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INTRAOPERATIVE AND POSTOPERATIVE EFFECTS OF DEXMEDETOMIDINE ON HAEMODYNAMIC STRESS RESPONSES TO SURGERIES

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Abstract

Introduction : . Stress response to surgery is characterized by increase in secretion of endocrinal system and activation of immunological and sympathetic nervous system. Alpha 2-adrenoceptor agonists have several beneficial actions during the perioperative period. They decrease sympathetic tone, with attenuation of the neuroendocrine and hemodynamic responses to anaesthesia and surgery; reduce anaesthetic and opioid requirements; and cause sedation and analgesia.

Aims and objectives ; The objective of this study is to evaluate the intra-operative, and post-operative haemodynamic stress responses in patients, when Dexmedetomidine is used as an anaesthetic adjunct.

Materials and Method : After the approval from Ethical Committee of Guntur medical college , Guntur, A.P, 100 patients scheduled for elective surgery planned to be done under general anaesthesia were included in the study.Patients were randomly divided into two equal groups, according to the study drug administered, each group include 50 patients in number (n=50), group I (the control or placebo group) and group II (Dexmedetomidine group). Patients received either Dexmedetomidine hydrochloride (available as 100 μg/ml) in group II or saline solution in group I in equal amount.

Data were collected and entered into the software STATA (version 11.0). $P<0.05$ was considered significant and $P>0.05$ was considered insignificant.

Results : There was no significant difference in the base line parameters among the groups. Dexmedetomidine decreased heart rate significantly compared to control group. Dexmedetomidine reduced the intraoperative use of Propofol and Fentanyl significantly compared to control group.

Conclusion : The perioperative infusion of Dexmedetomidine appears to be effective to attenuate stress induced haemodynamic fluctuation, reduced Propofol requirements, decreased the intra and post-operative narcotic analgesic administration, produced perioperative sedation in patients who underwent elective surgeries when compared with placebo.

KEY WORDS : Stress response, Dexmedetomidine hydrochloride, Propofol and Fentanyl

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Introduction : Stress response is the term given to the hormonal and metabolic changes, which follow injury or trauma. [1]**.** Stress response to surgery is characterized by increase in secretion of endocrinal system and activation of immunological and sympathetic nervous system. Strenuous effort have been done to attenuate the cardiovascular, neuroendocrine and inflammatory response to surgery to improve the outcome and the effect on organ function**..**[2]

The first alpha 2-adreneceptor agonist was synthesized in the early 1960s to be used as a nasal decongestant. Early application of the new substance, now known as Clonidine, showed unexpected side effects, with sedation for 24 hours and symptoms of severe cardiovascular depression. Subsequent testing led to the introduction of Clonidine as an antihypertensive drug in 1966. Over the years, Clonidine gained acceptance as a powerful therapy not only for high blood pressure but also for the management of alcohol and drug withdrawal, for adjunctive medication in myocardial ischaemia, and for pain and intrathecal anaesthesia.[3]

Since the first report of Clonidine, the indications for this class of drugs have continued to expand. Alpha 2-adrenoceptor agonists have several beneficial actions during the perioperative period. They decrease sympathetic tone, with attenuation of the neuroendocrine and hemodynamic responses to anaesthesia and surgery; reduce anaesthetic and opioid requirements; and cause sedation and analgesia. They allow psychomotor function to be preserved while letting the patient rest comfortably. With this combination of effects, alpha 2-adrenoceptor agonists may offer benefits in the prophylaxis and adjuvant treatment of perioperative myocardial ischemia. Further-more, their role in pain management and regional anaesthesia is expanding. It has recently become evident that complete anaesthesia is possible by employing new, more potent alpha-2 agonist, such as medetomidine and its stereoisomer, Dexmedetomidine **.**[4]

Dexmedetomidine is a specific and short acting alpha-2 adrenoceptor agonist with an alpha-2a to alpha-1 ratio of 1300 and alpha-2a to imidazoline selectivity ratio of 32. Dexmedetomidine is a potent drug, at plasma concentrations less than 1.0 ng/ml it can produce profound physiological alterations. Dexmedetomidine is an isomer and the active component of medetomidine**.**[5]

Dexmedetomidine was approved by the Food and Drug Administration at the end of 1999 for use in humans as a short term medication (for less than 24 hours) for analgesia and sedation in the intensive care unit (ICU). Its unique properties render it suitable for sedation and analgesia during the whole perioperative period. Its applications as a premedicant , as an anaesthetic adjunct for general and regional anaesthesia, and as a postoperative sedative and analgesic are similar to those of the benzodiazepines, but a closer look reveals that the alpha-2 adrenoceptor agonist has more beneficial effects **.**[6]

Dexmedetomidine has no respiratory depression effect; a feature that makes it suitable to be given even to an extubated or spontaneously breathing patients so it is safely and effectively used in ICU surgical patients prior to, during and after extubation **.**[7]

Alpha-2 adrenoceptor agonist side effects consist of mild to moderate cardiovascular depression with slight decrease in blood pressure and heart rate.

The development of new, more selective alpha 2-adrenoceptor agonists with less side effect profiles may provide a new concept for the administration of perioperative anaesthesia and analgesia **.**[8]

Thus this study finds the intraoperative and postoperative effects of dexmedetomidine on haemodynamic stress responses to surgeries.

Aims and objectives ; The objective of this study is to evaluate the intra-operative, and post-operative haemodynamic stress responses in patients, when Dexmedetomidine is used as an anaesthetic adjunct.

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MATERIAL AND METHODS

After the approval from Ethical Committee of Guntur medical college , Guntur, A.P, 100 patients scheduled for elective surgery planned to be done under general anaesthesia were included in the study, after obtaining written consent from them.

INCLUSION CRITERIA:

- Age: 18-60 years of either sex
- ASA score I and II
- Surgeries lasting for more than one hour

EXCLUSION CRITERIA:

- Age below 18 years or above 60 years
- Morbid obesity
- History of heart disease (like ischemia, dysrhythmia, sinus bradycardia, heart block)
- History of chronic pulmonary disease
- Chronic endocrinal disease (like thyroid gland disease or diabetes mellitus)
- Autoimmune disease
- Raynaud's disease
- Pregnant females also were excluded from the study

Patients were randomly divided into two equal groups, according to the study drug administered, each group include 50 patients in number (n=50), group I (the control or placebo group) and group II (Dexmedetomidine group).

Patients received either Dexmedetomidine hydrochloride (available as 100 μg/ml) in group II or saline solution in group I in equal amount.

The drug preparation was done as follows:

Mix 2 ml of Dexmedetomidine with 48 ml of normal saline (0.9% sodium-chloride) for a 50ml solution with a concentration of 4 μg/ml. Shake gently for loading or maintenance infusion. Group II received a loading dose of 1 μg/kg I.V. infusion over 10 minutes and a maintenance dose of 0.5 μg/kg/hour I.V. infusion. Group I received 2 ml of normal saline at the same rate and volume as group II. The study drugs was provided to the two groups according to patient weight and tables 4 and 5.

All patients took 0.5 mg oral Alprazolam the night before surgery.

On the left, zero mm represents no pain, while on the right, 100 mm denotes the severe discomfort. At the pre-anaesthetic checkup, the patient was taught how to mark the line to indicate their pain. Patients were informed that this tool would assess their pain following surgery. Patients were monitored by ECG, pulse oximeter, and non-invasive blood pressure in the surgical room 30 minutes before anesthesia induction.

The study drugs was administered 30 minutes before anesthesia and terminated 2 hours following surgery. Patient monitoring continued for 6 hours postoperatively.

All patients are premedicated for 1-2 minutes before anesthesia induction with Ranitidine 50 mg, Fentanyl (2μg/Kg),

Glyco pyrrolate (0.2 mg),and Metoclopramide 10 mg I.V.

A sleep dose of Propofol, 1.5 mg/kg succinylcholine, and endotracheal intubation caused anesthesia. After partial muscle power recovery, Vecuronium (0.08 mg/kg) was given. Through a closed circuit system with CO2 absorber, O2 1L/min, and N2O 1.5L/min, minute ventilation was controlled to maintain an end tidal CO2 concentration of 30-35 mm Hg. If lacrimation, perspiration, or elevated heart rate or blood pressure exceeded 30% of preanaesthetic levels, fentanyl (20 μg) was given and repeated as needed.

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Treating bradycardia (heart rate < 50 beats/min) with atropine 0.6 mg and hypotension (30% reduction in baseline MAP or MAP < 60 mmHg) with Ephedrine 6mg intravenous increments.

The residual neuromuscular block was reversed by Neostigmine 0.05 mg/kg and Glycopyrrolate 0.02 mg/kg after surgery.
Each 1 ml of blood loss was replaced by 3 ml of lactated Ringer's solution if no transfusion was needed and by 1 ml of whole blood if more than 15% of body volume was lost.

The mean arterial blood pressure (MAP) and heart rate (HR) monitoring began 30 minutes before anesthesia, was monitored every 15 minutes, and continued for 6 hours after operation.
Table shows the Ramsay Sedation Score (RSS) (Ramsay et al., 1974)[9] used to measure and record sedation before induction by one minute and after 2 hours in the post-anaesthetic care unit (PACU).

Weight (Kg)	Infusion rate (ml/hr) for 10 minutes only	Total dose of Dexmedetomidine in group II by (mcg)
40	60	40
45	67.5	45
50	75	50
55	82.5	55
60	90	60
65	97.5	65
70	105	70
75	112.5	75
80	120	80
85	127.5	85
90	135	90
95	142.5	95
100	150	100

Table 1 : Loading dose infusion (ml/hour), of Dexmedetomidine delivered over 10 minutes

Table 2 : Maintenance dose infusion (ml/hour) of Dexmedetomidine :

Weight (Kg)	**Infusion rate (ml/hr)**	**Total dose of Dexmedetomidine infused per hour (mcg/hour) in group II**
40	**5**	**20**
45	**5.625**	**22.5**
50	**6.25**	**25**
55	**6.875**	**27.5**
60	**7.5**	**30**
65	**8.125**	**32.5**
70	**8.75**	**35**
75	**9.375**	**37.5**
80	**10**	**40**
85	**10.625**	**42.5**
90	**11.25**	**45**
95	**11.875**	**47.5**
100	**12.5**	**50**

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	Ramsay Sedation Scoring System
1	Anxious and agitated, restless
2	Cooperative, Oriented, tranquil
3	Responding to verbal commands, drowsy
4	Asleep, responsive to light stimulation (loud noise, tapping)
5	Asleep, slow response to stimulation
6	No response to stimulation

Table (3) : Ramsay Sedation Score :

Data were collected and entered into the software STATA (version 11.0). P<0.05 was considered significant and P>0.05 was considered insignificant.

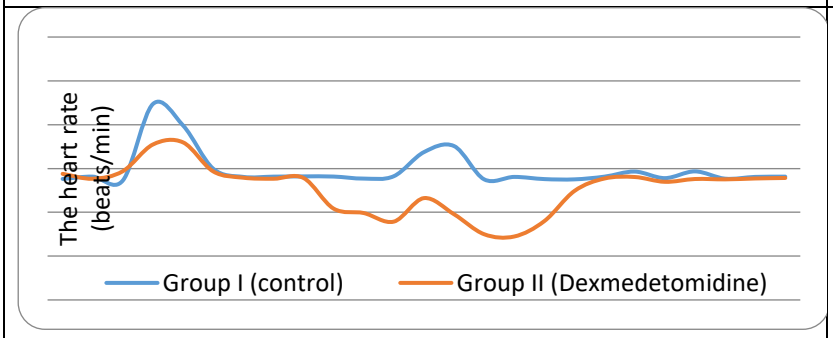
RESULTS :

Table (4): Demographic data of the 100 patients (50 in each group)in both groups. Values are mean (SD) or number patients

	Group I (control)	Group II (Dexmedetomidine)
Age	35.5(10.7)	33(10.32)
Gender(F/M)	28/22	31/19
Weight(kg)	55.3	56.5

There were no statistically significant differences in the demographic characteristics in both groups regarding the age, gender and weight. (table7)

The heart rate (beats/min) at the baseline, before induction, after intubation, during surgery and in the first 6 hours after end of surgery (in PACU).Values are mean (SD).



The mean arterial blood pressure (mm Hg) at the baseline, before induction, after intubation during surgery and in the first 6 hours after end of surgery (in PACU). Values are mean

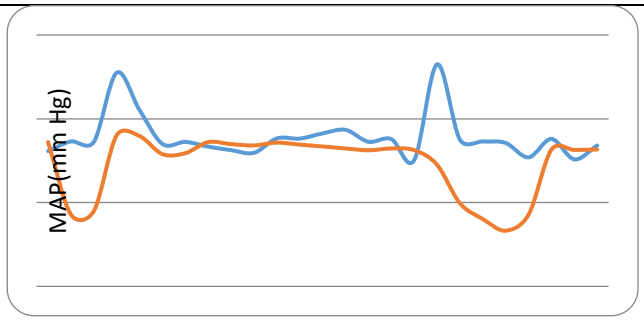


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Fig 1 No significant difference in baseline HR mean values between groups. (P<0.05) • Dexmedetomidine significantly decreased heart rate before anaesthesia. • Heart rate increased in both groups after intubation, significant in the control group but not in the Dexmedetomidine group. • Dexmedetomidine significantly reduced heart rate during surgery. (P<0.05 • Heart rate values in Dexmedetomidine group significantly lower than control group and baseline. • Heart rate values in Dexmedetomidine group significantly less after 15, 60, 120, 180 minutes in Post Anaesthesia Care Unit. • No significant difference in heart rate values after 240, 300, 360 minutes in PACU. • No electrocardiographic changes observed in patients, except sinus bradycardia. • Response to atropine was adequate.	• No significant difference in baseline values between groups. • Dexmedetomidine group had lower Mean Arterial Pressure (MAP) than control and baseline groups. • Blood pressure increased after endotracheal intubation in both groups. • Dexmedetomidine attenuated this response compared to saline. • During surgery, Dexmedetomidine significantly reduced MAP. • Control group MAP increased significantly after 120 and 135 minutes. • In PACU, Dexmedetomidine MAP values were lower than control group after 15,60,120,180, and 240 minutes.

Table (5):Timing ,Adjuvant Drug and Ramsay sedation score Before and After Induction

Parameter		Group i (control)	Group ii (dexmedetomidine)	P value
Timing	Sleep dose of propofol (mg)	112.2(7.90)	92.04(2.84)	0.0001*
	Intraoperative fentanyl (µg)	105.4(9.08)	81.5(2.31)	0.0001*
Adjuvant drug	Atropine	3(6%)	10(20%)	0.0197*
	Ephedrine	3(6%)	5(10%)	0.228
The level of sedation in each group (before induction) Ramsay sedation score	1. Anxious and agitated or restless	19(38)	0(0)	0.0006*
	2. Cooperative, oriented tranquil	16(32)	27(54)	0.2189
	3. Responding to verbal commands, drowsy	15(30)	18(36)	0.6518
	4. Asleep, responsive to light stimulation	0(0)	5(10)	0.0006*
	5. Asleep, slow response to stimulation	0(0)	0	
	6. No response to stimulation	0(0)	0	

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The level of sedation in each group (two hours post operative)	1. Anxious and agitated or restless	13(26)	0(0)	0.006*
	2. Cooperative, oriented tranquil	15(30)	22(44.90)	0.354
	3. Responding to verbal commands, drowsy	13(26)	15(30.61)	0.722
	4. Asleep, responsive to light stimulation	9(18)	9(18.37)	1.00
	5. Asleep, slow response to stimulation	0(0)	3(6.12)	0.006*
	6. No response to stimulation	0(0)	0(0)	

Dexmedetomidine's Effect on Postoperative Sedation Levels

Preoperative Sedation Levels:
• Dexmedetomidine significantly reduced sleep dose of Propofol and intraoperative Fentanyl compared to control group. ($P< 0.05$)
• Bradycardia patients required Atropine more than control group. ($P<0.05$) .significant
• Hypotension patients required Ephedrine more than control group. ($P>0.05$) which is not significant
• Dexmedetomidine reduced hourly postoperative analgesia requirements in PACU in the first 6 hours compared to saline. not significant in the 300 and 360 minutes ($P>0.05$)

Postoperative Sedation Levels:
• Dexmedetomidine significantly reduced patients with Ramsay Sedation Score (RSS) 1 and increased it to 4 compared to control group.
• Postoperatively, Dexmedetomidine patients with Ramsay Sedation Scores 1 and 5 were significantly lower than control group. ($P<0.05$) significant .
The number of patients with Ramsay Sedation Score of 2, 3, and 4 was higher in Dexmedetomidine group than the control group but not significant.($P>0.05$)

Discussion:

Dexmedetomidine is a novel lipophilic imidazole derivative with 100 times higher affinity for alpha-2- adrenoceptors compared to the prototype drug clonidine. . Sympathetic-adrenomedullary stress response was measured by blood pressure and heart rate.

Stress from surgery, endotracheal intubation, and anaesthesia can raise catechol amines, stress hormones, heart rate, and blood pressure (Aantaa et al., 1990)[10]. Hypertensive and coronary artery disease patients show more dynamic cardiovascular reactions to operation stress. Surgical events that increase sympathetic activation are connected to perioperative myocardial ischemia and infarction (Slogoff and Keats, 1985)[11].
Modern anaesthesiology reduces stress, especially in high-risk patients.

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This study demonstrated that preanaesthetic Dexmedetomidine dramatically decreased MAP without subjective complaints.

Laryngoscopy and endotracheal intubation raised control group arterial blood pressure and heart rate, but Dexmedetomidine lowered these.

Tachycardia patients at risk of myocardial ischemia may benefit.
Stress increased saline group heart rate and arterial blood pressure during procedure. Dexmedetomidine lowered surgery-related heart rate and blood pressure. This study's findings on surgery-related haemodynamic stress response match prior research on Dexmedetomidine's effects on heart rate and blood pressure.

Our findings reflected Abdalla & Soliman (2003)[12]. A single dosage of 2.5 μg/kg intramuscular Dexmedetomidine decreased the haemodynamic response to intubation. Inhibiting sympathetic activity with dexmedetomidine may lower blood pressure and heart rate. These features may reduce fatigue and myocardial ischemia after severe intubation and extubation (Venn and Grounds, 2001).[13.]
Dexmedetomidine's sympatholytic effect is likely caused by activation of inhibitory α2-adrenergic receptors in the CNS and peripheral sympathetic nerve endings (Presynaptic auto-receptors). This reduces heart rate and blood pressure by inhibiting sympathetic nerve ending norepinephrine release (Scheinin et al., 1991).[14.]
By activating ventro-lateral medulla imidazoline receptors, especially in the nucleus tractus solitaries 1, dexmedetomidine can produce bradycardia and hypotension 1.
Atropine was utilized to treat sinus bradycardia (heart rate <50 beats/min) in 20% of Dexmedetomidine patients.
In the Dexmedetomidine group,

10% of patients took ephedrine for hypotension (30% basal MAP decline or MAP < 60 mmHg). Dexmedetomidine can considerably influence haemodynamics below 1.0ng/ml (Khan et al., 1999).[7]. Patients with bradycardia, heart conduction abnormalities, hypotension, or hypvolaemia may not benefit from this medication. Other studies by Aho and Colleagues (1992a)[15,]
Some studies recommended anticholinergics for all dexmedetomidine patients under 40 (Peden et al., 2001)116. Jolonen and colleagues (1997)34 found that the mean hypotension ephedrine dose in the Dexmedetomidine group was much greater than in the control group.

A UK four-center study found that 18 of 66 ICU patients receiving Dexmedetomidine experienced hypotension (<60mm Hg or >30% drop from pre-infusion values) or bradycardia (<50 beats/min).
Central, peripheral, and autonomic ganglia have presynaptic and postsy naptic alpha-2-adrenoceptors. Central alpha-2-adrenoceptor stimulation reduces norepinephrine, sympathetic activity, sedation, anxiolysis, analgesia, and anesthesia (Duke et al., 1998[16]).
Dexmedetomidine significantly reduced Propofol sleep dosage compared to the control group.
Dexmedetomidine, a potent α-2-agonist, can minimize anesthetic requirements and act as an anesthetic at high doses.

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Research indicates that α-2-agonists like Dexmedetomidine reduce anesthetic demands by targeting pre and post-synaptic α-2-adrenoceptors in the central nervous system .Alpha-2-agonist hypnotic-anesthetic activity may be mostly located in the locus coeruleus (Correa-Sales et al., 1992)[17] Scheinin et al. (1992)[18] showed that Dexmedetomidine required less fentanyl than control.

Off-pump coronary artery bypass graft patients used less fentanyl after preoperative Dexmedetomidine infusion.
Nakagava and colleagues (1990)[19] suggest that the spinal noradregergic system and serotonin may influence ascending nocioceptine activation via alpha-2-adrenergic mechanisms. Dexmedetomidine induced Ramsay drowsiness Score, but patients were responsive, free from subjective side effects, calm in beds, and easily awoke to full consciousness. Dexmedetomidine's sedation matches alpha-2-adrenoceptor agonist pharmacology and previous studies. Bachand, Martin, and Bahana et al. found that dexmedetomidine significantly lowered Ramsay Sedation Score 1 (anxious, agitated, or restless) patients compared to placebo. . Traditional sedation assessments like the Ramsay Sedation Score may upset patients and encourage medication use.

Thus, non-invasive bispectral index (BIS) may be better for sedation monitoring. Triltsch and colleagues (2002)[20] admitted thirty major surgery patients to the ICU to maintain a BIS range of 60–70 during mechanical breathing.
Sedation with dexmedetomidine required far less propofol. Studies suggest that Dexmedetomidine-induced sedation triggers an endogenous sleep pathway. Dexmedetomidine induces sedation by activating post synaptic alpha-2-adrenoceptors in the locus ceruleus, which slows the firing rate of the biggest noradrenergic neurons and disinhibits ventrolateral preoptic nucleus activity. Alpha-2-agonists increase GABA release at the ventro-lateral preoptic nucleus, decreasing wake promoter area firing and causing sedation, according to Nelson et al. (2003)[21].

Summary : Study on Intraoperative and postoperative effects of dexmedetomidine on haemodynamic stress responses to surgeries Conducted at Guntur medical college , Guntur
• Randomly selected 100 patients for elective surgeries.
• Dexmedetomidine used as an anesthetic adjunct in general anesthesia.
• Patients were divided into two groups: control (control/placebo) and Dexmedetomidine group.
• Dexmedetomidine loading dose 1 μg/kg I.V infusion over 10 minutes given, and maintenance 0.5 μg/kg/hour I.V. infusion continued.
• Baseline mean arterial blood pressure (MAP) and heart rate monitored 30 minutes before induction, every 2 minutes during induction, every 10 minutes after tracheal intubation, every 15 minutes during surgery, and continued after surgery for six hours.
• Data collected and entered into STATA software.
• No significant difference in base line parameters among the groups.
• Dexmedetomidine significantly decreased heart rate, MAP, and intraoperative use of Propofol and Fentanyl.
• 20% of patients required Atropine to treat bradycardia.
• Dexmedetomidine reduced post-operative analgesic requirement and patients with RSS of one preoperatively and post-operatively.

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