A Comparison between DexmedetomedineVersusPropofol for Management of Emergence Agitation and Facilitation of Extubation in the Surgical Intensive Care Unit Patients After Major Pelviabdominal Surgeries

Thesis
Submitted for Partial Fulfillment of the Degree of M.D.
In Anesthesiology

Presented by
Ahmad Mohamed EhabMoawad
M.B., B.Ch., M.Sc. Anesthesiology
Faculty of Medicine-AinShamsUniversity

Under Supervision of

Prof.Dr. Ibrahim AbdElghani Ibrahim
Professor of Anesthesia and Intensive Care
Faculty of Medicine-AinShamsUniversity

Prof.Dr.Ayman MokhtarKamaly
Professor of Anesthesia and Intensive Care
Faculty of Medicine-AinShamsUniversity

Prof. Dr. HazemM. AbdelrahmanFawzy
Professor of Anesthesia and Intensive Care
Faculty of Medicine-AinShamsUniversity

Dr.Ahmed SalahEldinOmran
Lecturer of Anesthesia and Intensive Care
Faculty of Medicine-AinShamsUniversity

Faculty of Medicine
AinShamsUniversity

2015

مقارنة بين الديكسميديتوميدين والبروبوفول لعلاج تهيج الصحو وتسهيل نزع الأنبوب الحنجرى للمرضى بالرعايه المركزه لحالات ما بعد الجراحه بعد الجراحات الكبرى للبطن و الحوض

رسالة توطئة للحصول علي درجة الدكتوراه
في التخدير

مقدمة من الطبيب /

أحمد محمد إيهاب معوض

تحت إشـــراف

أ.د/ إبراهيم عبد الغنى إبراهيم
أستاذ التخدير والرعاية المركزة
كلية الطب – جامعة عين شمس

أ.د/ أيمنمختار كمالى
أستاذ التخدير والرعاية المركزة
كلية الطب – جامعة عين شمس

أ.د/ حازم محمد عبد الرحمن فوزى
أستاذ التخدير والرعاية المركزة
كلية الطب – جامعة عين شمس

د/ أحمد صلاح الدين عمران
مدرس التخدير والرعاية المركزة
كلية الطب – جامعة عين شمس

كلية الطب
جامعة عين شمس
2015

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ICU	Intensive care unit
CNS	Central nervous system
VAS	Visual analogue scale
t1/2	Half life
EEG	Electro encephalo gram
GABA	Gamma amino butyric acid
NMDA	N-methyl D aspartate
CPP	Cerberal perfusion pressure
VAP	Ventilator associated pneumonia
MV	Mechanical ventilation
PEEP	Positive end expiratory pressure
TV	Tidal volume
MV	Minute ventilation
VC	Vital capacity
MVV	Maximum voluntary ventilation
MIP	Maximal inspiratory pressure
RSBE	Rapid shallow breathing index
PS	Pressure support
CPAP	Continues positive airway pressure
SBT	Spontanous breathing trial
PACU	Post anesthesia care unit
SAS	Sedation agitation scale
BIS	Bi-spectral index
RASS	Richmond agitation sedation scale
CPOT	Critical care pain observation tool
CVP	Central venous pressure

MAP	Mean arterial blood pressure
Vss	Steady state volume of distribution

Introduction

Sedation in the intensive care unit (ICU), long considered a necessary but relatively benign adjunct to patient management, is now recognized as an important determinant of patient morbidity ***(Kress et al., 2000)***.

Agitation is a common problem in the intensive care unit (ICU) and is often caused by delirium ***(Fraser et al., 2000)***. Agitation caused by disturbances of consciousness, attention, cognition, and perception, once referred to as ICU psychosis, is currently recognized as the hyperactive subtype of delirium, and has been referred to as agitated delirium ***(Meager et al., 2000)***.

The ideal sedative agent should allow for rapid modification of the sedation level by modifying the dosage (titratable) and should not have depressor effect on the cardiovascular or respiratory systems. It should be cheap and have short duration without cumulative effects, allowing for rapid recovery of effective spontaneous respiration after interruption of its administration in patients undergoing mechanical ventilation ***(Elbaradei et al., 2004).***

Dexmedetomidine is an alpha-2 adrenergic receptor agonist, with resulting sympatholytic and analgesic properties with no respiratory depressant effect ***(Hsu et al., 2004).***

Dexmedetomidine may enhance patient safety and comfort in long-term sedation ***(Ruokonen et al., 2009).***

Continuous sedation with propofol and midazolam were equally effective at achieving goal sedation in patients undergoing mechanical ventilation, but propofol was associated with significantly shorter times from drug discontinuation to extubation ***(Barrientos-Vega et al., 1997).***

Propofol has a slight, dose-dependent respiratory depressant effect. Respiratory depression is not of concern in patients undergoing mechanical ventilation but is an important consideration during weaning from ventilation ***(McKeage et al., 2003).***

Aim of the Work

The aim of this study is to compare the efficacy and safety profiles of Dexmedetomedine versus Propofol when used for weaning and facilitating extubation in the surgical intensive care unit patients.

Pharmacology of Dexmedetomidine

Dexmedetomidine is a highly selective α2 agonist (closely related to clonidine) with the potential advantages of anxiolysis and some analgesia without respiratory depression or amnesia ***(Wunsch., 2012).***

Mechanisms of action

Dexmedetomidine, an imidazole compound, is the pharmacologically active dextroisomer of medetomidine that displays specific and selective α2adrenoceptor agonism. The mechanism of action is unique and differs from those of currently used sedative agents, including clonidine. Activation of the receptors in the brain and spinal cord inhibits neuronal firing, causing hypotension, bradycardia, sedation, and analgesia. The responses to activation of the receptors in other areas include decreased salivation, secretion, and bowel motility in the gastrointestinal tract; contraction of vascular and other smooth muscle; inhibition of rennin release, increased glomerular filtration, and increased secretion of sodium and water in the kidney; decreased intraocular pressure; and decreased insulin release from the pancreas ***(Nakamura and Ferreira, 1988).***

In general, presynaptic activation of the α2 adrenoceptor inhibits the release of norepinephrine, terminating the propagation of pain signals. Postsynaptic activation of α2 adrenoceptors in the central nervous system (CNS) inhibits sympathetic activity and thus can decrease blood pressure and heart rate. Combined, these effects can produce analgesia, sedation, and anxiolysis. Dexmedetomidine combines all these effects, thus avoiding some of the side effects of multiagent therapies ***(Hunter et al., 1997).***

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 Ntype voltage gated calcium channels and is independent of cAMP and protein phosphorylation. It is mediated by G0 proteins. There are 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 ***(Gertler et al., 2001).***

One of the highest densities of α2 receptors has been detected in the locus coeruleus, the predominant noradrenergic nucleus in the brain and an important modulator of vigilance.

The hypnotic and sedative effects of α2adrenoceptor activation have been attributed to this site in the CNS. The locus coeruleus is also the site of origin for the descending medullospinal noradrenergic pathway, known to be an important modulator of nociceptive neurotransmission. In this region of the brain, α2adrenergic and opioidergic systems have common effectors mechanisms, indicating that dexmedetomidine has a supraspinal site of action ***(Gertler et al., 2001).***

Pharmacokinetics:

Following intravenous administration, dexmedetomidine exhibits the following pharmacokinetic parameters: a rapid distribution phase with a distribution half-life (t1/2) of approximately 6 minutes; a terminal elimination half life (t1/2) of approximately 2 hours; and steady state volume of distribution (Vss) of approximately 118 liters. Clearance is estimated to be approximately 39 L/h. The mean body weight associated with this clearance estimate was 72 kg ***(Venn et al., 2002).***

Distribution:

Dexmedetomidine protein binding was assessed in the plasma of normal healthy male and female volunteers. The average protein binding was 94% and was constant across the different concentrations tested ***(Dutta et al., 2000).***

Elimination:

Dexmedetomidine undergoes almost complete biotransformation with very little unchanged dexmedetomidine excreted in urine and faeces. Biotransformation to produce inactive metabolites involves both direct glucuronidation as well as cytochrome P450 mediated metabolism ***(Dutta et al., 2000).***

The terminal elimination half-life (t1/2) of dexmedetomidine is approximately 2 hours and clearance is estimated to be approximately 39 L/h. A mass balance study demonstrated that after nine days an average of 95% of the radioactivity, following IV administration of radio labeled dexmedetomidine, was recovered in the urine and 4% in the feces. No unchanged dexmedetomidine was detected in the urine. Approximately 85% of the radioactivity recovered in the urine was excreted within 24 hours after the infusion ***(Mantz, 2002).***