Comparative Evaluation of Hemodynamic Stability and Recovery During Conscious Sedation by Dexmedetomidine with Fentanyl Versus Ketamine with Fentanyl in Dilatation and Curettage

Thesis

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List of Contents

List of Tables

List of Figures

List of Abbreviations

Abb.	Full term
ASA	American society of anaesthesiology
CNS	Central nervous system.
D & C	Dilatation and curettage
D F	Dexmedetomidine and Fentanyl
Dex	Dexmedetomidine
HR	Heart rate.
K F	Ketamine and Fentanyl
MBP	Mean blood pressure.
NMDAR	N-methyl-D-aspartate receptor.
PACU	Post anesthesitic care unit.
SpO2	Arterial oxygen saturation.
T0	Before start of sedation.
T1	At 5min after start of sedation.
T2	At 10 min after start of sedation.
T3	After stop the infusion and before discharge from the PACU.
µg	microgram

INTRODUCTION

Conscious sedation is a technique of providing analgesia, sedation and anxiolysis while ensuring rapid recovery without side effects. Conscious sedation is administered with the dual goals of rapidly and safely establishing satisfactory procedural condition for the performance of therapeutic or diagnostic procedures while ensuring rapid, predictable recovery with minimal post-operative sequels ***(Jalowiecki et al., 2005).***

Dexmedetomidine is selective α2 adrenoceptor agonist that has sedative, sympatholytic, amnestic and analgesic effects ***(Carollo et al., 2008),*** it has been placed in a number of clinical trials as useful and safe substance. Providing an excellent analgesia, conscious sedation in patients who seem to be asleep, however can easily be awaken, in addition to no respiratory depression, make dexmedetomidine one of the widely used medication in anesthesia ***(Panzer et al., 2011).***

These properties of dexmedetomidine render it suitable for sedation and analgesia during the whole perioperative period. Its applications as a premedication, as an anesthetic adjunct for general and regional anesthesia and as a postoperative sedative and analgesic are similar to those of the benzodiazepines ***(Cheung et al., 2007).***

AIM OF THE WORK

The aim of this study is to investigate whether Dexmedetomidine with Fentanyl combination is an effective alternative modality to ketamine with fentanyl as sedation as regard hemodynamics stability and recovery for patients undergoing Dilatation and curettage procedure.

Chapter 1

CONSCIOUS SEDATION

Conscious sedation is defined as a medically controlled state of depressed consciousness in which patients retain their protective reflexes, maintain their airway independently, and respond to physical and verbal stimulation. Conscious sedation is intermediate in the spectrum of sedation, which ranges from anxiolysis and analgesia to general anesthesia. The key characteristics of conscious sedation are that it is of rapid onset, is titratable to an individual patient's desired level of sedation, and is associated with significant depression of consciousness, relief of anxiety, and analgesia. Retrograde amnesia of any pain associated with procedures is an additional benefit of conscious sedation. The effects of the medications most commonly used for conscious sedation are reversible with pharmacological antagonists ***(Clark and Tri, 2000).***

Definition of general anesthesia, level of sedation:

Minimal Sedation (Anxiolysis): is a drug-induced state during which patients respond normally to verbal commands. Although cognitive function and physical coordination may be impaired, airway reflexes, and ventilatory and cardiovascular functions are unaffected. ***(Coté et al., 2016).***

Moderate Sedation/Analgesia ("Conscious Sedation"): is a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain a patent airway, and spontaneous ventilation is adequate. Cardiovascular function is usually maintained ***(Coté et al., 2016).***

Deep Sedation/Analgesia:- is a drug-induced depression of consciousness during which patients cannot be easily aroused but respond purposefully following repeated or painful stimulation. The ability to independently maintain ventilatory function may be impaired. Patients may require assistance in maintaining a patent airway, and spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained ***(Coté et al., 2016).***

General Anesthesia:- is a drug-induced loss of consciousness during which patients are not arousable, even by painful stimulation. The ability to independently maintain ventilatory function is often impaired. Patients often require assistance in maintaining a patent airway, and positive pressure ventilation may be required because of depressed spontaneous ventilation or drug-induced depression of neuromuscular function. Cardiovascular function may be impaired ***(Coté et al., 2016).***

Chapter 2

DEXMEDETOMIDINE

(α2- adrenoceptor agonist)

The α2 receptors are are located on blood vessels, sympathetic terminals, central nervous system, and their activation leads to sedation, a reduction of tonic levels of sympathetic outflow, and an augmentation of cardiac-vagal activity ***(Thomas et al., 2000).***

Pharmacology of dexmedetomidine

Dexmedetomidine is an imidazoline derivative. Its chemical structure is 4-(S)-[1-(2,3-dimethylphenyl)ethyl]-1-H-imidazole mono hydrochloride. Dexmedetomidine is moderately lipophilic **(**Figure 1) ***(Kuusela et al., 2001).***

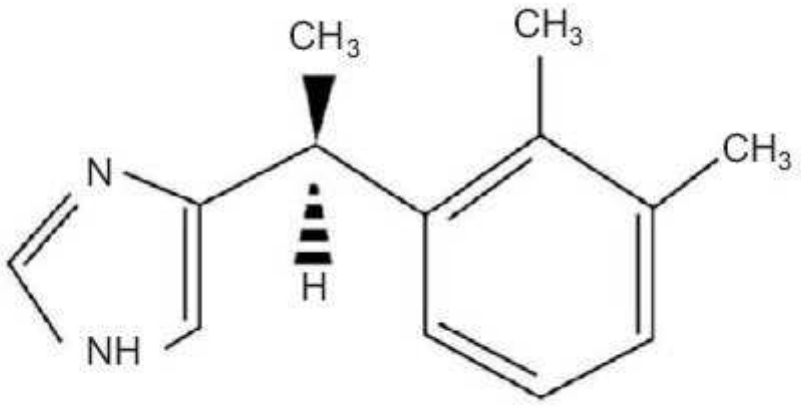

Figure (1): Chemical structure of dexmeditomedine ***(Kuusela et al., 2001).***

Pharmacokinetics:-

- **Absorption :**

Although dexmedetomidine is only registered for IV use, multiple routes of administration have been investigated. . After oral administration, an extensive first-pass effect is observed, with a bioavailability of 16%. Dexmedetomidine is well absorbed through the intranasal and buccal mucosae, a feature that could be of benefit when using dexmedetomidine in uncooperative children or geriatric patients ***(Li BL et al.2016).***

- **Distribution:**

Dexmedetomidine is a highly protein-bound drug. In plasma, 94% of dexmedetomidine is bound to albumin and α1-glycoprotein. In pre-clinical animal studies, it was found that dexmedetomidine readily crosses the blood–brain and placenta barriers Using non-compartmental analysis, a distribution half-life of about 6 min was found in healthy volunteers . After long-term infusion in ICU patients with hypoalbuminemia, an increased volume of distribution at steady state was observed ***(Välitalo PA et al ,2013)*** .

- **Metabolism :**

Dexmedetomidine is eliminated mainly through biotransformation by the liver. A hepatic extraction ratio of 0.7 was found . Less than 1% is excreted unchanged with metabolites being excreted renally (95%) and fecally (4%) .

Direct N-glucuronidation by uridine 5′-diphospho-glucuronosyltransferase (UGT2B10, UGT1A4) accounts for about 34% of dexmedetomidine metabolism. In addition, hydroxylation mediated by cytochrome P450 (CYP) enzymes (mainly CYP2A6) was demonstrated in human liver microsomes ***(Lee S, et al ,2016)***

- **Elimination:**

The hepatic extraction ratio of Dexmedetomidine has been previously estimated at about 70%, so changes in regional hepatic blood flow may have an effect on Dexmedetomidine pharmacokinetics, but the effect is small. Previous research has shown that 19% decrease in cardiac output resulted in an estimated 12% decrease in clearance. Changes in renal blood flow would not be expected to affect pharmacokinetics Additionally, the pharmacokinetics in subjects with normal renal function, mild, moderate and severe renal impairment, as defined by creatinine clearance, did not differ ***(Venn et al., 2002).***

For dexmedetomidine, prolonged as well as shortened elimination half-lives have been reported for patients with hypoalbuminemia. Clearance however, is only marginally affected by hypoalbuminemia ***(Zhang T et al ,2015).***

Pharmacodynamics:-

1- Analgesia

The mechanisms of the analgesic actions of α2 agonists have not been fully elucidated. A number of sites, both supraspinal and spinal, modulate the transmission of nociceptive signals in the CNS. Even peripheral α2 adrenoceptors may mediate antinociception ***(Nakamura and Ferreira, 1988).*** Drugs may act at any of these sites to reduce nociceptive transmission, leading to analgesia. The activation of inwardly rectifying G1-protein-gated potassium channels results in membrane hyperpolarization, decreasing the firing rate of excitable cells in the CNS. This is considered a significant mechanism of the inhibitory neuronal actions of α2-adrenoceptor agonists ***(Birnbaumer et al., 1990).***

Another prominent physiologic action ascribed to α2 adrenoceptors is their reduction of calcium conductance into cells, thus inhibiting neurotransmitter release. This effect involves direct regulation of calcium entry through N-type voltage-gated calcium channels and is independent of cAMP and protein phosphorylation. It is mediated by G0 proteins. These 2 mechanisms represent 2 very different ways of effecting analgesia: in the first, the nerve is prevented from ever firing, and in the second, it cannot propagate its signal to its neighbor ***(Birnbaumer et al., 1990).***

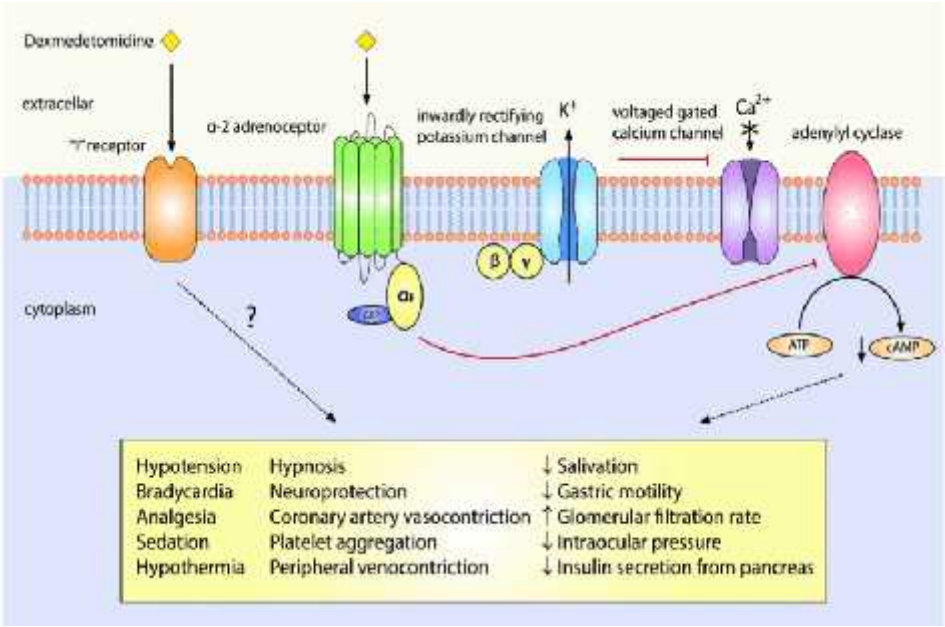

Figure (2): Mechanism of action of dexmedetomidine ***(Birnbaumer et al., 1990)***.

2- Sedation

The sedative action of Dexmedetomidine is mediated through its action on central α2-adrenoceptors in the locus ceruleus and receptors in the dorsal horn of the spinal cord are involved in these effects ***(Judith et al., 2000).***

Sedation after epidural administration of Dexmedetomidine likely reflects systemic and vascular redistribution to higher centers ***(Tanaka et al., 2000).***

Dexmedetomidine has been demonstrated to be an effective sedative in critical care settings. Early studies comparing premedication between Dexmedetomidine and