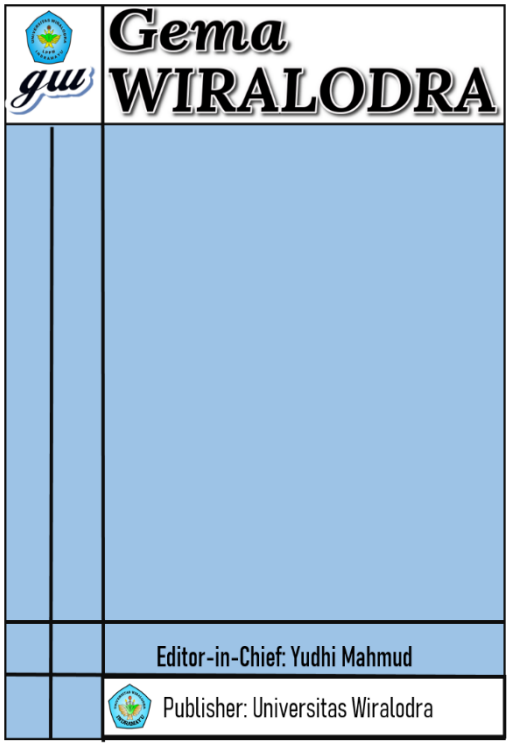
Gema Wiralodra

Publication details, including instructions for authors and subscription information:
https://gemawiralodra.unwir.ac.id



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Zulfikar
Universitas Andalas, Indonesia, zulfikarspan5@gmail.com

To cite this article:
Zulfikar. (2024). The use of dexmedetomidine in suppressing cardiovascular response due to intubation in general anesthesia. *Gema Wiralodra*, *15*(1), 151-155
To link to this article:
https://gemawiralodra.unwir.ac.id/index.php/gemawiralodra/issue/view/24
Published by:
Universitas Wiralodra
Jln. Ir. H. Juanda Km 3 Indramayu, West Java, Indonesia

Gema Wiralodra, 15(1), 151-155
https://gemawiralodra.unwir.ac.id/index.php/gemawiralodra
p –ISSN: **1693 - 7945**
e –ISSN: **2622 - 1969**

Original Article

The use of dexmedetomidine in suppressing cardiovascular response due to intubation in general anesthesia

Zulfikar
Universitas Andalas, Indonesia, zulfikarspan5@gmail.com

Abstract
Endotracheal intubation is commonly used to maintain a safe airway during general anesthesia. This intubation action can trigger a dangerous response for the patient, one of which is the cardiovascular system. Increases in arterial blood pressure, plasma catecholamine levels, and heart rate are responses that can occur during intubation. Therefore, various methods and treatments have been used to control this cardiovascular response, including dexmedetomidine. Dexmedetomidine is a highly selective α2-adrenergic receptor agonist that has analgesic, sympatholytic, and sedative effects with minimal depression of ventilation. Much research has been done on how well dexmedetomidine works to stop the cardiovascular response to intubation. Dexmedetomidine was significantly associated with reductions in heart rate, systolic blood pressure, and MAP.
Keywords: General Anesthesia, Intubation, Dexmedetomidine, Cardiovascular Response

1. Introduction

General anesthesia is the act of making the patient unconscious and unable to feel pain stimulation (Smith et al., 2023). Anesthesiologists ensure that the patient's airway is safe during anesthesia and surgery (Jarineshin et al., 2015). Airway management plays a vital role during general anesthesia. Various airway security methods have been used, such as orotracheal, nasotracheal, and tracheostomy (Firdaus et al., 2021). Laryngoscopy and tracheal intubation are standard measures to maintain airway safety during general anesthesia. Laryngoscopy and endotracheal intubation can cause dangerous stimuli that can trigger sudden changes in the cardiovascular and physiological systems (Firdaus et al., 2021).

Endotracheal intubation directly affects the sympathoadrenal response, which increases arterial blood pressure, plasma catecholamine levels, and heart rate and can even cause dysrhythmias in some cases (Seangrung et al., 2021). The increase in arterial pressure generally peaks within 1-2 minutes and lasts for five minutes. These changes can cause severe morbidity in patients who have cerebrovascular and cardiovascular diseases (Mahiswar & Dubey, 2022).

Various methods and treatments are used to control the hemodynamic response during laryngoscopy and endotracheal intubation, such as increasing the depth of anesthesia, minimizing the duration of intubation (less than 15 seconds), administering drugs such as intravenous and endotracheal lidocaine, short-acting opioids, beta-adrenergic inhibitors, calcium channel blockers, vasodilator drugs, and even magnesium (Jarineshin et al., 2015). Drug administration to suppress cardiovascular response due to intubation action that is commonly used is fentanyl (Ariffianto et al., 2022). Fentanyl is a class of fast-acting synthetic μ receptor-stimulating opioids, generally reserved for the prevention of sympathetic stimulation during intubation (Teong et al., 2020). The use of Fentanyl in Indonesia is limited in quantity and use based on the Regulation of the Minister of Health of the Republic of Indonesia number 5 of 2023 concerning narcotics, psychotropics, and pharmaceutical precursors (Minister of Health, 2023). Another drug option that can be used to suppress cardiovascular response is dexmedetomidine.

Dexmedetomidine is a highly selective α^2-adrenergic receptor agonist that has an analgesic, sympatholytic, and sedative effect with minimal depression on ventilation (Lee, 2019; Mufti & Musba, 2023). Dexmedetomidine can reduce catecholamine levels in plasma and resist the release of catecholamines. Dexmedetomidine attenuates potentially harmful

p –ISSN: **1693 - 7945**
e –ISSN: **2622 - 1969**

cardiovascular reactions during the induction of anesthesia. The use of dexmedetomidine has been widely reported to be effective in inhibiting adverse cardiovascular responses due to intubation (Ariffianto et al., 2022; Mahiswar & Dubey, 2022).

2. Research Methods

In the compilation of this literature review, a systematic approach was undertaken to gather a diverse range of scholarly materials, encompassing both Indonesian and English literature. The search was conducted on prominent platforms such as PubMed, Google Scholar, Elsevier, and Research Gate, covering the extensive period from 2015 to 2022. To ensure a thorough exploration of the chosen topic, a set of carefully selected keywords, including "Management of Airway During General Anesthesia," "Cardiovascular Effects of Anesthesia," "Complications of Intubation during and after General Anesthesia," "Haemodynamic Response to Intubation during General Anesthesia," "Pharmacokinetics and Pharmacodynamics of Dexmedetomidine," and "Effect of Dexmedetomidine on Haemodynamic Response to Tracheal Intubation," served as guiding parameters for the search. The wealth of discovered journals and books, predominantly in English, provided a robust foundation for understanding the various dimensions of airway management during general anesthesia. This literature review places a particular emphasis on the cardiovascular effects of anesthesia, complications arising from intubation processes, and the intricate pharmacokinetics and pharmacodynamics of Dexmedetomidine. The meticulous selection of articles and journals was driven by a commitment to relevance and coherence with the chosen topic, ensuring that the synthesis of these scholarly resources contributes substantively to the understanding and advancement of knowledge in the field of anesthesiology.

3. Results and Discussion

Pharmacokinetic Dexmedetomidine

Absorbs

The use of dexmedetomidine is currently only registered for intravenous use, but several other routes of administration have been investigated. Extravascular administration can avoid the high peak plasma levels that usually occur after intravenous administration. Oral administration can be observed wide first cross effect, with a bioavailability of 16%. Dexmedetomidine is well absorbed through the intranasal and buccal mucosa, so it can be beneficial when using dexmedetomidine in uncooperative children or geriatric patients (Weerink et al., 2017).

Distribution

Dexmedetomidine is a drug that is strongly bound to proteins. As much as 94% of dexmedetomidine in plasma is bound to serum albumin and glycoproteins (Li et al., 2016). Pre-clinical studies in animals, it was found that dexmedetomidine can easily cross the blood-brain barrier and placenta. Research conducted by Weerink et al in 2017 on healthy volunteers obtained a half-life of dexmedetomidine distribution of about 6 minutes. Distribution volume was found to be associated with body weight, with distribution volume at stable conditions in healthy volunteers around 1.31–2.46 L/kg (90–194 L) (Weerink et al., 2017).

Metabolism

Dexmedetomidine is mostly metabolized in the liver via glucuronidation by uridine 5'-diphosphate-glucuronosyltransferase (UGT2B10, UGT1A4) and hydroxylation by cytochrome P450 (CYP2A6). The main metabolites in humans are the two glucuronide N-isomers G-Dex-1 and G-Dex-2, the O-glucuronide of the hydroxylated N-methyl dexmedetomidine (H1), and the oxidation product of the imidazole H3. As much as 95% of unchanged metabolites of dexmedetomidine are excreted through the kidneys, while the rest is fecally (Li et al., 2016; Weerink et al., 2017; Dijkman et al., 2019).

p –ISSN: **1693 - 7945**
e –ISSN: **2622 - 1969**

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Farmakodynamic Dexmedetomidine

The main pharmacological effects of dexmedetomidine are sedation and analgesia which have cardiovascular effects that have an impact on blood pressure, heart rate, and cardiac output (Li et al., 2016). Sedative and hypnotic effects are thought to be mediated through activation of central a2 receptors before and after synaptics at the locus coeruleus. Dexmedetomidine is also thought to affect endogenous sleep improvement pathways (Weerink et al., 2017).

The sedation effect of dexmedetomidine depends on its concentration in plasma. Plasma concentrations of 0.2-0.3 ng/mL can cause significant sedation. Deep unawakened sedation is thought to occur at plasma concentrations above 1.9 ng/mL. The analgesic effects of a2 agonists are thought to be mediated by binding to a2 receptors in central a2 receptors and the spinal cord. The transmission of pain is suppressed by hyperpolarization of interneurons and reduction of the release of pronociceptive transmitters such as substances P and glutamate (Weerink et al., 2017).

Use of Dexmedetomidine in Suppressing Cardiovascular Response Due to Intubation Action

Cardiovascular Effects of Dexmedetomidine

The act of laryngoscopy and tracheal intubation under general anesthesia leads to an increase in heart rate and arterial pressure. This statement is supported by Mahiswar et al's 2022 study that tracheal laryngoscopy and intubation caused significant increases in heart rate and arterial pressure in the placebo group but not in the dexmedetomy group (Mahiswar & Dubey, 2022). The same study conducted by Ariffianto et al. (2022) found that there was an increase in systolic, diastolic, mean arterial pressure, and heart rate after laryngoscopy and intubation.

A meta-analysis conducted by Cassai et al in 2021 showed that the administration of dexmedetomidine before endotracheal intubation significantly blunted the patient's hemodynamic response during laryngoscopy. Dexmedetomidine was significantly associated with reduced heart rate, systolic blood pressure, and MAP compared to those without dexmedetomidine. The decrease in sympathetic activity is supported by a decrease in norepinephrine levels in patients receiving dexmedetomidine, resulting in a decrease in adrenergic response at the time of induction, surgical incision, and extubation. These hemodynamic modifications should also be weighed against the potential risks of hypotension and bradycardia, since dexmedetomidine can cause a significant decrease in heart rate, which can lead to sinus arrest, especially in patients with high vagal tone (Cassai et al., 2021).

Dexmedetomidine produces a typical biphasic hemodynamic response. This response results in hypotension at low plasma concentrations and hypertension at higher plasma concentrations. The administration of IV bolus dexmedetomidine, which results in a high plasma (peak) concentration, results in an increase in blood pressure, a decrease in heart rate, and an increase in systemic vascular resistance. This is thought to be due to activation of α^2 receptors in vascular smooth muscle, resulting in peripheral vasoconstriction and causing hypertension. This is accompanied by a rapid decrease in heart rate, which can be caused by the baroreceptor reflex. (Weerink et al., 2017),(Yuan et al., 2019).

After a few minutes, when the plasma concentration of dexmedetomidine decreases, vasoconstriction weakens. This causes dexmedetomidine to also activate α^2 receptors in vascular endothelial cells, leading to vasodilation. α^2 receptors together with presynaptic α2-adrenoreceptor receptors that inhibit sympathetic catecholamine release and increased vagal activity will cause a phase of hypotension. The average decrease in arterial blood pressure (MAP) is on average 13-27% and is maintained for a long time after the initial dose. A decrease in circulating plasma catecholamine levels of 60-80% is dose-dependent, consistent with the long-term sympatholytic effect of dexmedetomidine. Like high initial plasma concentrations after IV bolus or fast-loading doses, higher maintenance doses are associated with progressive

p –ISSN: **1693 - 7945**
e –ISSN: **2622 - 1969**

increases in MAP. The hypertensive effect of dexmedetomidine can overcome the hypotensive effect at concentrations between 1.9 and 3.2 ng/mL (Weerink et al., 2017).

Dose

Research conducted by Mahiswar et al concluded that dexmedetomidine 0.5 mcg/kgBB administered bolus was as effective as fentanyl in weakening the hemodynamic response accompanying laryngoscopy and tracheal intubation without causing hemodynamic side effects. Therefore it can be considered as an alternative to opioids (Mahiswar & Dubey, 2022) This study is similar to Ariffianto et al (2022) study that dexmedetomidine 0.5 mcg/kgBB is more effective in preventing post laryngoscopy and intubation hemodynamic fluctuations compared to fentanyl 2 mcg/kgBB, especially in preventing increased heart rate.

4. Conclusion

Dexmedetomidine, recognized for its efficacy, plays a crucial role in mitigating the cardiovascular effects induced by laryngoscopy and intubation during general anesthesia. Notably, it demonstrates the capability to lower systolic, diastolic, and mean arterial pressure, along with reducing heart rate following these procedures. This observed impact positions dexmedetomidine as a valuable pharmacological intervention in the perioperative setting, effectively addressing the hemodynamic fluctuations associated with airway management. The utilization of dexmedetomidine is particularly advantageous in maintaining cardiovascular stability, and its incorporation into anesthetic protocols highlights its potential as a strategic agent for optimizing patient outcomes and ensuring the safety of individuals undergoing intubation procedures in the context of general anesthesia.

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