Effectiveness of Dexmedetomidine and Ketamine in Controlling Post Spinal Anesthesia Shivering

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Abstract

Background: Shivering can be caused by neuraxial as well as general anaesthesia. Because of the heterogeneity of the studies, estimating the incidence of shivering secondary to neuraxial block is tricky, however it is estimated to be around 55%. Spinal anaesthesia lowers core body temperature faster than epidural anaesthesia in the first 30 minutes following the block. Both strategies cause the temperature to drop at the same rate after 30 minutes. Shivering not only causes psychological stress in the patient, but it also causes physiological changes such as increased oxygen consumption by 200–600%, increased carbon dioxide production, increased blood pressure, increased risk of myocardial ischaemia, infection, and bleeding, and increased minute ventilation. It also causes hypoxaemia, lactic acidosis, increased intraocular pressure, and intracranial pressure, as well as impeding patient monitoring tools like the electrocardiogram (ECG), non-invasive blood pressure (NIBP), and peripheral oxygen saturation (SpO_2). Temperature monitoring is required for patients receiving anaesthesia, but due to the unavailability of an accurate non-invasive core temperature monitor, core temperature is frequently under-monitored during spinal anaesthesia, and significant hypothermia often goes unnoticed in these patients. For monitoring core temperature, disposable thermocouple and thermistor probes are utilized. They are a reasonably accurate (±0.5°C), low-cost, and dependable method. Infrared monitors detect the heat emitted by radiation and can measure the temperature of the tympanic membrane and forehead skin, but they are less accurate. Dexmedetomidine is effective and comparably better than ketamine in preventing shivering after spinal anesthesia. Dexmedetomidine also provides sedation without respiratory depression and favorable surgical conditions. However, with its use a fall in blood pressure and heart rate is anticipated.

Keywords: hypothermia, Shivering, anaesthesia

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Introduction

Shivering is an involuntary, oscillatory muscular activity that augments metabolic heat production up to 600 % above basal metabolic rate (BMR) and is clinically associated with clonic or tonic skeletal muscle hyperactivity of different frequencies. It's usually triggered by hypothermia. However, it occurs even in normothermic patients during the perioperative period **(1)**.

Etiology of shivering:

The etiology of shivering has not been understood sufficiently, several hypotheses have been raised to explain the occurrence of perioperative shivering. These include; perioperative hypothermia, postoperative pain, perioperative heat loss, hypercapnia, respiratory alkalosis, the existence of pyrogens, hypoxia, early recovery of spinal reflex activity and sympathetic overactivity. Of all the different hypotheses, only perioperative hypothermia and pain have been clearly verified **(2)**.

Pathophysiology of shivering:

The recording of post-anesthesia shivering electromyographic (EMG) patterns enables the identification of three types of EMG signals **(3)**:

1. Tonic pattern which shows a constant sinusoid form of normal shivering and it seems to be a thermoregulatory answer to intraoperative hypothermia **(Fig. 1).**

2. Clonic phasic pattern similar to pathologic clonus and it seems to be specific for recovery from volatile anesthesia. It might come from the loss of inhibition produced by general anesthesia in the control of spinal reflexes **(Fig. 2).**

3. Waxing and waning signals identical to those obtained during cold-induced shivering in non-anesthetized patients and is always preceded by cutaneous vasoconstriction (CVC) confirming their central thermoregulatory origin **(Fig. 3).**

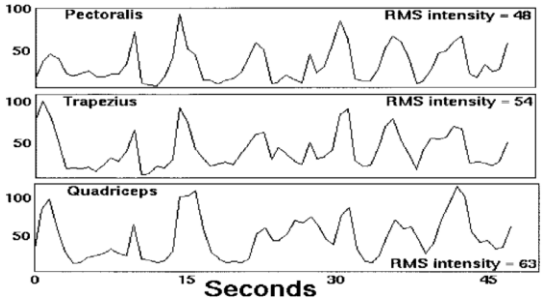

Fig. (1): Tonic pattern of shivering (4)

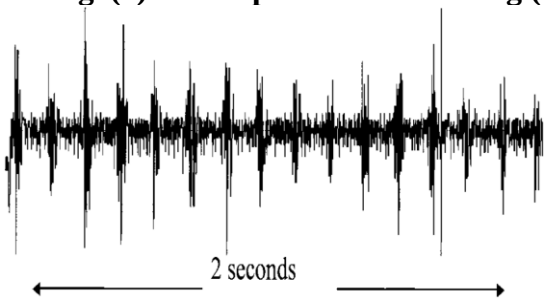

Fig. (2): Clonic pattern of shivering (4)

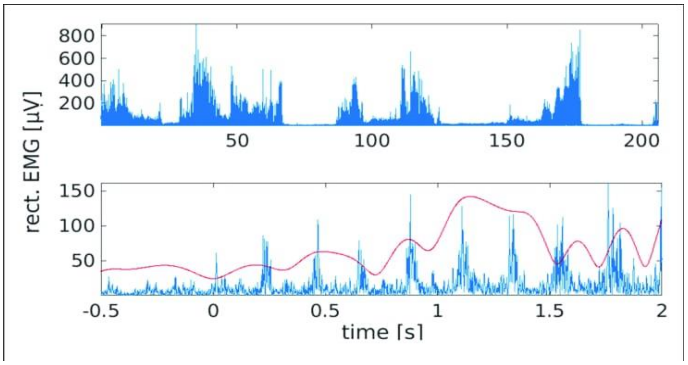

Fig. (3): Waxing and waning pattern of shivering (5)

<u>Mechanism of hypothermia during spinal anesthesia:</u>

Hypothermia is defined by the American Society of Peri-Anesthesia Nurses (ASPAN) guidelines **(6)** and the Association of Women's Health, Obstetric and Neonatal Nurses **(7)** guidelines as a core temperature (Tc) of less than 36°C {96.8 Fahrenheit (°F)}.

Inadvertent perioperative hypothermia has long been a recognized complication of general anesthesia. However, it is also common in patients receiving spinal anesthesia, with the incidence reported as high as 91%. This high incidence of perioperative hypothermia isn't surprising, as spinal anesthesia significantly impairs autoregulation by inhibiting the vasomotor and shivering responses and causes a thermal redistribution from the core to peripheral tissues. Spinal anesthesia also blocks tonic cold sensory input from the lower limbs to thermoregulatory centers **(8)**.

Risk factors of perioperative hypothermia:

Patient temperature <37.1°C upon arrival in the operation room (OR) and low body mass index (BMI) are the main risk factors of perioperative hypothermia **(9)**. Advanced age also is a major risk factor for the development of hypothermia due to impaired thermoregulation in elderly. For each year of increasing age, there is a 0.03 °C decrease in Tc **(10)**.

High level of spinal blockade is a significant predictor of low Tc. The effect of increasingly high block level is a 0.15°C decrease in Tc for each additional dermatomal level **(11)**.

Hypothermia may also be associated with other factors such as; cold OR temperature, long duration of surgery, administration of cold intravenous (IV) fluids, body surface exposure and excessive blood loss **(12)**.

Phases of intraoperative hypothermia under anesthesia:

There are a characteristic 3-phase pattern of hypothermia under anesthesia **(Fig. 4):**

Phase 1 (redistribution phase):

During general anesthesia, there is a rapid reduction in Tc of 1–1.5°C, while peripheral tissue temperature gains up to 2°C within the first 30–45 minutes. This is attributable to vasodilation (VD) which inhibits normal tonic vasoconstriction (VC) resulting in a core to peripheral temperature gradient and redistribution of body heat from core to peripheral tissue. General anesthesia also reduces the threshold for activation of thermoregulation **(13).**

During neuraxial anesthesia, there is a similar pattern of distribution phase to that of general anesthesia, but because redistribution during neuraxial anesthesia is usually confined to the lower half of the body, the initial core hypothermia is not as pronounced as in general anesthesia (approximately 0.5°C), but at the same time the mass of the legs is sufficient to produce substantial core hypothermia **(13)**.

Phase 2 (linear phase):

During general anesthesia, there is more gradual (linear) reduction in Tc of a further 1°C over the next 2–3 hours of anesthesia. It results from heat loss exceeding metabolic heat production. The main reasons for this imbalance are exposure of the body to a cold OR environment, evaporation of cold surgical skin preparation solutions, loss of heat from surgically exposed sites and reduction of heat production as a result of general anesthesia **(14)**. During neuraxial anesthesia, there is a similar pattern of linear phase to that of general anesthesia **(13).**

Phase 3 (plateau phase):

During general anesthesia, after patients have become sufficiently hypothermic, usually after 3–5 hours of general anesthesia, core temperature often does not further decline. This phase starts when the VC threshold is reached at around 34.5°C resulting in reactivation of thermoregulatory VC which decreases cutaneous heat loss and constrains metabolic heat to the core compartment **(15).**

However**,** plateau phase does not emerge during neuraxial anesthesia because VC is blocked**,** and this is the major difference between general and neuraxial anesthesia regarding the patterns of hypothermia **(13).**

The combination of general-neuraxial anesthesia potentiates the risk of perioperative hypothermia by overlapping the effects of redistribution and VD and reducing the VC threshold significantly. Consequently, combined anesthesia has additive effects on the impairment of the thermoregulatory system compared with general or neuraxial anesthesia alone. **(16)**.

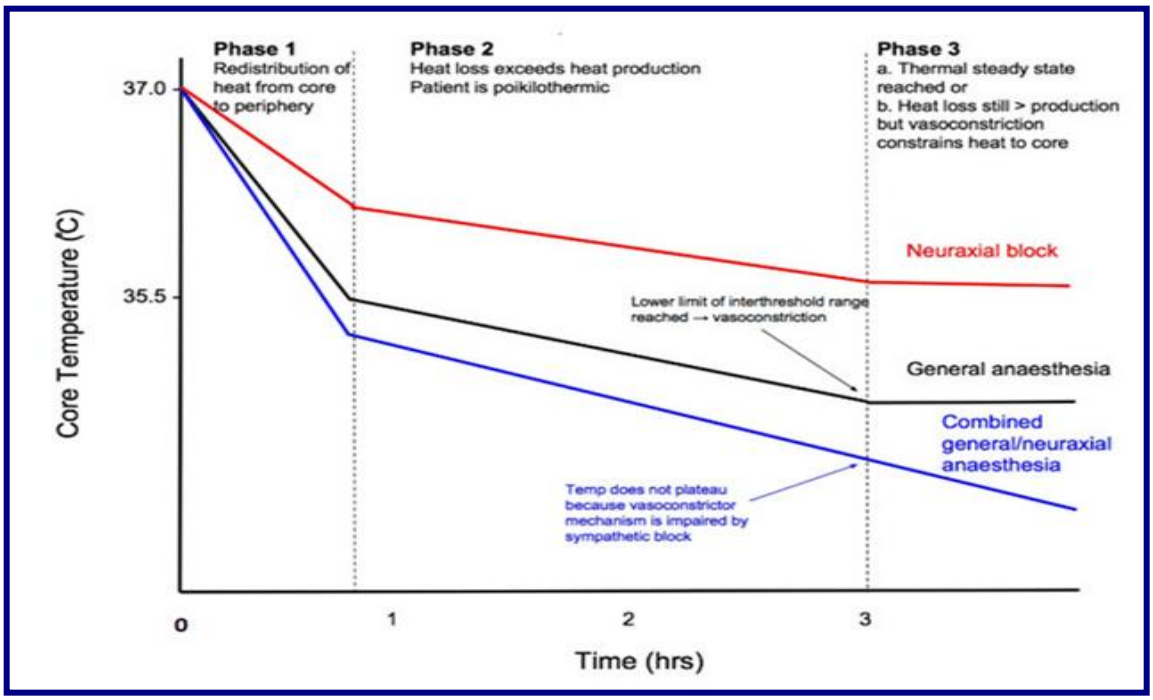

Fig. (4): Phases of intraoperative hypothermia under different types of anesthesia (17).

Prevention and treatment of shivering:

A. Non-pharmacological measures:

These methods work by preserving or restoring the body temperature above the shivering threshold or by masking the central shivering reflex via warmed skin sensory input. To inhibit post-anesthesia shivering, the average skin temperature must be raised by at least 4°C, which results in a 1°C decline in shivering threshold **(18).** These measures include:

1. Active cutaneous warming:

Forced air warming devices:

Forced-air body warming devices have become a key area in the prevention of perioperative hypothermia as it is easy to use, inexpensive and for most patients and surgery has a good cost/benefit ratio. The large surface area of the skin provides an efficient and safe way for these devices to both transfer heat to the body and reduce heat losses. Covering the patient with a forced-air warmer for 30 minutes before the induction of anesthesia is enough to eliminate the phenomenon of internal redistribution **(19)**.

Resistive heating:

It's a low-voltage electric current passed through a semiconductor, thus generating heat. Generally, these devices may provide broadly similar results to forced-air warming devices but have the potential to be cheaper, quieter and more efficient for accidental hypothermia because of its ability to transfer a large fraction of heat **(20)**.

Circulating water mattresses and garments:

Circulating water mattresses are less efficient than forced-air body devices in adults, as blood flow of the patient's back is reduced by compression produced by the body weight and this further reduces the ratio between transferred and dissipated heat. On the contrary, these systems maintain an acceptable efficiency in pediatric patient due to the more favorable proportion of warmed skin surface and the reduced effects of body weight on the back's blood flow **(21)**.

Negative-pressure water warming devices:

They work by improving skin perfusion and mechanically distending subcutaneous blood vessels. If the subcutaneous vascular structure of the hand of a hypothermic individual can be dilated by using sub-atmospheric pressure applied to the skin, a thermal link between the skin and the body core would be created allowing transfer of applied heat to the core **(22)**.

2. Passive insulation:

They include cotton blankets, surgical drapes, plastic sheeting and reflective composites. A single layer of passive insulation reduces cutaneous heat loss by 30%. However, it is essential to determine that the layer does not actively transfer heat into the body, even by adding several extra layers of insulation. Consequently, passive insulation can decrease heat loss but will not add any benefit in the maintenance of perioperative normothermia **(8)**.

3. Body core warming:

Intravenous fluid warming:

Intravenous infusion of each liter (L) of fluid at ambient temperature or each unit of blood infused at 4°C decreases the mean body temperature by approximately 0.25°C. However, fluid warming is of limited benefit at best, as the temperature of the infusion (usually not warmer than 38–39°C) can only slightly exceed Tc. Consequently, active warming of the patient is basically impossible unless very large amounts of fluid are given over a short period of time **(23)**.

As parturients undergoing CS receive relatively large amounts of fluid during surgery, warmed IV fluid may be particularly effective in these patients **(23)**.

Airway heating:

Warmed and humidified air can raise nasopharyngeal, esophageal and Tc by reducing heat loss from respiratory evaporation of dry gases. However, only 10% of heat loss occurs by evaporation, therefore warmed air has little effect on shivering **(2)**.

Also warmed CO_2 used for insufflation for patients undergoing laparoscopic surgery demonstrated to be moderately effective. **Dean et al., (24)** reported that the use of warmed and humidified CO_2 was associated with a significant increase in intraoperative Tc (mean change 0.3 °C).

4. Vascular heat exchange catheters:

They transfer much more heat compared to skin-warming devices. On the other hand, heat exchange catheters are quite expensive and its placement is invasive. Thus, their use is mostly restricted to patients requiring a rapid onset of hypothermia, for example after distinct accidental hypothermia **(8)**.

B. Pharmacological measures:

Many drugs have been shown to be effective on the prevention and treatment of post-anesthesia shivering such as **(25)**.:

- Centrally acting analgesics (tramadol).
- Opioid receptor agonists (meperidine, fentanyl).
- Cholinesterase inhibitors (physostigmine).
- NMDA receptor antagonists (ketamine, $MgSO_4$).
- α_2-central agonists (clonidine, dexmedetomidine).
- Antiserotonergic (ondansetron).
- Anti-inflammatory drugs (dexamethasone).

Medications which interfere at different levels of the thermoregulatory loop (opioid agonist, NMDA antagonist) have more efficacy than those with only one function (α_2-receptor agonist, antiserotonergic agents) or only at the peripheral level (nonsteroidal anti-inflammatory agents) **(18)**.

Park et al., (26) identified that clonidine, meperidine, tramadol, and nefopam were the best performing pharmacological agents. However, few of them were recommended for the prevention of post-anesthesia shivering due to various side effects.

Dexmedetomidine (DEX)

Chemical properties:

Dexmedetomidine hydrochloride (precedex®) is the S -enantiomer of medetomidine and is chemically described as (+)-4-(1S)-[1-(2,3- dimethylphenyl)ethyl]-1H-imidazole. Its molecular formula is C13H16N2. It has a molecular weight of 236.7 g/mol and pH of 4.5 **(27).**

Chemical structure **(Fig. 5)**:

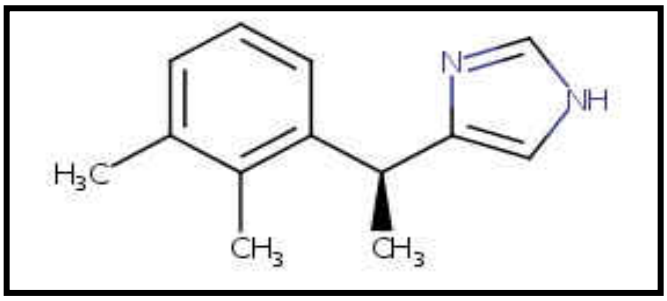

Fig. (5): Chemical structure of dexmedetomidine (27)

Mechanism of action:

Dexmedetomidine is a highly selective α_2 adrenoceptor (AR) agonist which produces clinical effects after binding to G-Protein-coupled α_2-AR, of which there are three subtypes (α_2A, α_2B, and α_2C). These receptor subtypes are found ubiquitously in the central, peripheral and autonomic nervous systems, as well as in vital organs and blood vessels. Locus coeruleus of the brain stem is the principal site for the sedative action and spinal cord is the principal site for the analgesic action, both acting through α_2A-AR. Higher affinity to α_2 receptor selectively leads to vagomimetic action on heart (bradycardia) and VD. Dexmedetomidine has a low affinity for β adrenergic, muscarinic, dopaminergic and serotonin receptors. It suppresses shivering possibly by activity at α_2B-AR receptors in the hypothalamic thermoregulatory center of the brain (**28**).

Pharmacokinetics:

1. Absorption:

Oral bioavailability is poor because of extensive first-pass metabolism. However, bioavailability of intranasal (IN) and sublingually administered dexmedetomidine is high (84%), offering a potential role in pediatric sedation and premedication **(29)**.

2. Distribution:

Dexmedetomidine is a highly protein-bound drug. In plasma, 94% of dexmedetomidine is bound to albumin and α_1-glycoprotein. The distribution phase is rapid, with a distribution half-life ($t_{1/2}$) of approximately 6 minutes **(30)**.

3. Metabolism and elimination:

Dexmedetomidine undergoes almost complete biotransformation through direct N-glucuronidation, and cytochrome P-450 (CYP 2A6)-mediated aliphatic hydroxylation to inactive metabolites. Metabolites are excreted renally (95%), fecally (4%), and less than 1% are excreted unchanged **(31)**.

Dosage and routes of administration (Table 1):

Table (1): Doses and routes of administration of dexmedetomidine:

Route	Dose
Intravenous	Loading dose of 1 mcg/kg over 10-20 minutes followed by a maintenance infusion in the range of 0.2- 0.7 mcg/kg/hr.
Intramuscular (IM)	IM injection (2.5 mcg/kg) of DEX has been used for premedication.
Spinal	0.1-0.2 mcg/kg
Epidural	1-2 mcg/kg
Peripheral nerve block	1 mcg/kg
Buccal	1-2 mcg/kg
Intranasal	1-2 mcg/kg

Pharmacodynamics:

Cardiovascular system (CVS):

Dexmedetomidine evokes a biphasic blood pressure (BP) response; a short hypertensive phase and subsequent hypotension. The two phases are considered to be mediated by two different α_2-AR subtypes; the initial hypertensive phase is most likely due to VC induced by activation of α_2B-AR, whereas hypotension is

mediated by the α_2A-AR, which results in vasodilatation**.** The dose-dependent bradycardia seen with dexmedetomidine is mediated primarily by a decrease in sympathetic tone, and partly by baroreceptor reflex and enhanced vagal activity **(32)**.

Respiratory effects:

Dexmedetomidine induces minimal respiratory depression, even when higher doses are used. This property provides great protection in specific situations such as awake craniotomy, awake fiberoptic intubation and weaning and extubation in intensive care unit (ICU) patients **(33)**.

Central nervous system (CNS):

Dexmedetomidine administration produces sedation and anxiolysis, thought to be mediated by its inhibitory effect on noradrenergic neurons in the locus coeruleus. The sedative effects are unique, as an arousable sedation state is induced, similar in nature to natural sleep. Dexmedetomidine reduces cerebral blood flow (CBF) and the cerebral metabolic rate. In patients who undergo surgery, dexmedetomidine can reduce intracranial pressure (ICP) and cerebral O_2 metabolism and maintain the balance of cerebral O_2 supply and demand**.** It decreases the area of cerebral infarction in the early stage of cerebral ischemia–reperfusion by reducing the heterogeneity of mixed SvO_2, reducing regional CBF and cerebral O_2 consumption **(34).**

Renal effects:

Dexmedetomidine has a diuretic effect by; inhibiting the antidiuretic action of vasopressin (AVP) at the collecting duct and preserving the cortical blood flow by decreasing renal release of norepinephrine (NE) **(35).**

Role of dexmedetomidine in shivering:

Dexmedetomidine is a potent, selective α_2-adrenoceptor agonist eight times stronger than clonidine. The antishivering effects of dexmedetomidine are induced by binding to the α_2 receptor, which causes VC. In addition, it has a thermoregulatory impact on the hypothalamus **(36).**

The exact mechanism of dexmedetomidine for shivering control is unclear and complex. Dexmedetomidine reduces shivering by inhibiting central thermoregulatory control, inhibiting neuronal conductance, suppressing VC, and reducing shivering thresholds without altering the sweating threshold **(37).**

Dexmedetomidine was used in various studies in order to prevent the post anesthetic shivering related to general anesthesia at doses of 1 μg/kg **(38,39)** and 0.5 μg/kg **(28)** and found to be effective. Since the half duration of dexmedetomidine elimination was short (2 h) and had a single dose application, long-term postoperative follow-up was not found to be necessary.

A meta-analysis done by **Liu et al., (40)** which included thirty-nine trials that studied the efficacy of dexmedetomidine on prevention of shivering. They reported that dexmedetomidine reduced postoperative shivering compared to placebo with a minimum effective dose of 0.5 μg/kg. However, dexmedetomidine may increase the incidence of sedation, hypotension, bradycardia and dry mouth.

Yu et al., (36) reported that patients undergoing cesarean section (CS) under spinal anesthesia and experienced shivering, all responded to 0.5 μg/kg dexmedetomidine within 15 min. Also, the results of the study by **Lamontagne et al., (41)** showed that IV administration of dexmedetomidine (30 μg) reduced the duration of shivering in women undergoing CS under spinal and epidural anesthesia compared to placebo (2.6 min vs. 17.9 min). The shivering stopped in 90% of patients in the dexmedetomidine group versus 22.5% in the control group after 15 min of drug administration.

Adverse effects of dexmedetomidine:

The most frequently observed adverse effects include hypotension, bradycardia, dry mouth and nausea. Other reported adverse effects include fever, rigors, cyanosis and muscle weakness.

It may lead to arrhythmias, atrioventricular (AV) block, cardiac arrest, T-wave inversion, angina pectoris, pulmonary edema, bronchospasm, respiratory depression, syncope, neuropathy, paresthesia, paresis, hyperkalemia, lactic acidosis and hyperglycemia. Abrupt discontinuation after long-term use of dexmedetomidine may lead to a withdrawal syndrome of nervousness, agitation, headaches and hypertensive crisis **(42)**.

Contraindications of dexmedetomidine:

The use of dexmedetomidine is contraindicated in patients with advanced (grade 2 or 3) heart block (unless paced), hemodynamic instability, uncontrolled hypotension, bradycardia, acute cerebrovascular conditions or hypersensitivity to the drug **(43).**

Ketamine

Chemical properties:

Ketamine (ketalar®) is chemically (+/−) 2-(2-chlorophenyl)-2-(methylamino)-cyclohexanone. Its molecular formula is $C_{13}H_{16}ClNO$. It has a molecular weight of 237.7 g/mol, and pH of 3.5 – 5.5.

Chemical structure (Fig. 6):

Ketamine has a chiral structure consisting of two optical isomers, S+ ketamine and R-ketamine **(Fig. 7)**, because of an asymmetric carbon atom in the C2 position. Clinically, the anesthetic potency of the S(+) isomer is approximately three or four times that of the R(−) isomer **(44)**.

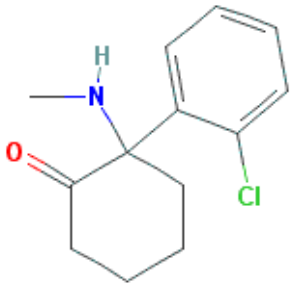

Fig. (6)*:* Chemical structure of ketamine (45).

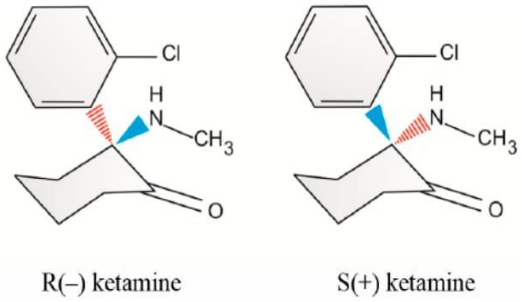

Fig. (7)*:* The optical isomers of ketamine (45).

Mechanism of action:

Ketamine effects are mediated primarily by non-competitive antagonism at the N-methyl-D-aspartate (NMDA) receptor calcium (Ca^{2+}) channel pore in the brain and spinal cord **(46)**.

Other mechanisms of action of ketamine include:

1. Interaction with opioid receptors, with a preference for μ and kappa (κ) receptors **(47).**
2. It reduces the presynaptic release of glutamate, and has antagonistic interaction with cholinergic, muscarinic, and nicotinic receptors **(46)**.
3. It inhibits the uptake of dopamine, serotonin, and noradrenaline (NA) in dose-dependent fashion in human embryonic kidney cells **(48).**
4. Ketamine at high doses has local anesthetic (LA) properties; these may be through its ability to inhibit neuronal sodium channels **(49).**

Pharmacokinetics:

1. Absorption:

Ketamine is water and lipid soluble, allowing it to be administered conveniently via various routes including IM, IV, intranasal, epidural, rectal and as an oral elixir. Oral bioavailability of ketamine is limited to 16%–29%, due to extensive first-pass hepatic metabolism. Intranasal and rectal ketamine bioavailability is 45%–50% and 25%–30%, respectively **(50).**

2. Distribution:

Ketamine is rapidly distributed into highly perfused tissues, including the brain, and has a plasma protein binding between 10% and 50%, with a distribution $t_{1/2}$ of 10 minutes **(50).**

3. Metabolism:

Ketamine undergoes extensive metabolism, initially via nitrogen demethylation to norketamine, a reaction that is catalyzed primarily by the cytochrome P450 liver enzymes CYP2B6 and CYP3A4. Norketamine is further metabolized to the hydroxynorketamines (HNKs) and dehydronorketamine (DHNK) **(51).**

4. Elimination:

Elimination of ketamine is primarily performed by the kidneys, with low levels excreted as ketamine (2%), norketamine (2%), and DHNK (16%). The majority of the drug (80%) is excreted as the glucuronic acid-labile conjugates of HK and HNK, which are eliminated in urine and bile **(52)**.

Dosage and routes of administration (Table 2):

Table (2): Dose and routes of administration of ketamine:

Route	Dose	
Intravenous	Racemic ketamine	S(+) ketamine
1) Induction of anesthesia:	1-2 mg/kg.	0.5-1 mg/kg.
2)Maintenance of anesthesia:	1-6 mg/kg/h.	0.5-3 mg/kg/h.
3) Analgesia and sedation:	0.25-0.5 mg/kg.	0.125-0.25 mg/kg.
IM		
1) Induction of anesthesia:	4-10 mg/kg.	
2) Analgesia and sedation:	2-4 m/kg, followed by continuous infusion of 5-20 mcg/kg/min.	
Rectal	8-10 mg/kg	
Intranasal	5 mg/kg	

Pharmacodynamics:

Central nervous system:

Ketamine produces the so-called 'dissociative' anesthetic state, in which the eyes remain open with a slow nystagmic gaze, whereas the corneal and light reflexes remain intact. Ketamine causes cerebral vasodilation and increased CBF and cerebral perfusion pressure (CPP). The metabolic rate of O_2 increases in the frontal lobes and the insula, while decreases in the temporal lobes, the cerebellum or pons. Regarding ICP, early reports documented elevated ICP associated with its use. However, recent studies conducted in human revealed that ketamine administration doesn't result in increased ICP. Additionally, it is able to decrease seizures and non-convulsive epileptic activity. Ketamine has neuroprotective effects by reducing glutamate levels and inhibiting cortical spreading depressive depolarization **(53)**.

Cardiovascular system:

Ketamine is usually associated with tachycardia, increased BP, and increased cardiac output (CO). However, in the absence of autonomic control, ketamine has a direct myocardial depressant effect, which is usually overridden by the central response. It is possible to reduce the undesirable cardiovascular effects by giving ketamine as a continuous infusion and use of a benzodiazepine **(54)**.

Respiratory system:

Ketamine has minimal effect on central respiratory drive. It causes bronchial smooth muscle relaxation, so it has a special role in intractable asthma.

Although swallowing, cough, sneeze, and gag reflexes are relatively intact with ketamine, silent aspiration can occur. Laryngospasm is frequently cited as an adverse effect of ketamine, but it is rarely observed **(55).**

Role of ketamine in shivering:

Ketamine, a competitive NMDA receptor antagonist, modulate thermoregulation in various levels and probably control shivering by non-shivering thermogenesis either by influencing the hypothalamus or by the beta-adrenergic effect of norepinephrine **(56).**

Ketamine has been shown to have anti-shivering properties in doses of 0.25 to 0.75 mg/kg during spinal anesthesia **(57,58).** But following the use of these doses, side effects, such as drowsiness, hallucination, delirium, and postoperative cognitive dysfunction may appear **(59).**

Kose et al., (60) examined the prophylactic effect of two different doses of ketamine in the prevention of shivering in CSs during spinal anesthesia with 15 mg bupivacaine. They found that the incidence of shivering decreased from 37% to 6.6% and 3.3% by 0.25 and 0.5 mg/kg prophylactic ketamine, respectively. Also, **Lema et al., (61)** evaluated the effects of ketamine on incidence and intensity of shivering following spinal anesthesia in CSs patients. Both the incidence and severity of shivering decreased by 0.2 mg prophylactic ketamine.

A meta-analysis done by **Zhou et al. (62)** who evaluated the safety and efficacy of the prophylactic ketamine use to prevent post-anesthesia shivering and reported that ketamine markedly decreased the incidence of post anesthetic shivering when compared to placebo.

Dal et al., (57) and Sagir et al., (63) reported that ketamine 0.5mg/kg prevented effectively postanesthetic shivering in patients receiving general anesthesia and spinal anesthesia respectively.

Contraindication of ketamine:

Contraindications of ketamine include; intraocular pressure pathology (glaucoma or acute globe injury), previous psychotic illness (because of potential activation of psychoses), hyperthyroidism or thyroid medication use (because of potential for severe tachycardia or HTN), porphyries (because of possibility of triggering a porphyric reaction), first trimester of pregnancy since ketamine is ranked category B for pregnancy, during preeclampsia, and in CSF obstructive states (severe head injury, central, congenital, or mass lesions) (controversial) **(55)**.

Conclusion:

Intravenous dexmedetomidine could significantly reduce shivering associated with spinal anesthesia during surgical procedures and provide sedation without any major adverse effect during the perioperative period. Also, intravenous ketamine could be used in the prophylaxis of post-spinal shivering with a good hemodynamic stability. Therefore, we conclude that both intravenous dexmedetomidine and ketamine are effective in prevention of shivering during spinal anesthesia.

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