldiers from war zones undergoing surgery, showed that 50% of patients who experienced recovering agitation had a previous psychiatric diagnosis, such as anxiety, post-traumatic stress disorder, or depression. Not only war, stress disorders experienced in victims of natural disasters can also increase the incidence of agitation to recover consciously.[28,31,34]

2.1.4 Agitation Assessment regained consciousness

The diagnosis of conscious recovery agitation in adults is a challenge for a clinician. This is because unlike in pediatric patients, there is no validated diagnostic test to establish conscious agitation. Most studies use the Riker Agitation Agitation Scale (SSAR) or the Richmond Sedation Agitation Scale (SASR) to diagnose conscious recovered agitation, but both tools were only validated in intensive care unit patients. The SASR value used as the definition of conscious recovery agitation varies in various studies, but it can be concluded that some use the SASR value $\geq +1$, SASR $\geq +2$, and SASR $\geq +3$. The validity and reliability of SASR have also been tested in Indonesia by Pradian et al. (2014) with the results of reliability and validity being better than the Ramsay scale.[35] SASR measurement has also become the standard standard at Cipto Mangunkusumo Hospital (RSCM) based on the President Director's Regulation on RSCM Disorderly Disorder Service Guidelines. In this guideline, the patient is said to be hyperactive delirium when SASR ≥ 1.[36] A third diagnostic tool, known as the Aono four-point scale, can also be used. The advantage of this scoring is that all of these scores provide clear observer criteria between scores to minimize subjectivity and do not require the addition of category components. The thing to remember about this test tool is that it is all an agitation measurement tool and does not assess cognitive impairment.[1,2,9]

Table 2.1 Riker sedation-agitation scale (SSAR)

Score	Categories	Description
7	Dangerous agitation	Trying to remove the monitor and device or trying to get out of bed; fidgeting with restlessness; assault staff.
6	Very restless	Remains restless despite getting periodic verbally soothing words, biting the endotracheal tube, needing *restrain*.
5	Restless	Anxious or restless; trying to move; be calm by providing guarantees or reinforcement.
4	Calm and cooperative	Calm, easy to wake up, able to follow instructions.
3	Sedated	It is difficult to wake up, respond to verbal cues or gentle vibrations, but then fall back asleep.
2	Highly sedated	Unable to communicate, responding to physical stimuli but not verbal cues, may move spontaneously.
1	Unresponsive	Unable to communicate, little or no response to painful stimuli.

Source: Tolly B, Waly A, Peterson G, Erbes CR, Prielipp RC, Apostolidou I. Adult Emergence Agitation: A Veteran-Focused Narrative Review. Anesth Analg. 2021; 132(2):353–64

Table 2.2. Richmond agitation-sedation scale (SASR)

Score	Categories	Description
+4	Combative	Overtly resisting, aggressive, a direct threat to staff.
+3	Very agitated	Removing or removing the endotracheal tube or catheter; be aggressive.
+2	Agitated	Aimless frequency movement, against the ventilator.
+1	restless	Anxious but not aggressive or strong movements
0	Conscious and calm	Spontaneous full contact
-1	Drowsy	Not fully conscious, but can remain awake for a long time (opening eyes/eye contact) with a loud stimulation (>10 seconds).
-2	*Light sedation*	Drowsiness but waking up briefly with eye contact to sound (<10 seconds)
-3	Deep sedation	There is no response to sound, but there is movement or eye opening in response to physical stimuli.
-4	*Unarousable*	There is no response to sounds or physical stimuli.

Source: Tolly B, Waly A, Peterson G, Erbes CR, Prielipp RC, Apostolidou I. Adult Emergence Agitation: A Veteran-Focused Narrative Review. Anesth Analg. 2021; 132(2):353–64

Table 2.3. Aono's four-point scale

Score	Categories
1	Calm down
2	Not quiet, yet can be calmed down easily
3	Difficulty calming down, moderate agitation or agitation
4	Fighting, disorientation, hyperactivity

Source: Tolly B, Waly A, Peterson G, Erbes CR, Prielipp RC, Apostolidou I. Adult Emergence Agitation: A Veteran-Focused Narrative Review. Anesth Analg. 2021; 132(2):353–64

2.1.5 Agitation Prevention Strategy to Recover Consciousness

Prevention of agitation of conscious recovery can be done in pharmacological and non-pharmacological ways. Non-pharmacologically in adult patients, patients are educated about pain expectations and minimize the use of invasive devices attached to the patient. Pharmacologically, modifying anesthesia techniques and drug selection and the way they are administered can reduce agitation to recover consciously. In a randomized clinical trial, TIVA with propofol and remifentanil reduced the incidence of conscious recovering agitation compared to volatile induction and maintenance of anesthesia with sevofluran in children aged 2–6 years, after strabismus surgery. In adults, the effect of anesthesia techniques on the incidence of conscious recovery agitation showed mixed results. In a prospective study with 1,359 patients and a retrospective study with 488 patients, the incidence of conscious recovery agitation was no different from the anesthesia techniques used. Another study showed that conscious recovery agitation was less common with TIVA compared to inhalation anesthesia in a prospective observational study with 2,000 patients, and a retrospective study with 792 patients. In a randomized clinical trial in 80 patients undergoing nasal surgery, conscious recovery agitation

was reduced in incidence with TIVA compared to inhalation. In another randomized clinical study in 90 patients, it was found that TIVA can shorten the duration of conscious recovery agitation experienced by patients. Thus, it can be said that the use of TIVA anesthesia techniques can be considered if patients are estimated to be at high risk of agitation to recover consciousness.[9,25,33,37]

Propofol is the drug of choice for the prevention and treatment of conscious recovery agitation in pediatric patients. In a meta-analysis in pediatric patients, propofol showed a prophylactic effect on recovering agitation, depending on the time of administration. Continuous infusion of propofol during maintenance of anesthesia, or the addition of a propofol bolus at the end of surgery, showed a preventive effect against conscious recovery agitation in pediatric patients undergoing general anesthesia. However, there have not been enough studies that discuss the effect of a single dose of bolus propofol at the end of surgery on agitation of regaining consciousness in adult patients.[38]

Prophylactic administration of μ-opioid agonists (such as fentanyl, sufentanil, alfentanil, or remifentanil) has been shown to reduce the incidence of agitation of regaining consciousness after anesthesia with sevoflurane in a metaanalysis of the pediatric population. The effects of opioids on agitation of conscious recovery in adult patients have not been widely evaluated. Several studies have shown that administering opioids during recovery can reduce the occurrence of recovering agitation, but result in delays in regaining consciousness in patients.[9]

Another therapy that can reduce agitation to recover consciousness is the administration of Ketamine. Ketamine is a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, which has sedative, amnestic, and analgesic properties. Administration of ketamine (0.25 mg/kg and 0.5 mg/kg) 10 minutes before the end of surgery contributed to the prevention of agitation, recovering consciousness without delayed recovery in children after sevofluran anesthesia. Other drugs that can be given to prevent agitation recover from consciousness are magnesium sulfate and alpha 2 agonists such as dexmedetomidine.[9]

Dexmedetomidine acts on α2-adrenoreceptor receptors as an agonist agent. Its sedative and analgetic effects work to suppress the incidence of agitation to recover

consciousness. The effective dosage of dexmedetomidine has been extensively researched in several studies. There was a double-blinded randomized controlled trial that examined 3 different doses in adult patients, namely 0.25, 0.5, and 1 mcg/kg. In the study, it was shown that the dose was significantly as good in reducing agitation to recover consciousness, but the effect of cough suppression was superior when using a dose of 1 mcg/kg.[39] Studies in other pediatric populations showed that a dose of 0.5 mcg/kg compared to 1 mcg/kg was equally effective in reducing the incidence of resuscitation agitation, but a dose of 0.5 mcg/kg had a shorter duration of extubation, wakefulness, and post-anesthesia treatment duration than 1 mcg/kg.[12] In geriatric patients over 70 years of age, the required dose of dexmedetomidine infusion is even lower. In this population, ED50 prevention of conscious recovery agitation was achieved at a dose of 0.3 mcg/kg/hour while ED95 was predicted to be 0.42 mcg/kg/hour.[40] The timing of administration of dexmedetomidine for the prevention of conscious recovery agitation is still not standard, but there is 1 study that shows that giving dexmedetomidine at the end of the action is better at preventing conscious recovery agitation compared to giving it at the beginning of the action. In 1 metaanalysis, it was stated that in addition to agitation of regaining consciousness, other problems such as cough, nausea and vomiting, chills, and pain can be prevented also by dexmedetomidine with the disadvantage of prolonging the extubation time but the length of duration is not clinically significant, with an estimated 1-8 minutes and an average time of 2 minutes. [41,42]

Magnesium sulfate is one of the agents that can prevent agitation from recovering consciously.[43] As an NMDA antagonistic agent, magnesium sulfate can act as a sedative and analgesic agent. In studies in adult patients undergoing mastectomy and in pediatric patients undergoing ophthalmology surgery, administration of magnesium sulfate 10% bolus 30 mg/kg followed by an infusion of 10 mg/kg/h was effective in reducing the incidence of regaining consciousness. In urological and abdominal surgery, magnesium sulfate can reduce discomfort due to the insertion of a urinary catheter. Until now, there is no standard dose used.[44–46]

2.2 Pharmacology of Dexmedetomidine

Dexmedetomidine, or 4-[(1S)-1-(2,3-dimethylphenylethyl]-1H-imidazole, with the chemical group C13H16N2 is a S-enantiomer dextrorotation of medetomidine, a kind of agent used in veterinary medicine. α2-adrenoreceptor receptor agonist agents (clonidine and dexmedetomidine) have sympatholytic, analgesic, and sedative properties. Several studies have shown that α2 agonists can reduce the incidence of agitation, recover consciously, and are much superior compared to midazolam to reduce the incidence. In pediatric patient studies, Dexmedetomidine was found to reduce the incidence of conscious recovery agitation compared to placebo. Moreover, it is said that its effect to reduce agitation of conscious recovery is superior compared to propofol, midazolam, fentanyl, and sufentanil.[1,2,9,47]

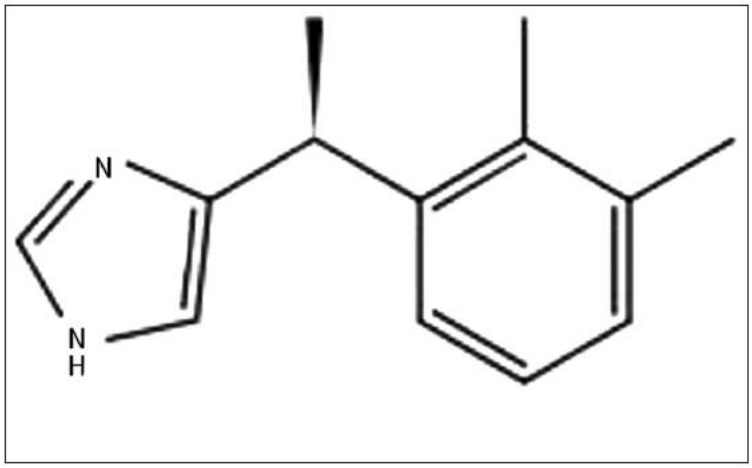


Figure 2.1 Chemical group dexmedetomidine

Source: Kaur M, Singh P. Current role of dexmedetomidine in clinical anesthesia and intensive care. Anesth Essays Res. 2011; 5(2):128

2.2.1 Pharmacokinetics Dexmedetomidine

Dexmedetomidine currently has only authorized use via intravenous (IV) infusion, but a variety of other methods of administration beyond the LEBL have been studied. Extravascular use of dexmedetomidine allows the avoidance of the drastic increase in plasma levels that is common after IV administration. When administered orally, a significant first cross-section phenomenon occurs, with a bioavailability rate of only 16%. If administered through IV, dexmedetomidine has a rapid distribution phase, with a distribution half-life of six minutes and a final

elimination half-life of about two hours. The drug exhibits linear kinetics at doses between 0.2 - 0.7 micrograms (mcg)/kg/hour through IV infusions lasting up to 24 hours. In the tune, the dispensing volume of dexmedetomidine is about 118 liters. Dexmedetomidine has a high affinity for plasma proteins, with 94% of the drug bound to albumin and α1-glycoproteins. After distribution, dexmedetomidine is metabolized in the liver with an extraction ratio of 0.7. The context-sensitive half-life of dexmedetomidine varies, ranging from 4 minutes after infusion for 10 minutes to 250 minutes after infusion for 8 hours.[47–49]

Dexmedetomidine undergoes a biotransformation process in the liver. This process involves N-glucuronidation directly by the uridine enzyme 50-diphospho-glucuronosiltransferase (UGT2B10, UGT1A4), which is responsible for approximately 34% of dexmedetomidine metabolism. In addition, within liver microsomes, dexmedetomidine undergoes hydroxylation triggered by the cytochrome P450 (CYP) enzyme, specifically CYP2A6. These two metabolic processes produce metabolites that are then excreted from the body, the majority through urine (about 95%) and the rest through feces (4%). In patients with impaired liver function, it is necessary to make dose adjustments due to the lower metabolic rate.[47–49]

2.2.2 Pharmacodynamics of Dexmedetomidine

Dexmedetomidine is a beneficial sedative agent with analgesic properties, maintaining hemodynamic stability, and the ability to restore respiratory function in patients who are receiving mechanical ventilation due to its non-depressive effects on breathing. The effects of sedation, anxiolysis, and analgesia are triggered depending on the dosage of the drug administered. Working on α2-adrenoreceptors, dexmedetomidine is a highly selective α2-adrenoreceptor agonist (α2:α1 ratio of 1620:1 vs. 220:1) with a 7 to 8 times higher affinity to α2-adrenoreceptors compared to clonidine. The effect of its work is caused when it is bonded to the *G-Protein-coupled* α2-adrenrereceptor agonists subtypes α2A, α2B, and α2C each of which provide different physiological effects.[47–49]

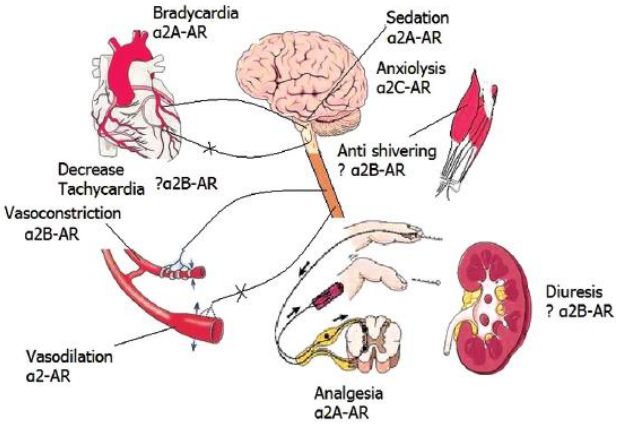


Figure 2.2. Effects of Dexmedetomidine

Source: Kaur M, Singh P. Current role of dexmedetomidine in clinical anesthesia and intensive care. Anesth Essays Res. 2011; 5(2):128

The sedative and hypnotic effects of dexmedetomidine are believed to occur through activation of α2-receptor presynapses and postsynapses at the locus coeruleus. Dexmedetomidine is also known to affect natural pathways in the body that support sleep. The sedative effect of dexmedetomidine depends on the concentration of the drug in the plasma. Plasma concentrations between 0.2 to 0.3 ng/mL produce significant sedation but still allow a person to be awakened. Deep and unawakening sedation is believed to occur at plasma concentrations above 1.9 ng/mL. The use of perioperative dexmedetomidine may reduce the dose of sevoflurane administered. In randomized studies of hyposcopy patients, it was found that doses of dexmedetomidine of 0.6, 0.8, and 1 mcg/kg reduced the MAC of sevoflurane by 38%, 48%, and 51%. In studies of patients with obesity, dexmedetomidine may reduce the MAC of sevoflurane by up to 40%.[2,9,47,50,51]

The analgesic effects of α2-agonists are believed to be mediated by binding to α2-receptors in the center and α2 receptors in the spinal cord. Pain transmission is suppressed through hyperpolarization of interneurons and reduced release of pronociceptive transmitters such as P substances and glutamate. Nonetheless, Dexmedetomidine in concentrations up to 1.23 ng/mL does not provide adequate analgesia to heat or electrical stimuli. In a crossover trial comparing the respiratory and analgesic effects of dexmedetomidine and remifentanil, plasma concentrations

of dexmedetomidine up to 2.4 ng/mL provided less effective analgesia compared to remifentanil.[9,47]

Dexmedetomidine produces a distinctive biphasic hemodynamic response, resulting in hypotension at low plasma concentrations and hypertension at higher plasma concentrations. It is thought to be derived from the activation of α2B receptors in vascular smooth muscles, which causes peripheral vasoconstriction thus causing hypertension. This process is accompanied by a rapid decrease in heart rate, which is caused by the baroreceptor reflex. After a few minutes, when the plasma concentration of dexmedetomidine decreases, vasoconstriction is weakened, as dexmedetomidine also activates α2 receptors in vascular endothelial cells, resulting in vasodilation. Together with presynaptic α2-adrenrereceptors that inhibit the release of sympathetic catecholamines, and increased vagal activity, this results in a hypotension phase. These hypotension and lowering pulse rate effects are beneficial for reducing intubation response, reducing intraoperative bleeding and creating a clearer field of operation for operators.[47,52–54]

The mechanism by which dexmedetomidine acts on peripheral α2-adrenoceptor receptors, makes dexmedetomidine also have decongestant and antisialagogue effects. Theoretically, it may reduce intestinal motility, although to the best of our knowledge, there have been no reports of associated complications. Dexmedetomidine suppresses the shivering process, possibly due to α2B receptor agonism in the hypothalamus. It provides a diuretic effect by inhibiting the action of antidiuretic hormones in the collective ducts.[48,55]

Dexmedetomidine is highly effective at preventing agitation from recovering consciousness in a multimodal manner. Activation of α2-adrenergic receptors by Dexmedetomidine produces sedative and hypnotic effects through increased activity of inhibitor neurons in the locus coeruleus of the brainstem, anxiolytic by reducing the release of stress hormones such as norepinephrine, and analgesics by reducing the release of substance P in the dorsalis cornea of the spinal cord. Some of these key mechanisms, especially their analgesic properties, make dexmedetomidine superior for preventing agitation from regaining consciousness.[56–58]

2.2.3 Drug Interactions

Dexmedetomidine reduces the need for other anesthesia such as isoflurane, sevoflurane, propofol, thiopental, and fentanyl. Observations made in abdominal surgery found that the required amount of sevoflurane was less when administered concomitantly with dexmedetomidine (*Loading Twelve* 1 μg/kg and maintenance dose 0.5 μg/kg/hour). In addition, the half-maximum effective concentration (EC_{50}) Sevoflurane to be 21% lower for insertion *Laryngeal Mask Airway* (AML) in pediatric patients when premediation with dexmedetomidine 2 μg/kg was administered intranasal For propofol, there are studies that show EC values$_{50}$ propofol for successful LMA insertion without relaxants was 3.18 μg/mL in the group receiving dexmedetomidine pre-anesthesia 1 μg/kg, compared with 6.75 μg/mL in the group receiving placebo saline.[52,59]

Dexmedetomidine can also be used for opioid-saving anesthesia. Dexmedetomidine is useful for reducing the effects of respiratory depression and nausea triggered by opioid administration. In patients who have been anesthetized, the administration of analgesics such as opioids is often given when heart rate and blood pressure rise. The lowering hemodynamic effects of dexmedetomidine may mask pain assessment and as a result lower intraoperative opioid consumption.[47,52]

The interaction between dexmedetomidine and antihypertensive agents has been investigated. Beta-blockers may cause increased effects of hypotension and bradycardia. Calcium channel blockers may relieve changes in heart rate and blood pressure associated with dexmedetomidine infusion without affecting catecholamine levels in plasma.[16]

2.2.4 Contraindications

Uncontrolled hypotension and second- or third-degree heart block (unless with a pacemaker) can potentially worsen as a result of dexmedetomidine. Comorbid acute cerebrovascular conditions are also considered contraindications because animal studies have shown decreased blood flow to the brain with dexmedetomidine. However, studies in humans have shown the maintenance of flow-metabolism linkage with decreased metabolic consumption levels in the brain that are in line with decreased cerebral blood flow.[48]

2.3 Pharmacology of Magnesium Sulfate

Magnesium (Mg++) is a divalent cation with a molecular weight of 24,303 u, the fourth most abundant cation in the body and the second at the intracellular level. Magnesium accounts for about 0.03% of the total body weight, 95% is filtered in the glomerulars and 5% is excreted through feces. Magnesium is concentrated mainly in bones (60%), muscles (20%), and soft tissues (20%). The Quarter Mg present in muscles and bones can be exchanged. Only 1% of the total is extracellular magnesium. There are three fractions of magnesium in serum: ionized (active form), bound to proteins, and contained in complex anions (phosphate and citrate). In adults, daily consumption is recommended as much as 250-350 mg (10.4-14.6 mmol) and plus 100-150 mg for pregnant women and pediatricians.[60,61]

Magnesium serves as a coenzyme for various biological processes, including protein synthesis, neuromuscular function, and nucleic acid stability. Magnesium is an intrinsic component of many adenosine 5-triphosphatase and an endogenous regulator of some electrolytes. As a noncompetitive inhibitor of calcium channels regulated by inositol triphosphate, magnesium functions as an endogenous calcium antagonist by influencing its absorption and distribution. Magnesium also exhibits a modulating effect on sodium and potassium currents, thus affecting the membrane potential. Magnesium also has a depressant effect on the intestinal nervous system because it functions as an antagonist of the N-methyl-D-aspartate (NMDA) glutamate receptor and an inhibitor of catecholamine release.[60–63]

2.3.1 Pharmacokinetics of Magnesium Sulfate

Magnesium sulfate has the chemical name magnesium sulfate heptahydrate (MgSO4.7H2O). The maintenance of magnesium homeostasis is largely regulated by intestinal absorption and renal excretion. Magnesium ions are absorbed by the small intestine, especially when administered orally. Magnesium is absorbed in the small intestine through two different pathways that depend on the dosage and dietary intake formula. Magnesium is absorbed via active transcellular transport at low intraluminal concentrations, but at high concentrations magnesium is absorbed through passive diffusion. When magnesium levels are normal, about 40-50% of the magnesium consumed can be absorbed. The absorption of magnesium appears to be somewhat inhibited by fiber, phytic, and oxalic acid through the formation of

complexes that are difficult to decompose. The binding of magnesium with anions (phosphates) or fatty acids also reduces the amount of magnesium absorbed. As the amount of magnesium consumed increases, the fraction of magnesium absorbed also decreases. A decrease in magnesium levels can also occur due to two main factors, namely loss of magnesium through digestion and kidneys. Loss of magnesium through digestion can occur as a result of various conditions that cause diarrhea or disorders of the bile ducts. Loss of magnesium through the kidneys can occur as a result of various conditions, such as the use of diuretics, gentamacis, cisplatin, and cyclosporine. When magnesium is administered intravenously (IV), onset is rapid, with peak effects obtained within 10 minutes, and with a duration of 30 minutes. For the intramuscular (IM) pathway, the onset is slower and only reaches the peak effect in 60 minutes with a half-life of 4 hours.[61,63]

The largest distribution of magnesium is intracellular. As much as 99% of the total magnesium is in the intracellular space (53% to 60% is found in bone tissue, 20% to 27% in muscle tissue, and 19% in soft tissue) and 1% is in extracellular (60% ionized, 30% protein-bound, and 10% anion-complex). The magnesium elimination route, mostly through the kidneys (figure 3). Magnesium excretion averages about 3-5 mmol/day, but can be reduced to 0.5 mmol/day when severely deficient in magnesium. About 80% of the magnesium flowing through the kidneys is ultrafiltrated and enters the tubules, but more than 95% is resorbed by small portions of the nephron. The most important part of this process takes place in the Henle ansa, the thick ascendant branch to be precise. In this part, about 70% of magnesium is reabsorbed passively, following the flow of sodium and chloride that are also reabsorbed. A special protein called claudin 16 plays an important role in this process. The loss of function of this protein due to genetic mutations can lead to a rare disorder in humans, in which magnesium is abundantly wasted through the urine.[61,63,64]

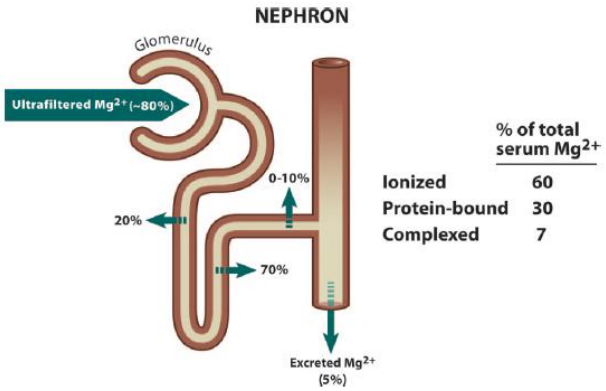


Figure 2.3. Excretion of magnesium

Source: Warner DS, Herroeder S, Scho ME. Magnesium — Essentials for Anesthesiologists. 2011; (4)

The regulation of magnesium transport has no specific endocrine control, although some hormones have been proposed to alter magnesium homeostasis. Parathormones and vitamin D stimulate magnesium reabsorption in the kidneys, specifically the henle anna and distal contortus tubules, and intestines. In addition to aiding in the absorption process of the kidneys and intestines, parathormones remove magnesium from the bones. While insulin can reduce the kidney's magnesium excretion and increase its absorption by cells.[61]

2.3.2 Pharmacodynamics of Magnesium Sulfate

Magnesium sulfate has several known mechanisms of action (Figure 4), namely the activation of the Na-K-ATPase pump which can be inhibited in the state of concentration of Mg^{2+} a high, competitive antagonist to calcium channels that provides the characteristics of blocking presynaptic acetylcholine release and increasing the potential threshold of postsynaptic action, blocking the release of catecholamines from the adrenal glands and adrenergic nerve endings, as well as reducing the release of cytokines (IL-1, IL-6, TNF-α, and substances P) and inhibition of platelet aggregation, non-competitive antagonists against R-NMDA, sinusoidal and atrioventricular (AV) blocks, PR prolongation, and QRS dilation. Each of these mechanisms is dose-dependent, which involves the risk of toxicity at high doses.[63]

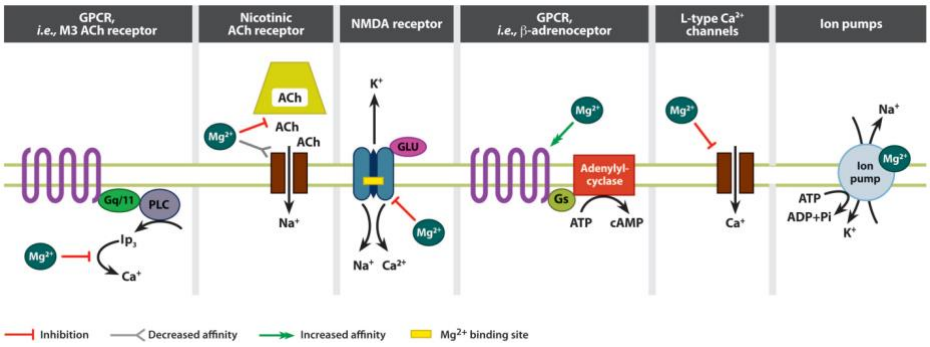


Figure 2.4. Magnesium Site and Mechanism of Action

Source: Warner DS, Herroeder S, Scho ME. Magnesium — Essentials for Anesthesiologists. 2011; (4)

Magnesium is important for regulating the flow of essential ions such as potassium and calcium within cells. If the magnesium level is too low, potassium will easily escape from the cell, interfering with cell function and metabolism. Magnesium also affects the movement of calcium through specialized channels in the cell membrane and within the sarcoplasma reticulum, the main place of calcium storage in cells. Magnesium acts like a "gatekeeper" that slows the entry of calcium and prevents the excretion of excess calcium from the sarcoplasmic reticulum. As a result, if magnesium deficiency (hypomagnesemia) occurs, calcium levels in the cells can actually increase.[60]

Magnesium sulfate as mentioned earlier, is a kind of noncompetitive NMDA receptor antagonist, which has a central sedative, neuroprotective, and analgesic saving-effect.[63,65] Its mechanism that is antagonistic to NMDA causes the inhibition of the entry of calcium to neurons and prevents other neurotransmitters from being released, as well as activating neuronal aptoptosis. Reduced release of catecholamines from the adrenal marrow and the antagonistic effects of calcium on vascular smooth muscle cells may also contribute to the effects of magnesium anesthesia. This effect makes magnesium sulfate one of the controlled hypotension agents that is quite effective in cases of synasal surgery.[66] In the case of neuromuscular blockade, inhibition of calcium-mediated acetylcholine release from presynaptic nerve terminals in the neuromuscular junctio plays an important role. Decreased postsynaptic sensitivity to acetylcholine and direct effects on myocyte

membrane potential may also contribute to the potentiating effects of neuromuscular blockade.[61,63]

The work of NMDA receptors with neuroprotective and anticonvulsant properties of magnesium sulfate can reduce the incidence of agitation of recovering consciousness. It is widely reported that magnesium sulfate reduces the consumption of propofol, neuromuscular inhibitors, and morphine postoperatively in gynecological surgical patients. In another study involving gynecologic patients undergoing laparotomy under TIVA, pain scores, analgesic consumption, and the incidence of chills were lower in the magnesium group compared to the control group, and it was concluded that magnesium sulfate improved the quality of postoperative analgesia during TIVA.[1,9,62,63]

2.3.3 Dosage and Drug Interactions

Magnesium (Mg) can be given orally or through intravenous (IV) injections. Administration via intramuscular injection is also possible although it can cause pain. Daily doses of magnesium given orally of more than 50 mmol can cause vomiting and diarrhea. In anesthesia and intensive care, IV administration is preferred. There are two forms of magnesium that can be injected, namely magnesium chloride and magnesium sulfate. Ten milliliters of 10% magnesium chloride solution provide 1 gram of Mg salt (118 mg Mg), while 10 mL of 10% magnesium sulfate solution also provides 1 gram of Mg salt (98 mg Mg).[60]

The dosage of magnesium is adjusted based on medical needs. To overcome magnesium deficit, a slow infusion of up to 10 grams per day is recommended. In use for pharmacological effects, a rapid infusion of 1-2 grams of MgSO4 for ten minutes, followed by a continuous infusion of 0.5-1 grams per hour (or 0.25 grams per hour for patients with kidney problems) is required to achieve the desired plasma concentration. Its use as intraoperative analgesia can be given at a loading dose of 30–50 mg/kg and continued infusion at 6–20 mg/kg/h until postoperatively or for 4 hours after the loading dose.[65,67] In obese patients with a BMI of 30-45 its use can be used either actual weight or corrected weight because there is no significant difference in the effect of its analgesia and the increase in its magnesium levels.[68]

Electrocardiography monitoring to serum magnesium concentration measurements are routinely performed in patients who are given magnesium, especially at large doses. The use of magnesium for tocolysis showed side effects such as fever and headache more frequently at high doses (5 g per hour) than at low doses (2 g per hour), with more cases of pulmonary edema in the high-dose group. However, in the MAGPIE trial, the risk of pulmonary edema between the magnesium and placebo groups recorded no significant difference. In another study, it was said that an intravenous regimen with an initial dose of 8 grams for 60 minutes followed by 2 grams/hour for 10 hours and 12 grams for 120 minutes followed by 2 grams/hour for 8 hours would produce magnesium concentrations below the toxic range. Another study comparing a dose of 2 g/hour with 1 g/hour, showed side effects at doses of 2 g/hour more frequently. However, the side effects caused are mild such as nausea, vomiting, dizziness, and redness without severe side effects. In this study of both groups, only 16% of the 2/hour dose group achieved magnesium levels of 4-7 meq/mL. From several studies that have been described, it can be said that magnesium sulfate has a wide therapeutic index so that its safety is quite good [45,60,67,69]

Magnesium abnormalities in the blood or dysmagnesemia can be in the form of hypermagnesemia or hypomagnesemia. Hypomagnesemia, defined as plasma magnesium levels below 0.7 mmol/L, can be caused by a variety of factors such as inadequate intake, impaired intestinal absorption, or increased renal excretion. Symptoms of hypomagnesemia are often non-specific and can overlap with other electrolyte disorders. Common clinical manifestations include muscle weakness, positive Trousseau and Chvostek signs, hypokalemia, and hypocalcemia.[60,61]

Magnesium is generally very safe for cardiovascular. Excessively high magnesium levels (hypermagnesemia) are rare, except in people with kidney disorders who are exposed to additional sources of magnesium. In the treatment of seizures due to eclampsia, the magnesium level that is considered beneficial is 4-8 mg/dL. If the level is above 9 mg/dL, magnesium is considered harmful. Early symptoms of magnesium poisoning are usually loss of knee reflexes (at 12 mg/dL), nausea, warmth, redness, drowsiness, double vision, glare speech, and weakness. Muscle paralysis and respiratory failure can occur at levels of 15-17 mg/dL, while cardiac

arrest at levels exceeding 25 mg/dL. Thus, in the administration of magnesium, especially in large doses, it is necessary to monitor electrocardiography, respiration, urine production, and tendon reflexes. There have been two reports of magnesium poisoning: the first was due to receiving 13 grams of magnesium through an IV for 40 minutes during surgery, and the second was due to the mistake of giving 25 grams of magnesium sulfate (which should have been 4 grams). When hypermagnesemia occurs, the main treatment is to stop the intake of additional magnesium. In emergency conditions, such as life-threatening neurological and cardiovascular complications, calcium infusions may be given temporarily to counteract the effects of magnesium. Calcium doses can be administered at about 2.5-5 mmol or 15 mg/kg through intravenous infusion slowly with a slow bolus with a rate exceeding 10 minutes or some sources do so with continuous infusions of 4 hours, until the heart's electrical conduction disorders disappear.[60,67,70,71]

Drug interactions need to be thought about when using magnesium sulfate. Magnesium sulfate can interact synergistically with hypnotic anesthetic agents (sevoflurane and propofol) and non-depolarizing relaxants, thereby reducing the dose of the drug administered. A meta-analysis showed that magnesium administration can accelerate onset and prolong the duration of rocuronium's action.[72,73] Calcium interacts antagonistically with magnesium sulfate, even becoming an antidote in cases of magnesium poisoning. Administration, along with antiarrhythmia drugs, needs to be careful, especially in calcium channel blockers which can synergistically lower blood pressure. The use of some types of corticosteroids can reduce serum magnesium levels.[63]

The benefits of magnesium for postoperative analgesia are not limited to general anesthesia. Recent studies suggest that magnesium sulfate may also have a beneficial role in spinal anesthesia when administered through the intravenous or intratecal route. Magnesium can prevent the induction of central sentivity from peripheral nociceptive stimuli at the spinal action site by inhibiting NMDA receptors. By the same mechanism, when small doses of magnesium sulfate are added to local anesthesia for spinal anesthesia, the duration of anesthesia becomes longer, the need for postoperative analgesics is reduced, and the side effects of high doses of local anesthesia and opioids can be reduced.[74,75] Intraoperative use of

magnesium sulfate may be associated with a reduced incidence of nausea and vomiting after surgery which may be due to the lower use of a volatile anesthetic (sevoflurane) than the antiemetic effect of magnesium sulfate itself.[62]

Magnesium sulfate also needs to be administered carefully by an anesthesiologist. The use of magnesium sulfate can cause cardiovascular depression by acting as a calcium channel blocker. The inhibition reduces the release of catecholamines thereby reducing the concentration of epinephrine and norepinephrine in plasma after endotracheal intubation, and thus reduces the hypertensive response during anesthesia induction. The use of magnesium sulfate should be done with caution in hypovolemic patients and in patients with limited cardiac capacity. In addition, an initial dose of magnesium sulfate at a slow pace (>10 minutes) can minimize cardiovascular side effects such as hypotension and bradycardia.[62]

2.3.4 Contraindications

Absolute and relative contraindications to magnesium sulfate administration include allergy to magnesium supplementation, atrioventricular block, and neuromuscular diseases such as myasthenia gravis.[61]

2.4 Theoretical Framework

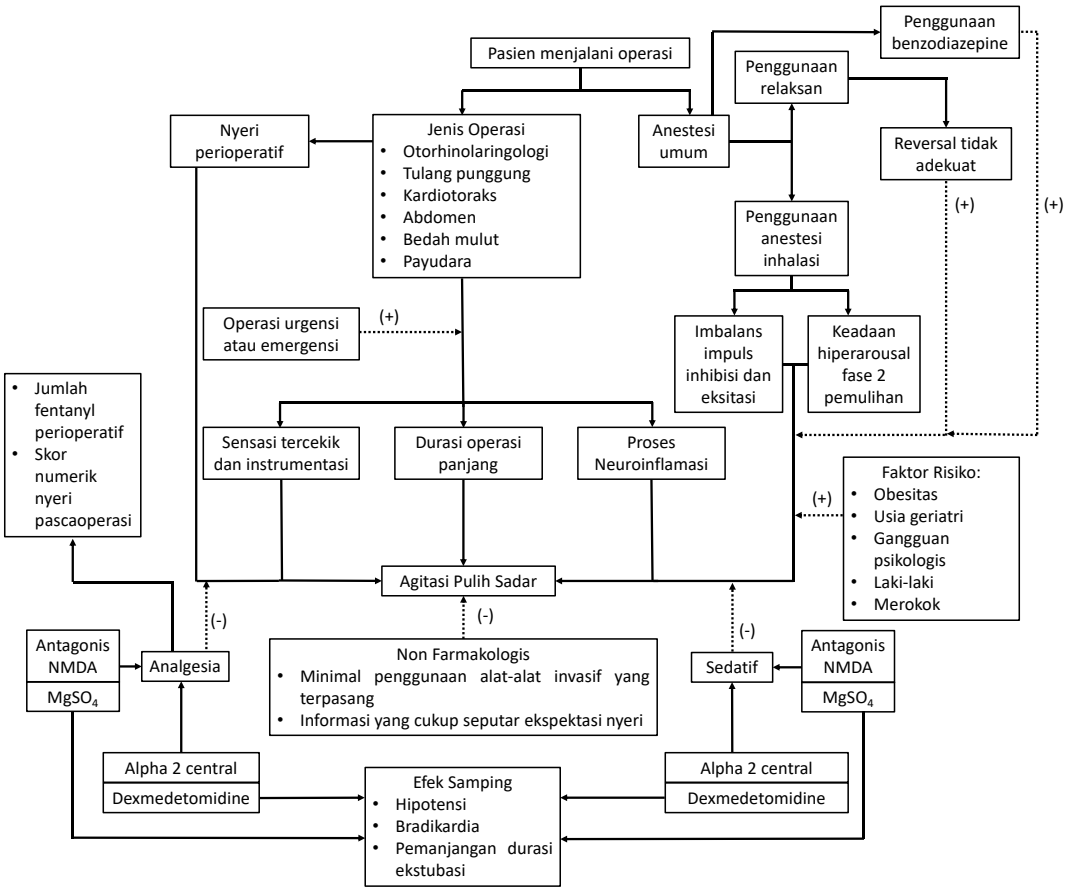


Figure 2.5 Theoretical Framework

2.5 Concept Framework

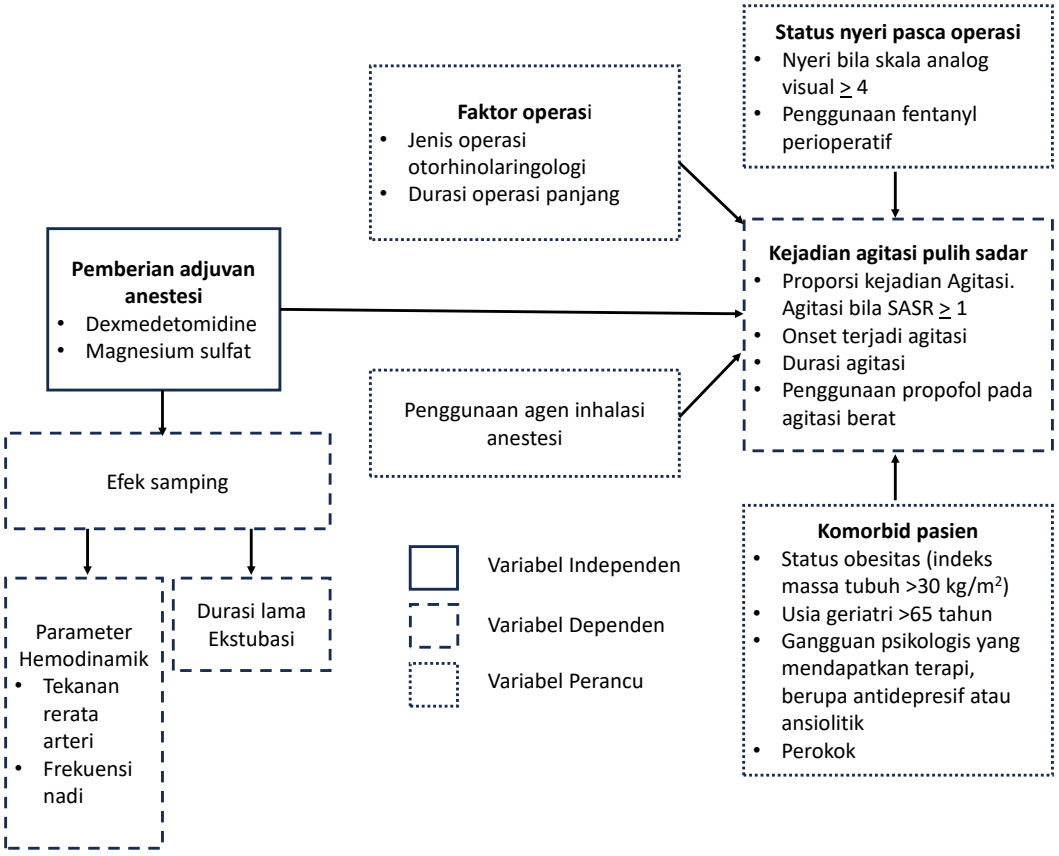


Figure 2.6 Concept Framework

BAB 3
RESEARCH METHODS

3.1 Research Design

The research design to be used is a controlled randomized trial design. This study will be conducted prospectively with sample allocation carried out randomly using random numbers on the randomization tool (randomization device according to www.randomizer.org). The data collection of this research will be carried out in a double disguise where the sample and the data taker, in this case the researcher, do not know the type of treatment obtained. In this study, those who know the treatment are third parties who are not involved in data collection and analysis.

3.2 Place and Time of Research

The research will be carried out in the operating room of the Kanigara National Central General Hospital (RSUPN) dr. Cipto Mangunkusumo and the central surgical installation of the University of Indonesia Hospital (RS) for 3 months. Sampling began in April 2024 to June 2024 after the ethics and location review was passed

3.3 Population and Research Sample

The target population of the study is adult patients who will undergo elective otorhinolaryngology region surgery. The affordable population in this study was adult patients undergoing otorhinolaryngology elective surgery in the Kanigara operating room of Dr. Cipto Mangunkusumo Hospital and the central surgical installation of the University of Indonesia Hospital. The research sample was adult patients who underwent otorhinolaryngology elective surgery in the Kanigara operating room of Dr. Cipto Mangunkusumo Hospital and the central surgical installation of the University of Indonesia Hospital from April to June 2024 who met the inclusion criteria and were not excluded by sample selection using a random sampling method.

3.4 Inclusion and Exclusion Criteria

3.4.1 Inclusion Criteria

a. Adult patients 18 – 70 years old
b. ASA elective surgical patients 1 and 2
c. Undergoing a general anesthesia procedure

3.4.2 Exclusion Criteria

a. Pregnant patients
b. Patients with severe cognition impairment and decreased consciousness
c. Patients refuse to participate in the study
d. Patients allergic to medications used throughout the study
e. Patients with contraindications to the administration of intervention agents: atrioventricular block, sinoatrial node dysfunction, renal failure
f. Patients with neuromuscular disorders
g. Patients with regular consumption of beta-blockers or clonidines
h. Postop patients are not extubated in the operating room or in the PACU
i. Patients with BMI ≥ 40

3.4.3 Production Criteria

a. Serious adverse events (mortality and serious morbidity)
b. Postoperative patients with no plans to the ICU on a ventilator

3.5 Large Sample

The sample size needed for each group in this study is based on the sample size formula of comparative analysis of unpaired categorical variables.

Large sample size of unpaired categorical variables:

$$n1 = n2 = \left(\frac{(Z_{1-\alpha} + Z_{1-\beta})^2 \, (P_1(1-P_1)+P_2(1-P_2))}{(|P1-P2|-\Delta)^2}\right)$$

n1 = n2 = sample size in one of the groups

N = 2n = total sample size

Alpha (α) = Type one error, set to 5%

Zα = 5% alpha standard value, i.e. 1.64

Beta(β) = Type two error, set 20%

Zβ = The standard beta value is 20%, which is 0.84.

P1 = Proportion of magnesium sulfate group. The proportions are set to be equivalent to dexmedetomidine

P2 = Proportion of dexmedetomidine group = 0.056 (Salman)[1]

Δ = The maximum margin of difference set so that magnesium is considered not inferior to dexmedetomidine. Researchers set 0.15

So with this value is obtained:

$$n1 = n2 = = 29 \left(\frac{(1.64+ 0.84)^2 \ (0.056(1-0.056)+0.056(1-0.056))}{(|0.28-0.28|-0.15)^2}\right)$$

Based on the formula above, the sample size was 29 people per group and added 10% drop out, so that the total number of samples was 64 (32 samples per group).

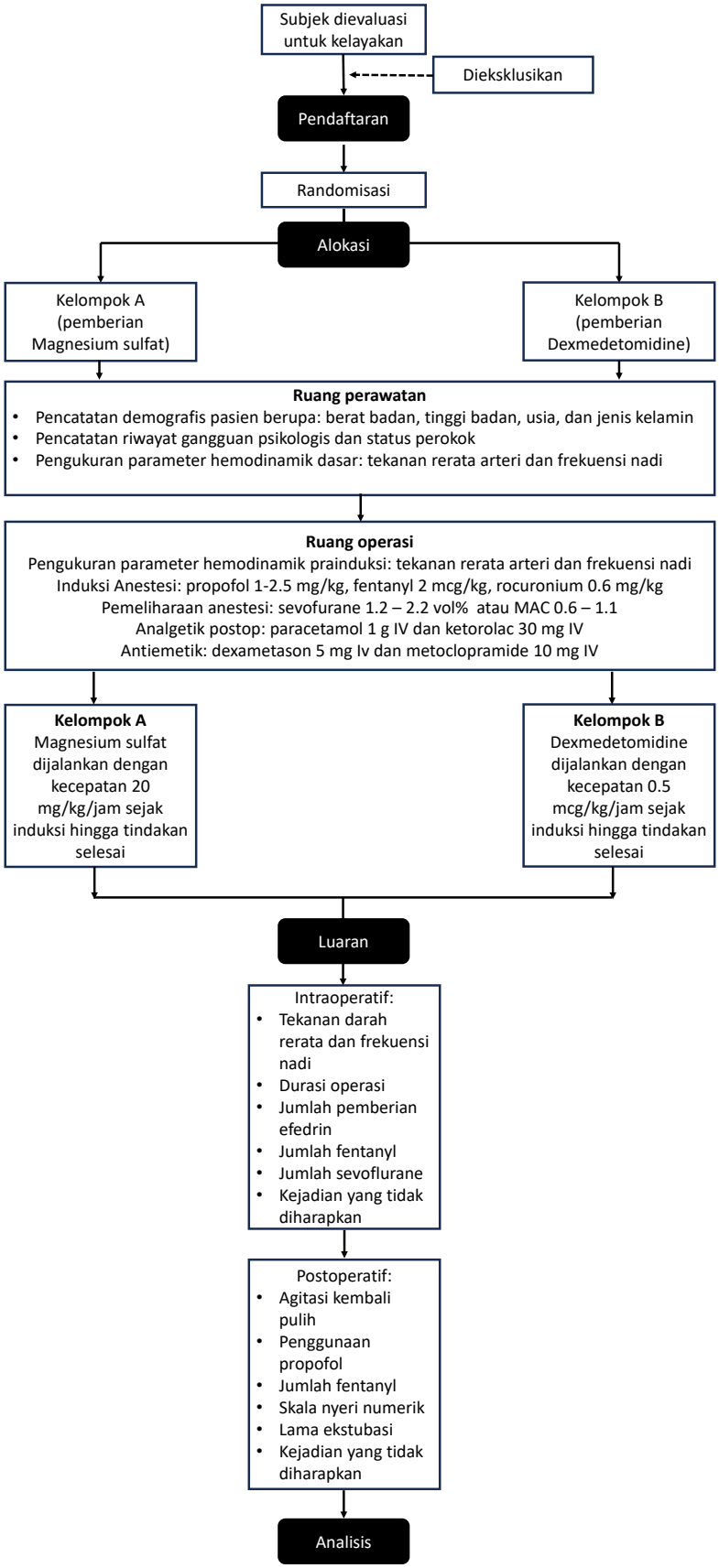
3.6 Tools and Workpieces

1. Work Tools
   a. Spray 50 mL
   b. Spray 3 mL
   c. Syringe 5 mL
   d. Spray 10 mL
   e. Perfuser pipe

f. *Syringe pump*
g. Non-invasive blood pressure, pulse frequency, oxygen saturation, end-tidal carbon dioxide and electrocardiogram
h. Anesthesia machine with oxygen and compressed air source
i. Intravenous catheter
j. Syringe 18 G
k. Endotracheal pipe no 7.0/7.5
l. Stationery
m. Research form

2. Workpiece
   a. Kabimidin® 100 mcg/mL
   b. MgSO4 20%
   c. NaCl 0.9% 100 mL
   d. Paracetamol 1000 mg IV preparation
   e. Ketorolak 30 mg/mL
   f. Fentanyl 50 mcg/mL
   g. Sevofluran
   h. Propofol 10 mg/mL
   i. Rocuronium 10 mg/mL
   j. Ephedrine 10 mg/mL
   k. Dexamethasone 5 mg/mL
   l. Metoclopramid 5 mg/mL
   m. Neostigmine 0.5 mg/mL
   n. Sulphas atropine 0.25 mg/mL
   o. Calcium gluconase 100 mg/mL

3.7 Research Flow



3.8 Research Procedure

1. Recruitment of subjects will begin after passing the ethics review and exit location permits
2. Patients who meet the inclusion criteria and do not meet the exclusion criteria will be given an explanation by the researcher. Patients are taken as research subjects after being educated to understand the researcher's explanation, approve, and sign the research approval sheet.
3. Randomization is done by a third party, who is not involved in the research process, to determine the type of treatment to be given. Randomization is carried out using random numbers on the randomization tool (randomization device according to www.randomizer.org). The treatment obtained can be divided into 2 groups with a ratio of 1:1, namely group A who received Dexmedetomidine therapy and group B who received 10% Magnesium sulfate. The results of this randomization were placed in a numbered envelope which was then handed to the researcher. In this case, the researcher does not know each of the contents of the envelope. This envelope, which contains the type of treatment given, is then handed over to the pharmacy team before starting anesthesia.
4. An instruction sheet on how to mix treatment drugs is handed over to the pharmacy team. The instruction sheet contains a speed formula that gives the same speed results between the 2 groups, so the type of treatment is unknown to the researcher and the anesthesia team (figure 4). The pharmaceutical team compounded the drugs according to the instructions which were then labeled with the patient's identity and the label "Research Drugs dr. Yunda" with calculated speed and research number.

CARA PERACIKAN OBAT PENELITIAN DR. YUNDA

Alat dan Bahan: Spuit 50 mL, NaCl 0.9% 100 mL, needle 18 G, perfusor/tabung ekstensi no 1, dan obat penelitian

Bila mendapatkan amplop Dexmedetomidine (200 mcg/2 mL):
1. Spuit 50 mL diisi dengan 1 mL Dexmedetomidine dan 39 mL NaCl 0.9%. Konsentrasi saat ini 2.5 mcg/mL
2. Hitung kecepatan dosis 0.5/mcg/kg/jam dengan rumus berikut:

$$\frac{BB \times 0.5 \times 40}{100} = \frac{BB}{5} = \text{xx mL/jam}$$

3. Tuliskan kecepatan obat di label yang telah disediakan

Bila mendapatkan amplop $MgSO_4$ 20% (5 g/25 mL):
1. Spuit 50 mL diisi dengan 20 mL $MgSO_4$ 20% dan 20 mL NaCl 0.9%. Konsentrasi $MgSO_4$ saat ini 100 mg/mL atau $MgSO_4$ 10%
2. Hitung kecepatan dosis 20 mg/kg/jam dengan rumus berikut

$$\frac{BB \times 20 \times 40}{4000} = \frac{BB}{5} = \text{xx mL/jam}$$

3. Tuliskan kecepatan obat di label yang telah disediakan

Figure 3.1. Instructions on How to Compound Research Drugs

The division of this therapy or treatment is unknown to the anesthesia team and the research team. As long as the action is the data is taken and recorded by the researcher, not by the anesthesia team.

5. The anesthesia procedure will be performed with the researcher and the anesthesia team of the operating room. The anesthesia team here is tasked with providing ventilation, intubating, and maintaining the condition of intraoperative patients. Researchers, in addition to data loggers, will be in charge of entering induction drugs and research drugs. Before the patient is pushed into the operating room, a venous access with the number 18 or 20 G is installed.
6. Upon arrival at the operating room. The patient was fitted with monitoring devices, in the form of: non-invasive blood pressure, ECG, oxygen saturation, etCO_2, and temperature. The researcher as a data taker will record the values of the average arterial pressure parameter and pulse frequency before induction. All treatment therapies, both group A and B are initiated when the patient is induced without using the initial charge dose.
7. After the monitor is installed and the treatment drug is ready to be installed in the patient's infusion, the research drug begins as soon as the patient starts preoxygenation 100% oxygen flow of 6 liters per minute with a duration of 3 minutes. After 3 minutes after administering the study drug, subjects were

given fentanyl opioids 2 mcg/kg IV body weight as coinduction and propofol titration induction agent 1-2.5 mg/kg body weight. Before being inserted into the relaxant, a neuromuscular monitor in the form of *a train of four* (TOF) was installed. Then it was followed by the administration of rocuronium 0.6 mg/kg. Before inserting the laryngoscope, propofol is given again at 0.3-0.5 mg/kg according to the patient's pulse rate and blood pressure. Then the anesthesia team intubated with ETT number 7.5 for men and 7.0 for women. Once intubated, sevoflurane can be delivered with a clinically appropriate target, MAC 0.6-1.1 or 1.2 – 2.2 vol%. The subjects' hemodynamic parameters, in the form of mean arterial pressure and pulse frequency were recorded by the researcher after induction and postintubation drug administration.

8. After the subjects were intubated, dexamethasone 5 mg IV was administered for the prevention of postoperative occurrence of nausea and vomiting. The administration of paracetamol 1 gram IV postoperative analgesia was also given within 30 minutes after intubation. Researchers recorded mean arterial pressure and pulse frequency shortly after the incision and 30 minutes post-incision
9. During the action, the maintenance of the depth of anesthesia is administered sevoflurane MAC 0.6-1.1 or 1.2 – 2.2 vol%. Fentanyl administration of 1 mcg/kg of body weight and rocuronium 0.2 mg/kg of body weight can be administered intraoperatively when deemed necessary. The ventilator is set in pressure or volume mode with a tidal volume of 6-8 mL/kg body weight and its breathing rate is set to the normocarb target ($etCO_2$ 35 – 45 mmHg). During intraoperatively, the average arterial pressure was kept from falling beyond 30% of baseline and the pulse rate did not drop <50 times per minute or drop more than 30% from baseline in the healthy adult population with an initial pulse value of 50-60 times per minute. If this happens, then the management is in accordance with the intraoperative emergency protocol. Ephedrine use is recorded over time. The temperature is also maintained in the range of 36 – 37^0 C. The

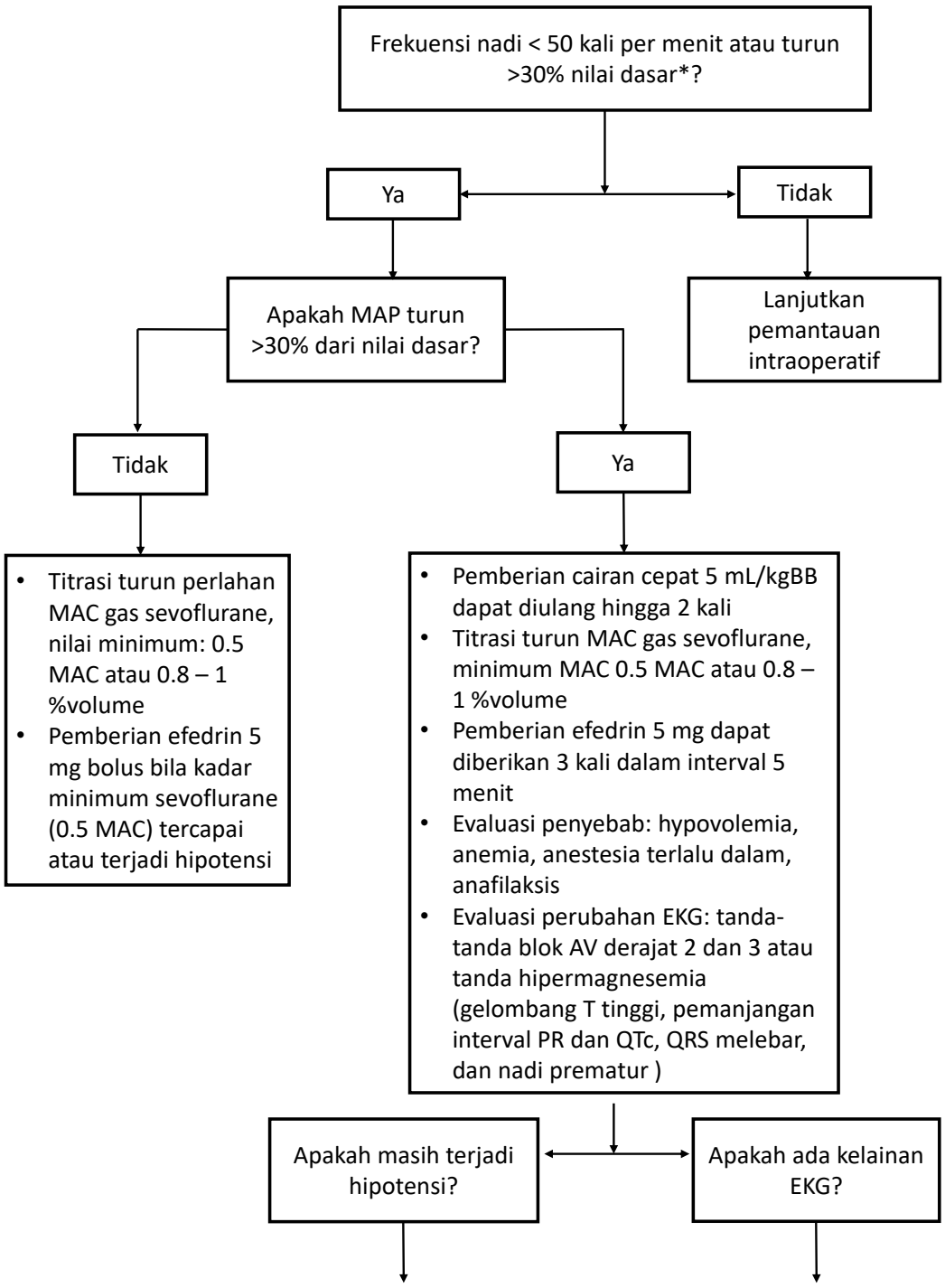
temperature will be maintained by providing a warming mat, a convective forced heating device, and warm infusion.

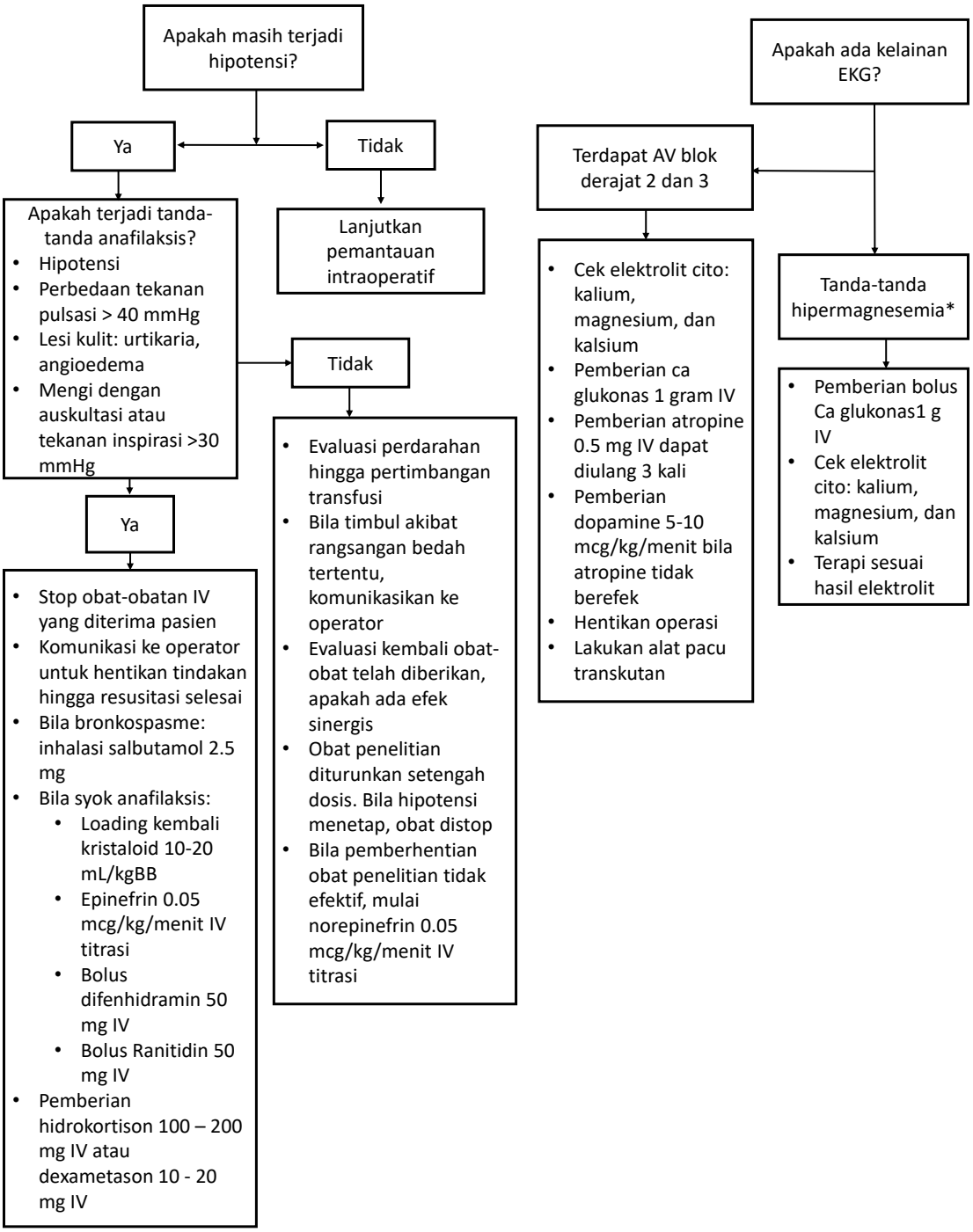
10. Study subjects will be given 10 mg metocloromidi for the prevention of nausea and vomiting and 30 mg IV ketorolac for postoperative analgesia at surgical completion and before extubation.
11. When the action was completed, the study subjects were given a neuromuscular block reversal agent in the form of neostigmine 0.04 mg/kg and sulphas atropine 0.02 mg/kg if the TOF count was 4 and the TOF ratio was at least 0.4. After that sevoflurane and research drugs were discontinued. An air flow of 6 liters per minute is set to drain out the sevoflurane. After the tidal volume was reached 6 mL/Kg with $etCO_2$ 35-45 and the subject responded to verbally, the subjects were consciously extubated without being stimulated by previous pain stimuli or repeated patting. Stimulation that can only be done is in the form of verbal stimulation or occasional touch.
12. The incidence of agitation recovering consciously was recorded in the form of a SASR score by the researcher. The zero time of agitation measurement is when the anesthetic gas is stopped and the end time is 30 minutes post-extubation. The SASR score recorded was the highest score in patients. When agitation occurs, namely SASR ≥1, the researcher records the onset and duration of agitation. If there is agitation that endangers the patient and the medical team with a SASR scale of ≥+3, the researcher or anesthesia team gives propofol 0.3 - 0.5 mg/kg body weight and can be repeated until calm. The number of doses of propofol used were recorded by the researchers. The length of the extubation was also calculated and recorded in the research sheet by the research team at the time the drug was discontinued until the patient could be extubated.
13. Patients were pushed to the recovery room or PACU to be evaluated for postoperative pain with a numerical pain assessment scale and re-evaluation of mean arterial pressure and pulse frequency 1 hour postoperatively. While at PACU, patients were also tested for tendon reflexes and muscle strength. If hyporeflexes and areflex occur, calcium gluconas as much as 15 mg/kg is given with a slow bolus of >10 minutes and the patient's magnesium levels

are checked. Patients can move to the room if the Aldrette score is ≥9 after 1 hour of observation

3.9 Perioperative Disorder Management Protocol

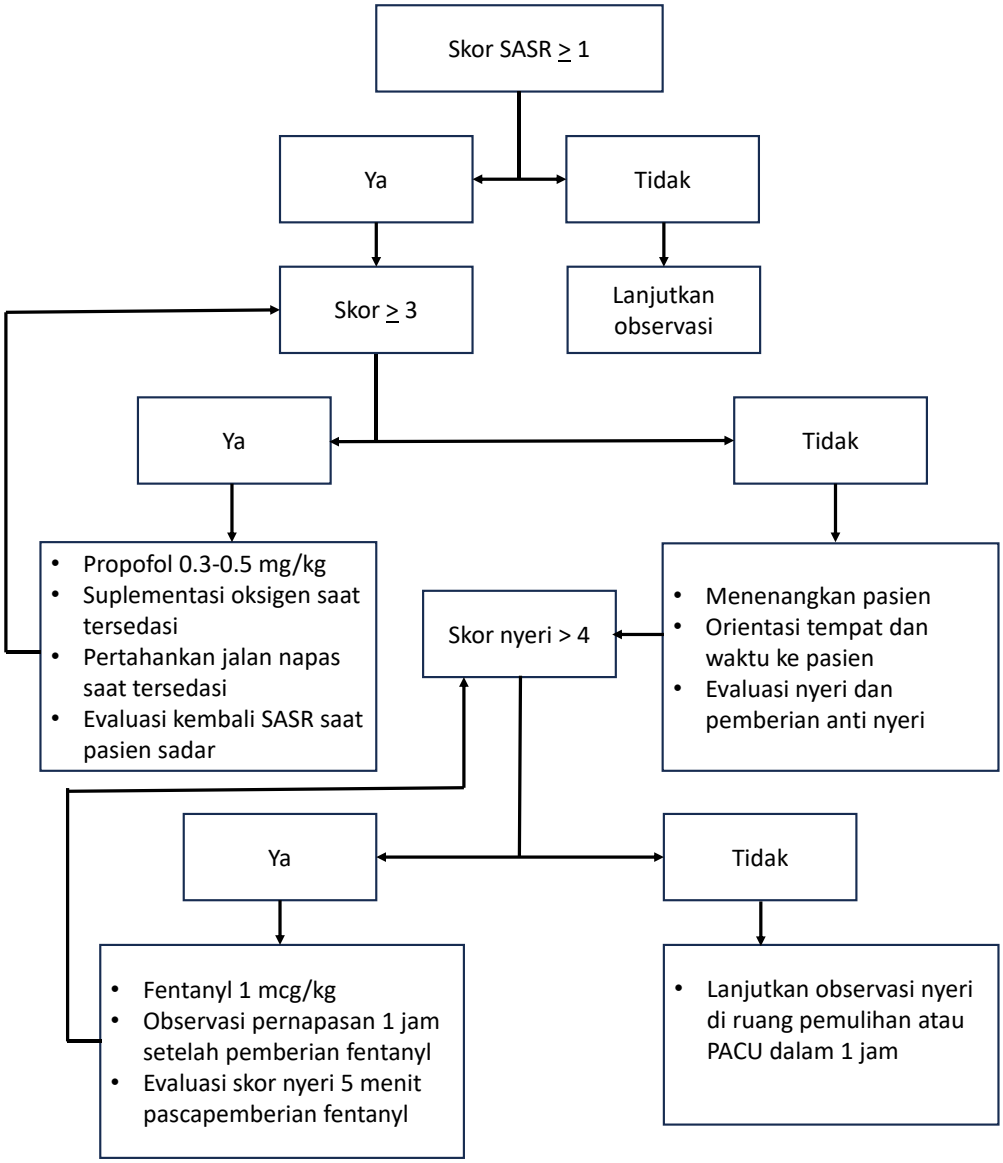
3.9.1 Intraoperative Hemodynamic Disorders Protocol





* Pada pasien dewasa sehat dengan nadi awal 50-60 kali per menit
** Gelombang T tinggi, pemanjangan interval PR dan QTc, QRS melebar, dan nadi prematur

3.9.2 Recovery of Consciousness Agitation Protocol



3.10 Operational Definition

Independent Variables

a. Subjects who get Dexmedetomidine
b. Subjects who get MgSO4

Dependent Variable

a. Events of agitation regain consciousness after surgery
b. The Onset of Conscious Agitation
c. The duration of the agitation regained consciousness

d. Intraoperative hemodynamic changes (mean arterial pressure and pulse rate)
e. Perioperative fentanyl administration
f. Administration of hemodynamic rescue drugs (ephedrine)
g. Administration of the Heavy Conscious Recovery Agitation Rescue Drug (Propofol)
h. Postoperative pain score in the numerical pain assessment scale
i. Length of extubation time

Perancu Variables

a. Comorbid obesity
b. Comorbid psychological disorders
c. Geriatric comorbidities
d. Gender
e. Smoking habits
f. Duration of operation
g. Intraoperative sevoflurane dosage
h. Types of Operations

3.10.1 Variable Operational Definition

Variable	Definition	How to Measure	Scale
Independent Variables			
Magnesium sulfate	The group received an infusion of $MgSO_4$ of 20 mg/kg/hr at a concentration of 10% (no dose fit at the beginning).	Patients were put into group A. Therapy was given during induction until the anesthetic gas (sevoflurane) was stopped. The drug label is written "Yunda research drug", the research number, the patient label and the speed	Categorical

		of administration in mL/hour	
Dexmedetomidine	The group received an infusion of dexmedetomidine of 0.5 μg/kg/hour (without a loading dose at baseline). The use of dexmedetomidine is used as a standard reference for the prevention of agitation and recovering consciousness In this study using Kabimidin®	Patients are placed in group B. Therapy is given during induction until the anesthetic gas (sevoflurane) is stopped. The drug label reads "research drug", the patient's identity and the speed of the recipient in mL/hour	Categorical
Dependent Variable			
Agitation regained consciousness	The dependent variable of conscious recovery agitation was operationally defined with a measurable SASR value of >+1 from the time the patient was stopped from inhalation anesthesia up to 30 minutes post-extubation	Patients are assessed by the anesthesia team with patient outputs will be categorized as 1. Yes (Experiencing Agitation, Recover Consciousness) 2. No (not experiencing agitation,	Categorical

		regaining consciousness)	
The Onset of Conscious Agitation	The first time conscious agitation occurred in patients with SASR 1-2	Onset is calculated when the anesthetic drugs and the study drug are stopped together up to 30 minutes after extubation. Onset is measured in minutes and is presented in mean or median form in groups A and B	Numerical
The duration of the agitation regained consciousness	The duration of the agitation is recovering consciously which can be overcome without the use of agitation rescue drugs. In	The duration is calculated from the initial time the patient experiences agitation until the agitation stops. If there is a recurrent occurrence of mild agitation, the duration used is the longest. Duration is measured in minutes and is presented as mean or median in groups A and B	Numerical
Hemodynamic parameters	The condition of circulatory dynamics during the procedure was in the form of	The patient's output is illustrated with average arterial pressure and pulse	Numerical

	pulse frequency and average arterial pressure during intraoperative. This figure is obtained from the measurement of non-invasive blood pressure of patients. Average arterial pressure is measured in mmHg while pulse frequency is measured in times per minute	rate. Recorded values: 1. Basic values 2. Pre-induction values 3. After induction 4. After intubation 5. After the incision 6. 30 minutes after incision 7. After extubation 8. At one hour postoperatively Minimum, maximum, and median or mean values will be presented in the data.	
Hemodynamic rescue drugs	Medication given when hypotension occurs (average blood pressure drops >30% base) or bradycardia occurs (pulse <50 times per minute). In this study, the drug in question was ephedrine 5 mg IV	The use of ephedrine as much as 5 mg IV will be recorded by the anesthesia team the amount of each time it is used (frequency of administration) and at any time of administration. The total amount of	Numerical

		ephedrine per action will be presented in mean or median form in groups A and B.	
Agitation rescue drugs regain consciousness	Drugs are given in the event of conscious recovery agitation that has the potential to harm both patients, medical staff, or the release of medical instruments that still need to be maintained. Objectively, the score value that is said to be harmful is the SASR score ≥3. In the study, the agent used was propofol 0.3-0.5 mg/kg and could be repeated until the patient calmed down with SASR 0	The use of propofol will be recorded for each administration and the amount is accumulated for each subject to get propofol up to SASR 0. Data will be presented with mean and median doses of propofol used in groups A and B	Numerical
Postoperative pain score	The assessed pain score uses a numerical pain assessment scale measured on a scale of 0 to 10 to describe the intensity of pain when the patient	Patients were asked objectively by the anesthesia team using a numerical pain assessment scale upon arrival in the postoperative room. Patients were	Categorical

	arrives at the recovery room	asked to describe their pain on a scale of 0 to 10. A scale of 0 patients had no pain at all, for a scale of 10 the pain was very severe and unbearable. Pain was then classified into: pain (pain numerical rating scale ≥ 4) and non-pain numerical rating scale of pain < 4)	
Perioperative opioid use	Number of doses of intravenous fentanyl use during the intraoperative and postoperative periods	It is calculated from the time the patient is installed on the monitor in the operating room (zero time) until the patient moves to the room. Total dose usage is calculated in micrograms (mcg). Its use will be compared in mean or median form in groups A and B	Numerical
Extubation duration	The length of time the patient can be consciously	The time will be measured by the anesthesia team as soon as the patient is	Numerical

	extubated after receiving therapy	stopped from the flow of anesthesia gas and stopped when the patient is awakely removed from the endotracheal tube. Data is presented in the form of minute units in groups A and B	
	Disruptive Variables		
Obesity	Patients were defined by a body mass index (BMI) > 30 kg/m2 calculated by the formula: body mass in kilograms (kg) divided by height in meters (m) squared	Patients are grouped into 2 groups: 1. Obesity (BMI $\geq$ 30) 2. Not obese (BMI < 30)	Categorical
Psychological disorders	The patient has previously been diagnosed with neurotic disorder (generalized anxiety disorder) or depression by a doctor and received regular therapy	Patients are grouped into 2 groups: 1. With distractions 2. Uninterrupted	Categorical
Geriatrics	Patients, both women and men, who are over 60 years of age	Patients are grouped into 2 groups: 1. Geriatrics	Categorical

		2. Non-geriatric	
Smokers	Female or male patients who regularly consume tobacco products, such as cigarettes, cigars, rolling. E-cigarettes and chewable nicotine do not fall into this category	Patients are grouped into 2 groups: 1. Smokers 2. Non-smokers	Categorical
Intraoperative use of sevoflurane	The use of sevoflurane for maintenance of anesthesia during the procedure	Zero time when the endotracheal tube is fixed and sevoflurane is turned on first until the flow of sevoflurane is stopped when the action is completed. Units measured: MAC, liters per minute, and %volume	Numerical
Duration of operation	The length of the duration of the surgery experienced by the patient.	It is calculated from the time the patient is initiated (zero time) until the surgical wound is completed. Units in minutes and presented in mean or median form in groups A and B	Numerical

Type of operation	Otorhinolaryngology patients are divided into otological surgery (ear area), rhinology (nose and sinus area), and laryngology (pharyngeal and laryngeal area)	Patients are put into the appropriate classification of the type of surgery. The amount will be calculated. The proportion of otology, rhinology, and laryngology patients will be compared in groups A and B	Categorical

3.10.2 Operational Definition of Term

Terms	Operational Definition
Otorhinolaryngology surgery	All surgical procedures are performed on the ear, nose, and throat regions. The action can be both invasive and minimally invasive. Some examples of actions that enter this definition: • Prhinology Septoplasty, rhinoplasty, sinus endoscopic functional surgery, dakriosistorhinostomy, turbinoplasty, sphenoidoidectomy, turbinoplasty, polypectomy, mass excision with minimal risk of bleeding, palatoplasty, mass biopsy • Otology Tympanoplasty, miringotomy, otoplasty, fistulectomy, mass

	excision with minimal risk of bleeding, mastoidectomy, Grommet tube insertion, mass biopsy, meatoplasty, canaloplasty, and auriculoplasty • Laryngology Polypectomy, tonsiladenodectomy, uvulopalatopharyngoplasty, diagnostic laryngoscopy or mass extraction, laryngoplasty, mass excision with minimal risk of bleeding, mass biopsy The actions taken are not extensive to include orbitotomy or opening the duramater.
Agitation regained consciousness	General postanesthesia psychomotor incidence measured with SASR ≥ 1: • Combative: Overtly resisting, aggressive, a direct threat to staff. Score 4 • Very agitated: Pulling or removing the endotracheal tube or catheter; be aggressive. Score 3 • Agitated: Aimless frequency movements, against the ventilator. Score 2 • Restless: Anxious but not aggressive or strong. Score 1 Its zero time was measured when sevoflurane gas and the research drug were stopped simultaneously for up to 30

	minutes after the endotracheal tube was pulled out
Effective	Therapy is said to be effective when the preventive effect of conscious recovery agitation is achieved as well or better than the best standard with the same or fewer side effects compared to the best standard
Basic values	Mean arterial pressure values and pulse frequency measured 1 day before surgery at the time in the room
Intraoperative hemodynamic disorders	Common disorders are a pulse frequency of <50 times per minute or a 30% decrease in pulse frequency from baseline in healthy individuals with 50-60 pulse frequency bradycardia and a decrease in mean arterial pressure >30% baseline
Research drugs	Drugs containing dexmedetomidine or magnesium sulfate that have been prepared by the pharmaceutical team. The researchers and the OK team do not know the exact content of the research drug.
Numerical scale of pain	A scale used to assess the degree of pain intensity. Subjects were asked to give a score from a score of 0 (no pain at all) to a score of 10 (the most unbearable pain)
Severe cognitive impairment	Patients who have been diagnosed with dementia in the geriatric population or severe mental retardation in non-geriatric

	populations who need full assistance to manage their daily activities
Deep tendon reflex	An involuntary muscle contraction movement that is triggered when a reflex hammer is tapped into a specific tendon. In this study, it will be tested on the achilles tendon or patella. The results obtained can be in the form of: • Hyperreflex • Normorefleks • Hyporeflexes • Reflexes

3.11 Data Analysis Plan

Data analysis will be carried out using a comparative hypothesis test (difference in proportion) using *the Statistical Package for Social Sciences* (SPSS) version 2.0. In this test, there were two groups that were not paired. The test test conducted on this subject is a two-proportion difference test using *chi-square*. A two-proportion difference test was also performed on secondary data in a categorical form in the group that received dexmedetomidine and that compared magnesium sulfate. In secondary data in the form of extubation duration and hemodynamic parameters of patients with a numerical scale, normality will be tested first with the Kolmogorov-Smirnov test. Then if the results of the normality test obtain a normal distribution, then the data will be presented in the form of mean and standard deviation followed by the analysis test of the unpaired student t-test. If the distribution of data is abnormal, the data will be presented in median, minimum, and maximum forms followed by the Mann-Whitney statistical analysis test.

3.12 Research Ethics and Consent

Researchers will submit proposals to obtain research ethics approval from the FKUI/RSCM Research Ethics Committee. The recruitment of research subjects is voluntary. All research subjects have the right to a complete explanation of the

procedure of this research and have the right to refuse to participate in the research. Research subjects who are willing to participate in the research will be asked to sign an *informed consent* and can resign at any time. The entire population continues to receive services according to standards.

3.13 Research Timeline

Table 3.1. Research Timeline

Activities	January 2024	February 2024	April 2024	May 2024	July 2024
Proposal creation	√				
Research ethics submission		√			
Managing location licensing		√			
Data collection			√	√	
Data analysis				√	
Creation of research reports					√

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Appendix 1. Research Explanation Sheet

COMPARISON BETWEEN INTRAVENOUS MAGNESIUM SULFATE ADMINISTRATION WITH INTRAVENOUS DEXMEDETOMIDINE TO REDUCE CONSCIOUS RECOVERY AGITATION IN ADULT PATIENTS UNDERGOING OTORHINOLARYNGOLOGY SURGERY

This research information sheet explains the purpose, procedure and usefulness of the research, so that you understand the research that will take place and can decide whether to participate or not. This sheet also contains about the rights of patients and our responsibilities as researchers in the implementation of this research.

Research Objectives

Agitation of conscious recovery or restless agitation during conscious recovery is a state that includes disturbing states, disorientation, aimless movements, inability to calm down, rebellious, and confused during the initial recovery from general anesthesia. Although it is commonly found in pediatric patients, it can occur in the adult population. The incidence rate increases in several types of surgeries, one of which is ear, nose, and throat surgery. This noisy incident of restless restlessness regaining consciousness causes undesirable consequences, such as injuries due to falls or the removal of medical instruments.

There are several drugs that can reduce the incidence of restless restlessness and regaining consciousness, including the administration of dexmedetomidine or magnesium sulfate during general anesthesia. Until now, dexmedetomidine is the best standard for the prevention of restlessness and regaining consciousness. However, there are some drawbacks to dexmedetomidine such as its high price,

uneven availability in Indonesia, and the time to fully recover from general anesthesia which is slightly extended.

Magnesium sulfate is a cost-effective alternative to preventing anxiety, restlessness, and recovering consciousness that is spread evenly throughout Indonesia. Several studies have proven that magnesium sulfate is effective in preventing restless noise. However, there has been no research that proves whether magnesium sulfate is no less good than dexmedetomidine in preventing restlessness from regaining consciousness.

The study will be conducted by the Department of Anesthesiology and Intensive Therapy FKUI of Dr. Cipto Mangunkusumo Hospital Jakarta which aims to compare the effects of magnesium sulfate administration with dexmedetomidine to prevent the occurrence of restless noise when recovering from consciousness in patients undergoing ear, nose and throat surgery. With the hope that magnesium sulfate can be used as an alternative that is no less good than dexmedetomidine.

Research procedure

After getting an explanation from the research team, if you agree to participate, you can sign this consent letter form stating that you have been given an explanation of this research and are willing to participate. If you agree to participate and have signed the consent letter form for this research, you can freely withdraw from this study at any time. If you refuse to participate or withdraw from this study, the decision will not affect your relationship with me and will not affect the services that apply at this hospital.

Participating patients are patients who will undergo general anesthesia to undergo ear, nose, and throat surgery. You will be prepared for surgery and anesthesia as usual. In this study, all participants will be randomly divided into 2 groups. During anesthesia and the act of getting additional anesthetics according to the group allocation, the first group will be given magnesium infusions with a dose of 20 mg/kg/hour starting from the beginning of anesthesia. The second group will be given dexmedetomidine infusion at a dose of 0.5 mcg/kg/hour. Throughout the

operation, you will be given anesthesia as usual and vital signs are closely monitored. When the surgery is complete, all medications are stopped and the patient is woken up. Incidents of restless rowdy were recorded from the time the patient stopped his medication until 30 minutes after the breathing tube was consciously released. In addition to the event of restless noise, the length of time the patient was removed from the breathing tube, blood pressure, pulse, amount of medication use during surgery (ephedrine, fentanyl, and sevoflurane), and postoperative pain score were recorded during this procedure.

Side effects and risks

The side effects obtained are usually minimal. The dosage of the research drug used is not large, but there is still a possibility of drug side effects. Side effects of the drug that may be encountered are a drop in pulse and blood pressure as well as a slightly elongated wake-up time with an estimated 1-8 minutes. We have prepared a handling protocol if this happens. During the action vital signs will be closely monitored, so that the side effects of the drug can be treated faster.

Benefits and confidentiality

The benefit that can be obtained is that you do not experience restless noise after postsurgery. If you wake up from surgery without making a fuss, then injuries due to restless noise can be minimized. Another benefit provided by these two drugs is a good anti-pain effect.

You will still receive services according to RSCM service standards. All data collected in this study will be kept confidential and used for research in accordance with permission by the Ethics Committee of the Indonesian Faculty of Medicine.

Contact Now

This research was organized by Dr. dr. Riyadh Firdaus, Sp.An-TI, Subsp. NA(K) at the Department of Anesthesiology and Intensive Therapy FK UI/RSCM. If you

need further information, you can contact dr. Girhanif Amri Yunda at 085921252918 cellphone number .

Thank you

Dr. dr. Riyadh Firdaus, Sp.An-TI, Subsp. NA(K)

Appendix 2. Research Participation Consent Sheet

CONSENT FORM FOLLOWING RESEARCH **(INFORMED *CONSENT FORM*)**			
Principal investigator		: Dr. dr. Riyadh Firdaus, Sp.An-TI, Subsp. NA(K)	
Whistleblower		: dr. Girhanif Amri Yunda	
Recipient of information Subject name Date of birth/age Gender Address Phone No. (HP)		: : : : :	
NO	**TYPES OF INFORMATION**	**CONTENTS INFORMATION**	**MARK**
1	Research title	Comparison between intravenous magnesium sulfate administration with intravenous dexmedetomidine to reduce conscious recovery agitation in adult patients undergoing otorhinolaryngology surgery	
2	Research objectives	Comparing the effects of magnesium sulfate administration with dexmedetomidine for preventing restlessness (agitation), regaining consciousness in patients undergoing ear, nose, and throat surgery (otorhinolaryngology)	

3	Research methods and procedures	1. Dear Sir/Madam/Brother on this occasion I ask you to participate in this research. The data in this study will be guaranteed confidentiality. 2. Ladies and gentlemen who meet the research requirements (acceptance and rejection criteria) will be explained about the research and asked to fill out a participation approval sheet if willing. 3. All participants will be randomized into two groups with the help of computers. The random results are known by a third party, unknown to the research team, the anesthesia team, and you. There are two groups, namely: • Group A: Participants who were given magnesium sulfate infusion 20 mg/kg of body weight per hour • Group 2: Participants who were given dexmedetomidine infusion 0.5 mcg/kg of body weight per hour 4. You will be asked about your smoking history and history of psychiatric illness in the room.	

		Measurement of vital signs in the room. Food fasting is carried out for 6 hours and for drinks starts 2 hours before surgery 5. You will be prepared for surgery according to the routine procedure, installed 2 infusions in the preparation room. After that you will enter the operating room 6. In the operating room, you will be given a research drug according to the previous random results, namely group A (magnesium sulfate) or group B (dexmedemidine), general anesthesia, and will be monitored during surgery. Data on vital signs and the use of other routine common anesthetics such as fentanyl, sevoflurane, and ephedrine will be recorded. 7. After the surgery is over, all medications are discontinued and the airway tube (endotracheal tube) is removed. The number of incidents of restless restlessness and regain consciousness will be recorded from the time the medication is stopped up to 30 minutes after the airway pipe is removed. The length of airway	

		pipe discharge was also measured since the drug was stopped 8. You are then taken to a recovering room, and will be observed for 1 hour, to then assess vital signs, pain scale and monitored for side effects of the medication	
4	Number of subjects	64 patients	
5	Research time	April – July 2024	
6	The benefits of the research include benefits for the research subjects	The benefit that can be obtained is not experiencing restless noise after postsurgery. If you wake up from surgery without making a fuss, then injuries due to restless noise can be minimized. Another benefit provided by these two drugs is a good anti-pain effect	
7	Risks & side effects in studies	Both drugs, both magnesium sulfate and dexmedetomidine, are widely used with a good level of safety. The dosage of the drug used is a relatively small dose of drugs but still effective in preventing restless noise, so that the side effects of the drug can be minimized. During the operation, we will closely monitor your condition so that the operation runs smoothly and the side effects of the medication can be detected quickly. The risks and side effects that can occur as experienced by patients under general anesthesia	

		usually are: decreased blood pressure and pulse. Other side effects: the full waking time of general anesthesia is slightly longer, about 1-8 minutes but the patient will wake up more comfortably.	
8	Compensation in case of side effects	You will be treated based on the protocol of side effects	
10	Data confidentiality	All data of this research will be kept confidential. Data storage is only carried out by the research team and on the research team's device, so it can only be accessed by the research team and not disseminated in any form. Presentations of research results in scientific meetings/conferences and publications in scientific journals will not include the name of the research subject. However, representatives of the ethics committee, and the governing national authority body will have access to the research data for verification	
11	Costs incurred by the subject	You are not charged any additional fees	
12	Incentives for subjects	None	

13	Name and address of the researcher and telephone number	**dr. Girhanif Amri Yunda** HP Number: 085921252918 Department of Anesthesiology and Intensive Therapy FK UI – RSUPN CM. Jl. Diponegoro No. 71 Central Jakarta. 10430.	

After listening to the explanation of the research to be conducted by dr. Girhanif Amri Yunda with the title: "Comparison Between Intravenous Magnesium Sulfate Administration and Intravenous Dexmedetomidine to Reduce Agitation to Recover Consciousness in Adult Patients Undergoing Otorhinolaryngology Surgery", I have understood the information well. By signing this form, I agree to be included in the above research voluntarily without coercion from any party. If at any time I feel aggrieved in any way, I have the right to revoke this agreement.

Subject name	Date
Subject signature or thumbprint	
Name of witness/guardian	Date
Signature of witness/guardian	

I have explained to the subject truthfully and honestly the purpose of the research, the benefits of the research, the research procedures, as well as the risks, and potential inconveniences that may arise (detailed explanation according to what I marked above). I have also answered research-related questions as best I can.

Signature of the researcher	Date
(Dr. dr. Riyadh Firdaus, Sp.An-TI, Subsp. NA(K) /	
(dr. Girhanif Amri Yunda)	

Appendix 3. Research Sheet

COMPARISON BETWEEN INTRAVENOUS MAGNESIUM SULFATE ADMINISTRATION WITH INTRAVENOUS DEXMEDETOMIDINE TO REDUCE AGITATION OF CONSCIOUS RECOVERY IN PATIENTS UNDERGOING OTORHINOLARYNGOLOGY SURGERY

A. Registration

Medical Record No.	:	Research Number	:
Surgery Day/Date	:	Surgical procedure	:
Diagnosis	:		

B. Identity

1. Patient's Initials :
2. Date of Birth (Age) :
3. Gender : L/P*
4. Height : cm
5. Weight : kg
6. IMT : kg/m2
7. Diagnosis :
8. ASA : I/II*
9. ASA Encryptioners :
10. Psychological disorders : Any/None*
11. Smoking habits : Any/None*
12. Type of operation : Rhinology/Otology/Laryngology*

(* circle according to answer)

C. Duration of Perioperative Action

Duration of operation : _____ hours _____menit

Length of extubation time : _____ minutes

D. Intraoperative Sevoflurane Use

	Concentration (%volume)	Flow rate (liters/min)	MAC Value
Postintubation			
At incision			
30 minutes after incision			
Shortly before the gas is stopped			

E. Intraoperative Hemodynamics

Time	**Average arterial pressure**	**Pulse rate**
Basic values		
Pre-induction values		
Post-induction		
Postintubation		
Post-Incision		
30 minutes post-incision		
Post-extubation		
1 hour postoperative		

E. Intraoperative amount of ephedrine

Drug dosage (mg)	Hours	Average arterial pressure	Pulse rate

F. Perioperative Fentanyl Use

- Intraoperative : _____ micrograms
- Postoperative : _____ micrograms
- Total : _____ micrograms

F. Agitation Events

Score	Categories	Description
+4	Combative	Overtly resisting, aggressive, a direct threat to staff.
+3	Very agitated	Removing or removing the endotracheal tube or catheter; be aggressive.
+2	Agitated	Aimless frequency movement, against the ventilator.
+1	restless	Anxious but not aggressive or strong movements
0	Conscious and calm	Spontaneous full contact

-1	Drowsy	Not fully conscious, but can remain awake for a long time (opening eyes/eye contact) with a loud stimulation (>10 seconds).
-2	*Light sedation*	Drowsiness but waking up briefly with eye contact to sound (<10 seconds)
-3	Deep sedation	There is no response to sound, but there is movement or eye opening in response to physical stimuli.
-4	*Unarousable*	There is no response to sounds or physical stimuli.

SASR Score :

Onset of agitation : _____ minutes

Duration of agitation : _____ minutes

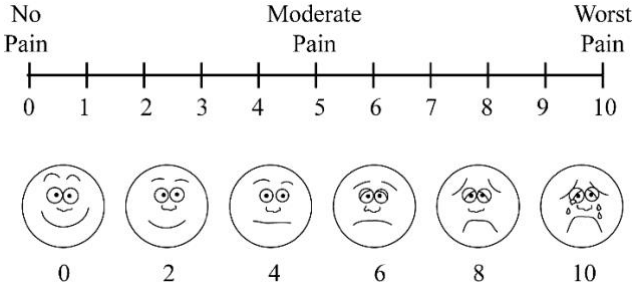
What is SASR ≥3? If so, do the heavy agitation rescue protocol and answer question G. If not, go directly to question H.

G. Use of Heavy Agitation Rescue Drug (propofol)

Total Dose of Propofol: ____ mg

G. Postoperative pain value

Numerical rating scale



Appendix 4. *Dummy Table*

Normally-distributed numerical data is presented in a standard intersection ± average; abnormally distributed numerical data are presented in median (minimum maximum); Categorical data is presented in amounts (percentages).

Table 1. Characteristics of research subjects

Variable	Group A (n)	Group B (n)	P
Age (years)	X+SD	X+SD	X
Geriatric status (>60 years)			
Geriatrics	X (X%)	X (X%)	X
Non-geriatric	X (X%)	X (X%)	X
Gender			
Male	X (X%)	X (X%)	X
Women	X (X%)	X (X%)	X
Weight (Kg)	X+SD	X+SD	X
Height (Cm)	X+SD	X+SD	X
BMI	X+SD	X+SD	X
Obesity status			
Obesity	X (X%)	X (X%)	X
Non-obesity	X (X%)	X (X%)	X
ASA physical status			
ASA 1	X (X%)	X (X%)	X
ASA 2	X (X%)	X (X%)	X
Duration of operation (minutes)	X+SD	X+SD	X
Smokers			
Yes	X (X%)	X (X%)	X
No	X (X%)	X (X%)	X

Psychological status			
With psychological disorders	X (X%)	X (X%)	X
No psychological disorders	X (X%)	X (X%)	X
Type of operation			
Otology	X (X%)	X (X%)	X
Prhinology	X (X%)	X (X%)	X
Laryngology	X (X%)	X (X%)	X

Table 2. Comparison of the proportion of *emergence agitation events*

Variable	Group A (n)	Group B (n)	P
With *emergence agitation* (SASR ≥1)	X (X%)	X (X%)	X
No *emergence agitation* (SASR <1)	X (X%)	X (X%)	X

Table 3. Comparison of average hemodynamic parameters

Variable	Group A (n)	Group B (n)	P
Average arterial pressure			
Pre-induction	X+SD	X+SD	X
Post-induction	X+SD	X+SD	X
Postintubation	X+SD	X+SD	X
Post-Incision	X+SD	X+SD	X
30 minutes post-incision	X+SD	X+SD	X
Post-extubation	X+SD	X+SD	X
1 hour post-extubation	X+SD	X+SD	X
Pulse frequency			

Pre-induction	X+SD	X+SD	X
Post-induction	X+SD	X+SD	X
Postintubation	X+SD	X+SD	X
Post-Incision	X+SD	X+SD	X
30 minutes post-incision	X+SD	X+SD	X
Post-extubation	X+SD	X+SD	X
1 hour post-extubation	X+SD	X+SD	X

Table 4. Comparison of the proportion of postoperative pain scores

Variable	**Group A (n)**	**Group B (n)**	**P**
VAS <4	X (X%)	X (X%)	X
VAS ≥4	X (X%)	X (X%)	X

Table 5. Comparison of the proportions of the frequency of ephedrine use

Variable	**Group A (n)**	**Group B (n)**	**P**
Ephedrine	X (X%)	X (X%)	X

Table 6. Dosage comparison of propofol use in heavy agitation

Variable	**Group A (n)**	**Group B (n)**	**P**
Propofol	X+SD	X+SD	X

Table 7. Comparison of the proportion of perioperative fentanyl use

Variable	Group A (n)	Group B (n)	P
Intraoperative	X (X%)	X (X%)	X
Postoperative	X (X%)	X (X%)	X

Table 8. Comparison of intraoperative sevoflurane use

Variable	Group A (n)	Group B (n)	P
Concentration (%volume)			
Postintubation	X+SD	X+SD	X
At incision	X+SD	X+SD	X
30 minutes after incision	X+SD	X+SD	X
Shortly before the gas is stopped	X+SD	X+SD	X
Flow rate (liters per minute)			
Postintubation	X+SD	X+SD	X
At incision	X+SD	X+SD	X
30 minutes after incision	X+SD	X+SD	X
Shortly before the gas is stopped	X+SD	X+SD	X
MAC			
Postintubation	X+SD	X+SD	X
At incision	X+SD	X+SD	X
30 minutes after incision	X+SD	X+SD	X
Shortly before the gas is stopped	X+SD	X+SD	X

Table 9. Comparison of the average time of conscious extubation

Variable	Group A (n)	Group B (n)	P
Average time of conscious extubation	X+SD	X+SD	X

Appendix 5. Research Organizations

Principal investigator : Dr. dr. Riyadh Firdaus, Sp.An-TI, Subsp. NA(K)

Researcher II : dr. Aino Nindya Auerkari, Sp.An-TI

Researcher III : dr. Girhanif Amri Yunda

Appendix 6. Research Fee Details

COMPARISON BETWEEN INTRAVENOUS MAGNESIUM SULFATE ADMINISTRATION WITH INTRAVENOUS DEXMEDETOMIDINE TO REDUCE AGITATION OF CONSCIOUS RECOVERY IN PATIENTS UNDERGOING OTORHINOLARYNGOLOGY SURGERY

Yes	Description	Percentage (%)	Amount (Rp)
1	Shopping for consumables	56%	4.384.032
2	Cost statistics	6%	500.000
3	Other operational costs	38%	3.057.000
	Total		7.941.032

Yes	Description	Justification for Use	Quantity	Unit Price (Rp)	Cost
		Consumables cost			
1	Kabimidin	Research drugs	32 vial	125.843	4.026.976
2	MgSO4 20%	Research drugs	32 flax	5.325	170.400
3	Spray 50 mL	Research materials	64 units	4.250	272.000

4	NaCl 0.9% 100 mL	Research materials	64 flask	8.000	512.000
5	Extension hose (perfusor)	Research materials	64 units	7.000	448.000
6	Intravenous catheter	Research materials	64 units	10.500	672.000
Subtotal (Rp)					6.101.376
		Cost statistics			
1	Consultation with a statistical and scientific preparation supervisor	Statistical consulting	1 meeting	500.000	500.000
Subtotal (Rp)					500.000
		Operating costs			
1	Photocopy of the approval sheet	Photocopying fees to double research approvals	64 units	1000	64.000
2	Photocopy of research proposal	The cost of photocopying the material submitted to the supervisor and the examiner board	15 units	15.000	225.000
3	Photocopy of research sheet	Photocopying fee for	48 units	1000	48.000

		duplicating research forms			
4	Unexpected costs	Anticipate additional costs	1 unit	500.000	500.000
5	Cost of research staff	Cost for the OK team that inputs data	64 samples	30.000	1.920.000
6	Ethical licensing management	Research licensing	1 unit	300.000	300.000
Subtotal					3.057.000