Effect of Intravenous Dexmedetomidine Infusion on Interleukin-6 (IL-6) and Plasma Cortisol in Open Heart Surgery

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Abstract:

Aim of the work: to evaluate the effect of intravenous dexmedetomidine infusion on patients undergoing open heart surgery regarding stress response markers as plasma interleukin-6 and plasma cortisol.

Patents and Methods: Fifty consecutive patients aged 18-70years, scheduled for elective open heart surgery using CPB technique were enrolled in this study at the Cardiothoracic Surgery Unit, Luxor international hospital, from July 2018 to May 2019. Patients randomly assigned using closed envelope technique into two equal groups according to the drug infused intraoperatively: 1st group (25 patients):- Dexmedetomidine group (Group D); received loading dose of intravenous dexmedetomidine infusion of 1 µg/kg IV dissolved in 20ml normal saline over 10 minutes followed by maintenance dose of 0.5 µg/kg/hr. till the end of surgery where 0.5 µg /kg/h was calculated for each patient and dissolved in 12.5 ml normal saline 2nd group (25 patients):- placebo group (Group P); receive 20ml intravenous infusion of normal saline 0.9 % over 10 minutes followed by continuous infusion of 12.5 ml of normal saline till the end of surgery.

Results: Our study revealed that HR and MAP wasn't significantly different between the two groups at the baseline, but significantly lowered in Dex. group after induction, during CPB, post CPB, and postoperative.Dexometomedine suppress the intraoperative and postoperative rise of IL-6 which was significantly higher in placebo group relative to Dex. group. Also dexometomedine has effect on stress hormone as serum cortisol and serum glucose decease in Dex. group relative to placebo group. None of studied cases revealed bradycardia or hypotention and there are no significant difference between groups regarding side effect drowsiness, nausea and vomiting

Conclusion: This study demonstrated that the continuous administration of dexmedetomidine during open heart surgery with CPB suppressed intraoperative and post-operative cytokine secretion, and improved post-operative inflammatory response indices in the present study. Also it stabilize blood pressure and heart rate and blunt cardiovascular response to CPB. These results could be attributed to the anti-inflammatory effects of dexmedetomidine.

Key words: dexmedetomidine, interleukin-6, plasma cortisol, open heart surgery

Introduction

Surgical trauma, cardiac arrest, aortic cannulation, exposure of blood to non-physiological surfaces of the cardiopulmonary bypass circuit, and ischemia/reperfusion injury trigger the excessive release of pro-inflammatory factors e.g. cytokines(IL-6) and stress hormone e.g. cortisol. An atypical inflammatory response observed in SIRS and after CPB has been reported to be associated with oxidative stress**(Rose , 2003).**

Safe and effective agents with anti-inflammatory properties to be used as anesthetics in major surgeries need to be identified. In this regard, DEX is considered as apromising candidate because α2-adrenergic agonist have been reported to modulate inflammatory responses**(Rodemeister et al., 2014).**

Dexmedetomidine, the highly selective α2-adrenergic agonist, has been used for sedative and analgesic purposes in intensive care units. In recent years, its anti-inflammatory effects have been highlighted. In in-vitro studies, α2-adrenoceptor treatment inhibited the release of cytokines with endotoxaemia and stress hormone**(Qiao et al., 2009).** Dexmedetomidine can reduce cytokine secretion and stress hormone, which subsequently alleviates inflammation and reduces mortality**(Venn et al., 2001).**It was thought that excessive activation of the sympathetic nervous system and inflammation caused by cytokine secretion secondary to immune system interactions were alleviated by central sympatholytic effects of dexmedetomidine. This evidence suggested that harmful inflammatory responses can be suppressed by dexmedetomidine administration in patients who were stressed and have enhanced inflammatory reactions due to surgery and anaesthesia. In addition, dexmed-etomidine had organ-protective effects and could inhibit apoptotic cell death that played a pivotal role in the pathogenesis of sepsis.

Aim of the study:

The aim of the present work was to evaluate the effect of intravenous dexmedetomidine infusion on patients undergoing open heart surgery regarding stress response markers as plasma interleukin-6 and plasma cortisol.

Patients and methods:

The protocol was approved by our Institutional Review Board and written informed consent was obtained from patients. Fifty patients scheduled for elective open heart surgery at the Cardiothoracic Surgery Unit,

Luxor international hospital, from July 2018 to May 2019, were included in the study.

Study protocol:

Fifty consecutive patients aged 18-70years, scheduled for elective open heart surgery using CPB technique were enrolled in this study.

Patients randomly assigned using closed envelope technique into two equal groups according to the drug infused intraoperatively:-
- 1st group (25 patients):- Dexmedetomidine group (Group D); received loading dose of intravenous dexmedetomidine infusion of 1 μg/kg IV dissolved in 20ml normal saline over 10 minutes followed by maintenance dose of 0.5 μg/kg/hr. till the end of surgery where 0.5 μg /kg/h was calculated for each patient and dissolved in 12.5 ml normal saline
- 2nd group (25 patients):- placebo group (Group P); receive 20ml intravenous infusion of normal saline 0.9 % over 10 minutes followed by continuous infusion of 12.5 ml of normal saline till the end of surgery.
- An informed written consent was signed.

Preoperative variables included demographic data, and co-morbid conditions such as DM and hypertension and medications.
*Intraoperative va*riables included operation time, duration of CPB, hemodynamic (HR and MAP), interleukin-6 and stress hormone.
Postoperative variables included hemodynamic (HR and MAP), interleukin-6 and stress hormone.

Patient's selection and exclusion criteria:

Patients between 18 and 70 years of age of both sexes who manifested good left ventricular function with an ejection fraction greater than 35% were included in this double-blinded prospective study. Patients receiving corticosteroids, those having severe asthma, diabetes, or obstructive pulmonary disease, patients undergoing emergency cardiac surgery, patients who underwent angiography within 24 h before the study, and patients with impaired

renal function (creatinine>2.0mg/dl) or impaired liver function (serum transaminase >50 U/l) were excluded from the study. Patients in the study groups were instructed on the use of Numeric Pain Intensity Scale (NPIS), which ranged from No pain (**0**) to Unable to move (**10**), and Modified Ramsay Score (MRS) used to assess sedation, which ranged from **1**, Anxious/agitated to **6**, Asleep, no response to light glabellar tap (LGT).

Anesthetic protocol:

Before induction of anesthesia, all patients in the study group were routinely monitored using ECG, pulse oximetry, and continuous invasive blood pressure using an intra-arterial catheter connected to strain gauge pressure transducers.

Anesthetic technique was standardized for all patients using intravenous fentanyl (5–10μg/kg), sodium thiopental (1–2mg/kg), and cisatracurium (0.2mg/kg) as a muscle relaxant, and additional maintenance doses 0.03 mg/kg were given.

Laboratory tests:

Venous blood was collected before anaestheisa induction and after the CBP and 24 hrs. after recovery. The samples were immediately centrifuged and examined for serum interlukin-6, cortisol, and blood sugar level

Sample size and Statistical analysis:

Sample size will be calculated using EP1 info program 2000 at power 80% and confidence interval 95% 25 patients in each group was found sufficient to detect significant differences between the two groups. The significance level was set at P < 0.05. Statistical analysis was performed with IBM SPSS Statistics Version 20 for Windows. Numerical data were explored for normality by checking the distribution of data and using tests of normality (Kolmogorov-Smirnov and Shapiro-Wilk tests). Qualitative data were presented as frequencies and percentages. Chi-square test was used for comparisons regarding qualitative data. For parametric data; Independent Samples T. Test was used to compare between each two groups.

For non-parametric data; Mann-Whitney U Test was used to compare between each two groups.

Result:

Demographic data Table (1)

There is no statistical significant difference between the two groups as regard demographic data.

Surgical time & the duration of CPB

The mean of operation time in the Dex.group was 5.13±1.76 hrs. While in the placebo group was 5.4±1.9 hrs. With no statistical significant difference (P- value >0.05) on comparing the two groups.
The mean of cardiopulmonary bypass time (CPB) in the Dex.was 65.7±21.7min. While in the placebo group was 63.4±22.8min. with no statistical significant difference (P- value >0.05) on comparing the two groups.

Hemodynamic (HR and MAP)   Chart (1, 2)

Heart rate wasn't significantly different between two groups at the base line, but HR was significantly lowered in Dex. group after induction, in post CPB time and then in Postoperative time

MAP wasn't significantly different between the two groups at the baseline, but significantly lowered in Dex. group after induction, during CPB, post CPB, and postoperative.

BP was stabilized in Dex group compared to placebo group (minimize both surge and drop in BP).

Interleukin-6(pg /ml) Chart (3)

Our study showed that the comparison between the two studied groups in IL6 (pg /ml), the mean Interleukin-6 before induction was 95.42±5.23 (pg/ml) in Dex. group, while in placebo group was 97.52±10.23 (pg/ml).

Interleukin-6 wasn't significantly difference between the two groups in the baseline, (P-value >0.05) on comparing the two groups.

Interleukin-6 was significantly difference between the two groups after CPB and 24 hrs. after recovery, as IL-6 was significantly low in group D relative to group P. There is highly significant difference in the same groups as regard time of sampling.

Plasma cortisol level (Ig/dl) Chart (4)

Our study showed that the comparison between the two studied groups in plasma cortisol level (Ig/dl), the mean cortisol level before induction was12.16±0.97 (Ig/dl) in Dex. group, while in placebo group was 12.11±0.98 (Ig/dl).

Cortisol level wasn't significantly difference between the two groups in the baseline, (P- value >0.05) on comparing the two groups.

The mean cortisol level after CPB and 24 hr. after recovery was13.69±1.03, 15.66±1.06 (Ig/dl) respectively in Dex.group, while in placebo group was 32.11±0.98, 47.11±0.98 (Ig/dl) respectively.

Cortisol level was significantly difference between the two groups after CPB and 24 hrs. after recovery, as cortisol level was significantly low in group D relative to group P. There is highly significant difference in the same groups as regard time of sampling.

Plasma glucose level (mg/dl) Chart (5)

Our study showed that the comparison between the two studied groups in plasma glucose level (mg/dl), the mean glucose level before induction was96.77±7.22 (Ig/dl) in Dex. group, while in placebo group was 96.03±7.37(Ig/dl).

Glucose level wasn't significantly difference between the two groups in the baseline, (P-value >0.05) on comparing the two groups.

The mean glucose level after CPB and 24 hr. after recovery was 99.77±7.22, 98.53±7.04 (Ig/dl) respectively in Dex. group, while in placebo group was 141.03±7.37, 141.03±7.37(Ig/dl) respectively.

Glucose level was significantly difference between the two groups after CPB and 24 hrs. after recovery as glucose level was significantly low in group D relative to group P. There is highly significant difference in the same groups as regard time of sampling.

Postoperative side effects Table (2)

Side effect of dexmedetomidine is drowsiness, nausea, vomiting, bradycardia and hypotension.

There is no significant difference between the two groups regarding the side effects, none of the studied cases revealed bradycardia or hypotension.

Table 1: Demographic data

	Group D (n=25)	Group P (n=25)	P. value
Sex			
Male [No. (%)]	13(52%)	15(60%)	0.776
Female [No. (%)]	12(48%)	10(40%)	
Age(y)			
Mean±SD	51.04±12.61	48.4±7.80	0.378
Weight (kg)			
Mean±SD	73.64±15.07	72.76±12.60	0.824
Height (m)			
Mean±SD	1.65±0.10	1.68±0.11	0.318
BMI			
Mean±SD	26.99±3.68	25.76±2.35	0.165
Type of operation			
Valve [No. (%)]	13(52%)	15(60%)	
CABAG [No. (%)]	12(48%)	10(40%)	0.776

Used Independent samples T Test and Chi-square test,
* Statistically significant difference (p<0.05), **highly statistically significant difference (p<0.01).
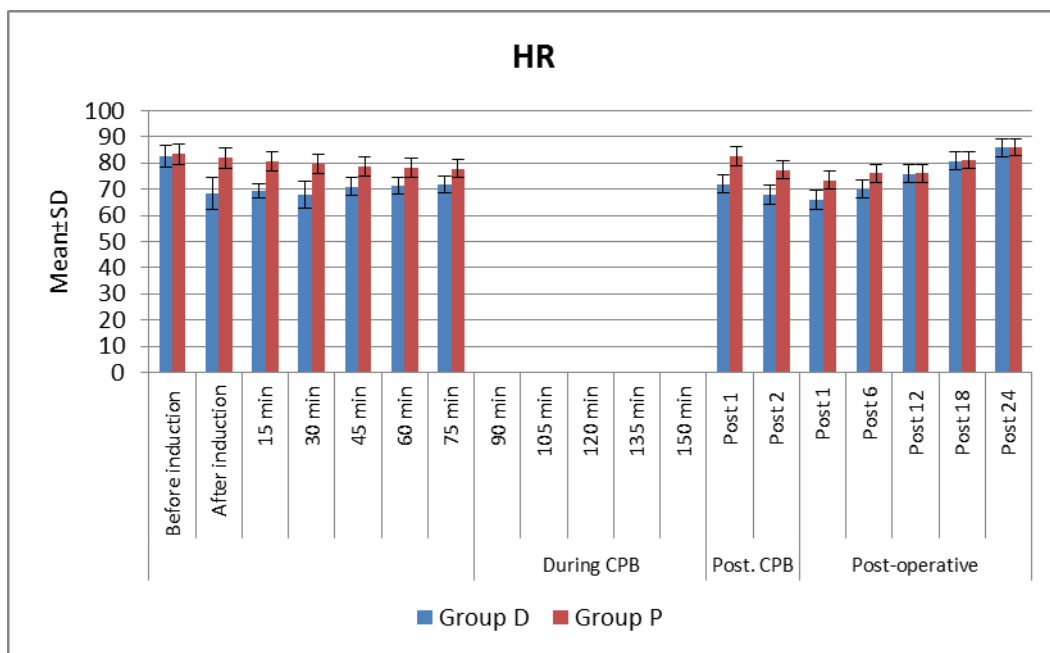

Chart (1) Clustered column chart showing (Mean±SD) of HR distribution between two groups.
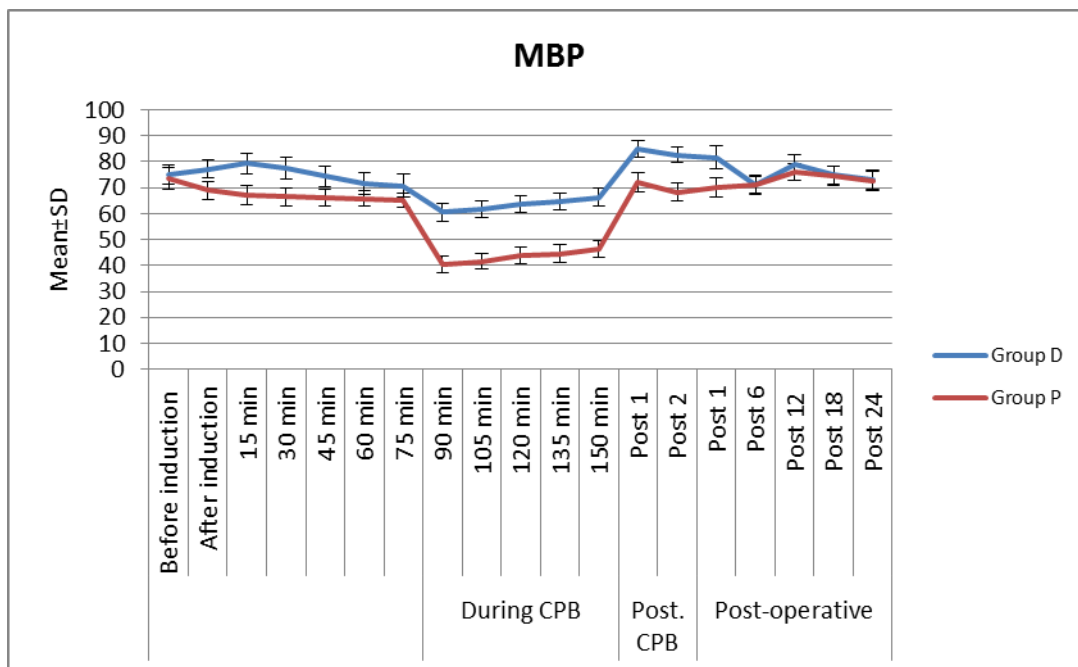

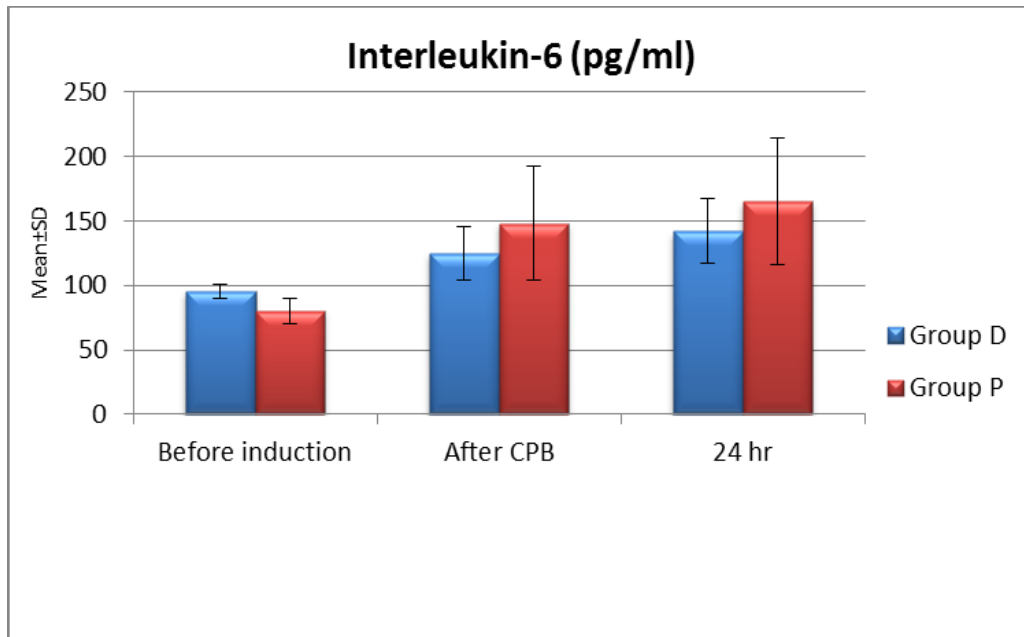**Chart (2)Line chart showing (Mean±SD) of MBP distribution between two groups**

Chart (3) Clustered column chart showing (Mean±SD) of Interleukin-6 (pg/ml) distribution between two groups.
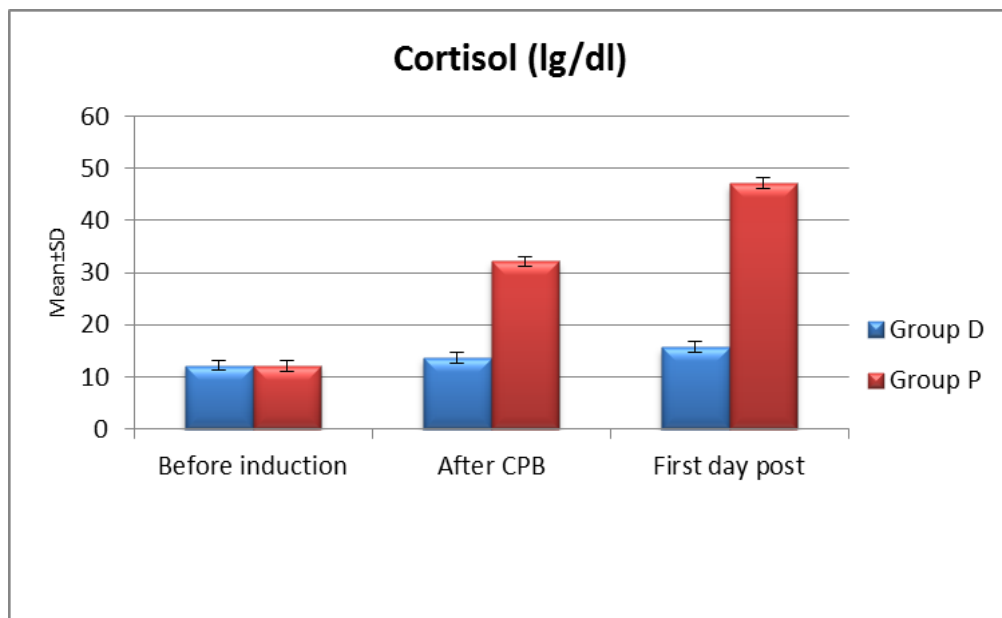

Chart (4) Clustered column chart showing (Mean±SD) of Cortisol (lg/dl) distribution between two groups.
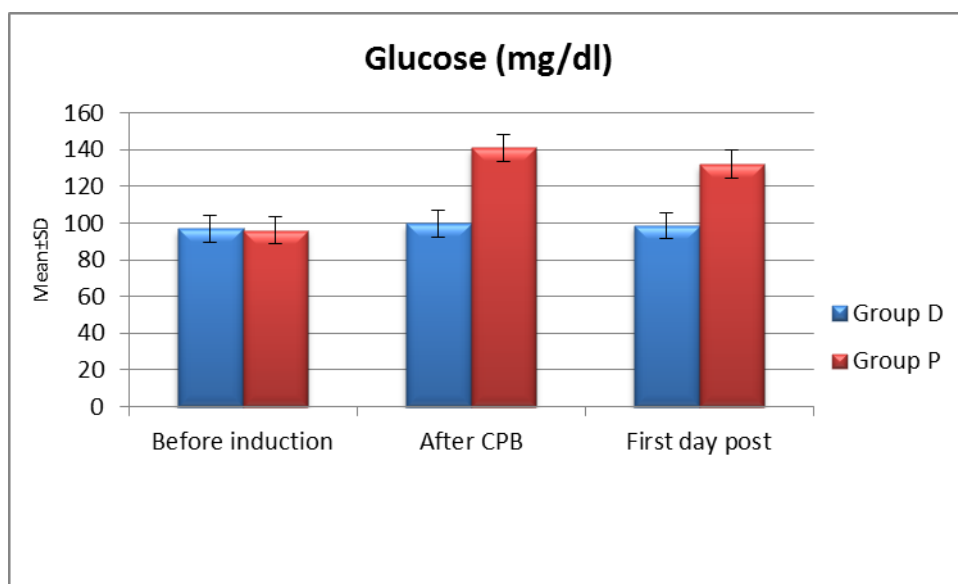
Chart (5) Clustered column chart showing (Mean±SD) of Glucose (mg/dl) distribution between two groups.

Table (2) Comparison between the studied groups in postoperative side effects.

Side effects	Group D (n=25) No. (%)	Group P (n=25) No. (%)	P. value
Drowsiness	`2(8%)	8(32%)	**0.077**
Nausea	5(20%)	4(16%)	0.741
Vomiting	15(60%)	6(24%)	0.258

Used Chi-square test,
* Statistically significant difference (p<0.05), **highly statistically significant difference (p<0.01).

Discussion:

Open heart surgery including sternotomy is a painful procedure that requires large doses of analgesic that can delay fast-track recovery(**Wijeysunderaet al., 2003).**Opioids are known to have a dose-dependent analgesic effect associated with side effects such as drowsiness, nausea, vomiting, depressed gastrointestinal motility, respiratory depression, and hemodynamic effects, especially with larger doses (**Biccardet al., 2008).**Nonopioid analgesics are used as opioid adjuncts to decrease opioid consumption, but their efficacy may be limited with potentially serious adverse effects such as increased bleeding and renal failure (**HoyandKeating, 2011).**

Dexmedetomidine (DEX) is highly selective α2-receptor agonist that provides better sedation, analgesia, and anxiolytic effect compared with clonidine. Dex shows a high ratio of specificity for the α2 receptor (α2/α1 1600:1) compared with clonidine (α2/α1 200:1), making it a complete α2 agonist

(**Mendaet al., 2010**).This property is considered unique among sedatives used for open heart surgery and intensive care patients (**Christensen,2009 ; Takasaki et al., 2009).**

In this study dexmedetomidine attenuated the stress response and so suppressed the intraoperative and postoperative rise of IL-6 which was significantly higher in group P relative to group D. IL-6 is a main proinflammatory cytokine produced as early as two to four hours after tissue damage. IL-6 level has a direct relation to the severity of inflammation and tissue injury.

In other clinical study, dexmedetomidine attenuated IL-6 elevation in postoperative patients **(Henneinet al., 1994).**It was showed that intravenous dexmedetomidine infusion decreases serum cytokine levels (TNF-α, IL-1 and IL-6) after abdominal surgery **(Zhou et al., 2006).**In in-vitro studies, dexmedetomidine had been shown that it could inhibit IL-6 production in peripheral blood mononuclear cells stimulated by lipopolysac-charides**(Dogrulet el., 2006).**In agreement with present study, Ahmed et al.IL-6 level was decreased in group D relative to group P intraoperative and during 24^{hr}.postoperative in major abdominal surgery**(Ahmed et al., 2011).**

One mechanism of stimulation of IL-6 release is via the intracellular cyclic adenosine monophosphate (cAMP) concentrations **(Naito et al., 1992).**Dexmedetomidine stimulates the postsynaptic a2-adrenergic receptors resulting in inhibitory feedback and decreased activity of adenylyl cyclase enzyme **(Correa et al., 1992).**

Stress hormone (serum cortisol and blood glucose) level were dereased in patient receive dexmedetomidine in our study as compared to placebo group.Aho et al., found that patients receiving dexmedetomidine had significantly lower intraoperative cortisol levels as compared with those who did not receive the drug before surgery. This supports the finding of the present study that dexmedetomidine administration resulted in lower levels of stress response markers to surgery**(Aho et al., 1992).**In agreement with the present study, Uyar et al., found that plasma concentration of cortisol and glucose had increased significantly in the placebo group, than in the dexmedetomidine group **(Uyar et al., 2008).**Interestingly, Mukhar et al., found that dexmed-etomidine did inhibit the hyperglycaemic response to surgery significantly more than placebo, and this may reflect attenuation of the sympatho-adrenal response **(Mukhtar et al., 2006).**In contrast to the present study, Aantaa et al., measured cortisol level in patients undergoing minor gynaecologic surgery and found that it was equally increased in saline and dexmedetomidine group. The results of the present study indicated that proinflammatory cytokine production (IL-6) was stimulated in the postoperative period following open heart surgery **(Aantaaet al., 1990).**

In the present study, HR and MAP were significantly lower but with hemodynamic stability, in group D relative to group P during most of the intra- and postoperative periods. Dexmedetomidine was able to blunt the increase in HR and MAP associated with endotracheal intubation in group D. Heart rate wasn't significantly different between two groups at the base line, but HR was significantly lowered in DEX group in post CPB time and then in Postoperative time. MAP wasn't significantly different between the two groups at the baseline, but significantly lowered in control group after induction, during CPB, post CPB, and postoperative. BP was stabilized in Dex. group compared to placebo group (minimize both surge and drop in BP).

BP was stabilized in Dex group compared to placebo group (minimize both surge and drop in BP). Although the real mechanism behind this is still unknown, several explanations have been suggested. The first mechanism is that using Dex as adjuvant could decrease hemodynamic response and the total dose of required hypnotic, less intraoperative opioid consumption **(Penget al., 2014).**Dex has been used as total intravenous anesthesia at doses as high as 10 μg/kg/h without inducing hypotension or severe bradycardia**(Shukryand Kennedy2007).**Also Dex has a binary effect: on one side decrease BP response to surgical stress and on the other side minimize surge in BP and HR post CPB and postoperative ICU. The use of α2‑agonists aims at blunting the hemodynamic stress response. Therefore, one would expect an increased BP and HR with placebo which is blunted by the administration of dexmed-etomidine**(Hashemianet al., 2017).**In addition sympathetic overstimulation could induce unsteadiness in BP and HR during CPB pump. Dex could centrally block α2 receptor and decrease excitation of sympathetic

neurons activity. This central inhibition of sympathetic system could minimize patient stress and instability in BP during and after CPB and in ICU. In addition, this central inhibition of sympathetic system could prevent sympathetic reservoir to be depleted and therefore Dex group have higher BP compared to placebo group.

In fact, Dex improves cardiovascular hemodynamics by decreasing dose of hypnotic for maintenance of anesthesia and its cardio depressant and vasodilator effect. Besides, Dexinfusionmay decrease the dose needed for Midazolam and fentanyl combination which depress the HR, BP, and cardiac index **(Rivenes et al., 2001).**

In summary, this study demonstrated that the continuous administration of dexmed-etomidine during open heart surgery with CPB suppressed intraoperative and post-operative cytokine secretion, and improved post-operative inflammatory response indices in the present study. These results could be attributed to the antiinflammatory effects of dexmed-etomidine.

Conclusion:
This study demonstrated that the continuous administration of dexmedetomidine during open heart surgery with CPB suppressed intraoperative and post-operative cytokine secretion, and improved post-operative inflammatory response indices and in the present study. Also it stabilize blood pressure and heart rate and blunt cardiovascular response to CPB. These results could be attributed to the anti-inflammatory effects of dexmedetomidine.

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