Original Article

Effect of Dexmedetomidine on Transcription Factors and Inflammatory Cytokines in Elective Aortic Aneurysm Repair Surgery

Faranak Behnaz[1], Ronak Karbalaeifar[1]*, Azita Chegini[2], Gholamreza Mohseni[1], Samad Valizadeh[2]

1. Anesthesiology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
2. Iranian Blood Transfusion Research Center, High Institute for Research and Education in Transfusion Medicine, Tehran, Iran

Corresponding Author: Ronak Karbalaeifar, MD, Anesthesiologist, Anesthesiology Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran. Tel: (+98) 21-22432572
Email: Ronak_k1990@yahoo.com

Abstract

Background: Aortic clamping during abdominal aortic aneurysm repair surgery leads to complications such as systemic inflammatory response (SIRS) and dysfunction in various vital organs. This study aimed to investigate the effect of dexmedetomidine infusion on transcription factors and inflammatory cytokines during elective open abdominal aortic aneurysm repair surgery.

Materials and Methods: A prospective, clinical trial performed on patients with abdominal aortic aneurysm surgery, which were divided into two groups (dexmedetomidine, 8 patients and control, 12 patients). Demographic characteristics, biochemical laboratory variables, fluid and blood transfusions during surgery, and levels of inflammatory cytokines and expression of inflammatory genes were evaluated and compared in both groups.

Results: There were no significant differences between the two groups regarding demographic characteristics, biochemical laboratory variables, fluids, and blood transfusions during surgery ($P > 0.05$). The level of inflammatory cytokines and the expression of inflammatory genes in both groups decreased significantly after surgery ($P < 0.05$). However, the level of inflammatory cytokines and the expression of inflammatory genes in the dexmedetomidine group were significantly lower at the end of the surgery ($P < 0.05$).

Conclusion: In abdominal aortic aneurysm surgery, dexmedetomidine could significantly reduce complications of clamping during surgery, which may result in hemodynamic stability and prevent significant inflammatory response to surgical stress and organ damage following ischemia-reperfusion damage.

Keywords: Abdominal aortic aneurysm, Inflammatory factors, Transcription factors, Blood transfusion, Hemodynamics, Clamping, Declamping

Please cite this article as: Behnaz F, Karbalaeifar R, Chegini A, Mohseni G, Valizadeh S. Effect of Dexmedetomidine on Transcription Factors and Inflammatory Cytokines in Elective Aortic Aneurysm Repair Surgery. J Cell Mol Anesth. 2020;5(3):131-42.

Introduction

The average prevalence of a ruptured abdominal aortic aneurysm (AAA or triple-A) is 5.6-17.5 per 100,000 people, and the mortality rate is about 80-90% (1-4). Despite advances in surgical procedures and preoperative care, AAAR is often associated with high mortality (5).

One of the most common complications leading to death during AAAR is acute organ injury following the intraoperative blood flow cessation due to aortic clamping (6). Clamping during AAAR leads to complications such as SIRS, dysfunction of various organs, which can even lead to death (7-9).

Aortic clamping leads to the release of catecholamines, followed by an increase in systemic vasospasm, resulting in arterial stenosis and a decrease in venous capacity (10). Following a rapid decrease in blood flow, oxygen decreases in the tissues distal to the aortic clamping, and oxygen uptake increases in the organs proximal to the clamp. Also, clamping leads to a disrupted cellular metabolism due to increased levels of inflammatory molecules, oxygen-free radicals, and the complement system (11).

Declamping is also associated with complications. The first hemodynamic response to declamping is a significant reduction in blood pressure, hypoxia-induced vasodilation of peripheral arteries, and excessive secretion of vasodilator metabolites from tissues distal to the clamp. Following clamping and blood flow retention, various inflammatory pathways are activated. Reperfusion leads to the production of oxygen-free radicals, activation of the complement system, and white blood cells, and platelet aggregation (12-19). Researchers attribute the inflammatory process in patients undergoing AAAR to several biochemical factors. Previous studies have shown that hypoxia-inducible factor-1A (HIF-1A) plays a key role in initiating inflammatory processes.

Extracellular adenosine has been identified as a key factor in controlling the inflammation caused by hypoxic and ischemic lesions (20).

Serum interleukin-1 (IL-1) and IL-6 levels have been shown to increase during AAAR and in the postoperative period. Increased serum tumor necrosis factor-α (TNF-α) levels during surgery are also associated with further postoperative complications (21-23).

Activation of T cells is controlled by a group of transcription factors such as Runx1 and Runx3, which are directly affected by the expression of T-bet, GATA-3, and RORγt gene (24, 25). The balance or imbalance between T helper1 / T helper 2 as well as T-helper1 / regulatory T cells plays an important role in many pathological processes such as surgical stress or ischemic-reperfusion processes and inflammatory responses can be measured by expression of T-bet, GATA-3, RORγt, and Foxp3 genes (26, 27).

Dexmedetomidine, a highly selective alpha-2 adrenergic agonist, is widely administrated as a premedication to induce anesthesia. Laboratory studies have shown that it has a preventive effect on the release of inflammatory cytokines and apoptosis (23, 28, 29).

The present study investigated the role of dexmedetomidine in AAAR on the serum levels of IL-1, IL-6, and TNF-α and expression of mRNAs related to systemic inflammation, and the production of cytokines such as GATA-3, T-bet, RORγ-T, and Foxp3.

There is limited information in the literature on the effects of dexmedetomidine on the level of the inflammatory cytokine, followed by AAAR. Considering the effect of the answer to this question on the postoperative prognosis and outcome, this study is one of the research priorities.

Methods

The present clinical trial was performed on patients undergoing elective open AAAR at Shohada-e Tajrish Hospital in Tehran between October 2017 and October 2019. AAAR patients entered the study after approval of the project and its methodology by the Iranian Registry of Clinical Trails (IRCT20190121042444N1) and the ethics committee of Shahid Beheshti University of Medical Sciences (IR.SBMU.RETECH.REC.1397.348) and obtaining permissions from the head of the Department of Anesthesiology of Shohada-e Tajrish Hospital.

Exclusion criteria include the previous history of aortic surgery, inflammatory bowel disease (IBD), malignancies, chronic inflammatory diseases, corticosteroid use, emergency surgery, and any patient instability during surgery. Before the start of the study, a researcher interviewed patients to describe the study,

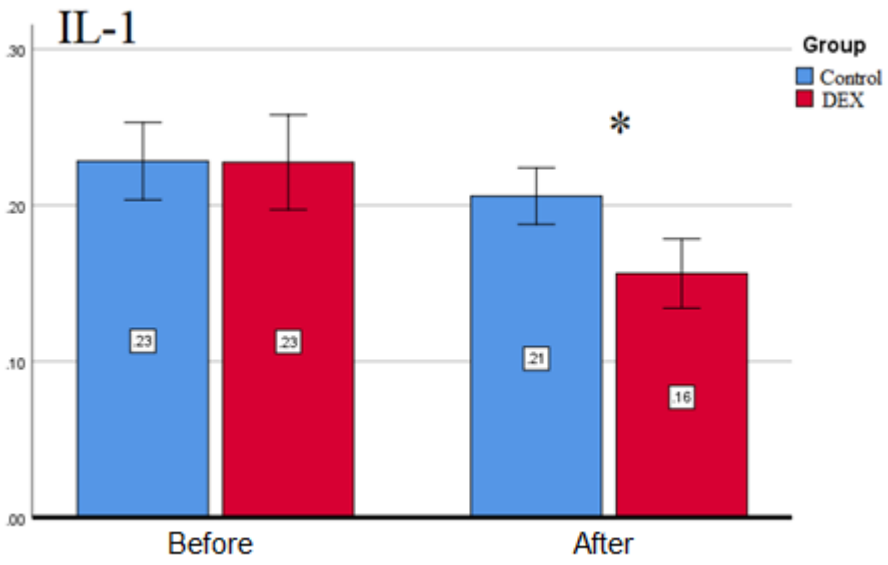

Figure 1. IL-1 level before and after surgery in control and experimental group.

the aim of the project, and the possible side effects of the project. Patients who signed the written consent were included in the study. After selecting eligible patients, they were randomly divided into control (n=12) and experimental groups (dexmedetomidine infusion) (n= 8).

Intraoperative care included invasive blood pressure monitoring, central venous pressure measurement, pulse oximetry, electrocardiography, and bispectral index (BIS). For induction of anesthesia in all patients, midazolam (0.01 mg/Kg), fentanyl (0.2mcg/Kg), lidocaine (1.5 mg / Kg), etomidate (0.2 mg/Kg), and cisatracurium (0.2 mg/Kg) were administrated, respectively. We used sevoflurane 1% for anesthesia maintenance and cisatracurium, and fentanyl was administrated every 45 minutes. After intubation, the CV line and arterial line were inserted for all patients, and surgery was started after completion of monitoring. In the experimental group, dexmedetomidine infusion was started immediately after intravenous injection of anesthetic (0.5 µg / Kg / h) and discontinued upon clamping.

Patient information such as the duration of the surgery, the duration of the aortic clamping, the amount of blood loss, the required intraoperative packed cell and FFP units, and the surgical complications, along with other demographic information prepared by the researchers, were recorded in questionnaires.

To measure serum IL-1, IL-6, and TNF-α levels and their gene expression and Foxp3, GATA3, RORγT, and T-bet expression once after induction of anesthesia before incision (baseline) and once 24 hours after completion of the surgery, blood samples were obtained through the patient's central venous catheter and collected in tubes containing ethylenediaminetetraacetic acid (EDTA). The blood samples were then placed in a centrifuge (2000 rpm) for 10 minutes; the sample plasma was removed from the surface, collected in glass tubes, and stored in a freezer at -80 °C until biochemical tests. The samples were then heated to reach a temperature of 4°C for biochemical evaluation. The level of inflammatory cytokines and the mRNAs expression were measured using laboratory kits.

The normal distribution of quantitative variables was investigated using the Kolmogorov-Smirnov test and box and normal probability plots. To compare the quantitative variables between the two groups, Student's t-test, and if necessary, the Mann–Whitney U test was used. Chi-square test was used to compare qualitative variables between the two groups and if necessary, Fisher's exact was done. A One-way ANOVA test was used to compare the normality between the three groups and the Kruskal–Wallis test was used in the case of non-normal data distribution. P-value< 5% was considered significant in all two-tailed statistical tests. Data analysis was carried out

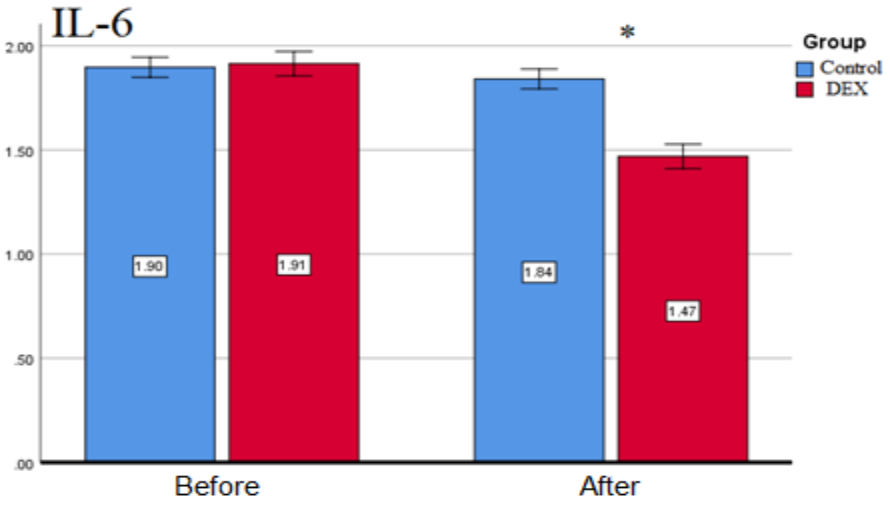

Figure 2. IL-6 level before and after surgery in control and experimental group.

using SPSS version 21; (version 11.5; SPSS Inc, Chicago, IL, USA).

Results

Demographic characteristics had no significant differences between the two groups (Table 1). The same was true regarding admission-related variables (Table 2). Systolic and diastolic blood pressure were higher in the dexmedetomidine group than the control group after clamping, being at times statistically significant. Besides, the mean central venous pressure (CVP) was generally higher in the dexmedetomidine group than the control group at all measured times, and this difference was sometimes statistically significant. It should be noted that dexmedetomidine infusion was stopped after clamping.

Tables 2 and 3, show the levels of expressed genes of inflammatory cytokines and compare their levels before and after surgery in each group alone, as

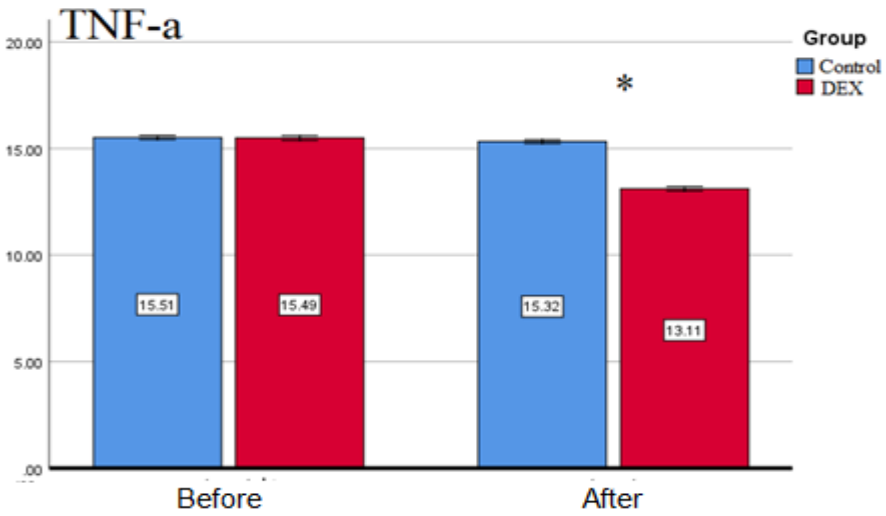

Figure 3. TNF-α level before and after surgery in control and experimental group.

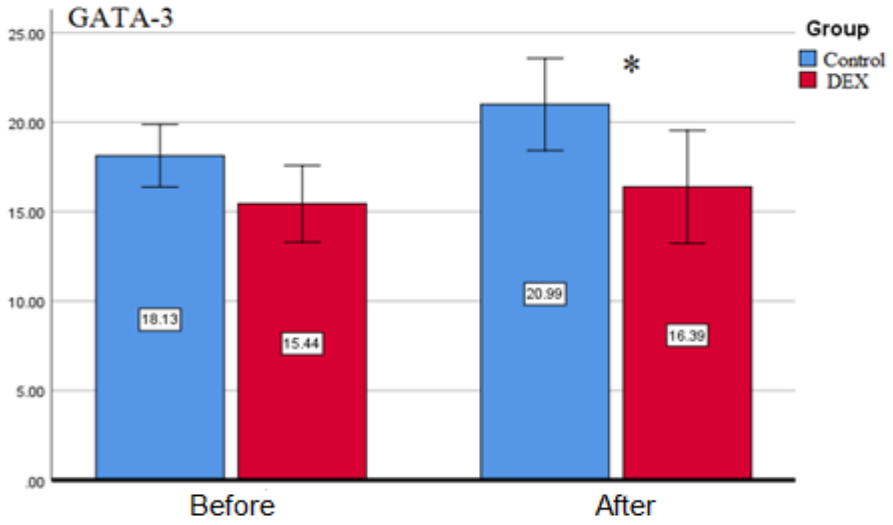

Figure 4. GATA-3 level before and after surgery in control and experimental group.

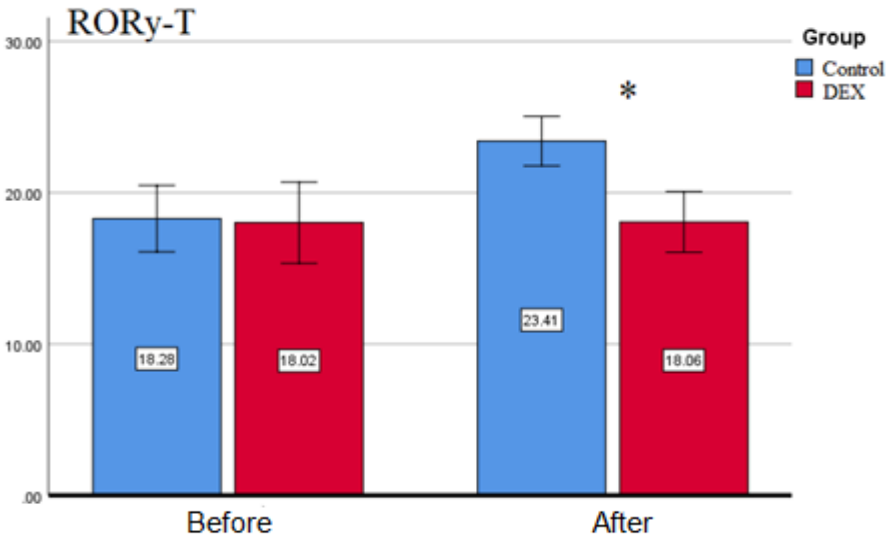

Figure 5. RORγ-T level before and after surgery in control and experimental group.

well as the expression levels of these genes between control and dexmedetomidine groups after surgery, respectively.

As shown in Table 3, there is a significant increase in IL-1, IL-6, and interferon-alpha (IFN-α) levels in the control group, as well as the expression of GATA3 and RORγ-T genes in the postoperative period, compared to the preoperative time (P<0.05). In contrast, such a significant increase in the inflammatory cytokines and T-bet gene expression was observed in the postoperative phase as compared to the preoperative phase (P<0.05).

Discussion

The present study aimed to investigate the effect of dexmedetomidine on the expression of inflammatory genes in patients undergoing elective open AAAR.

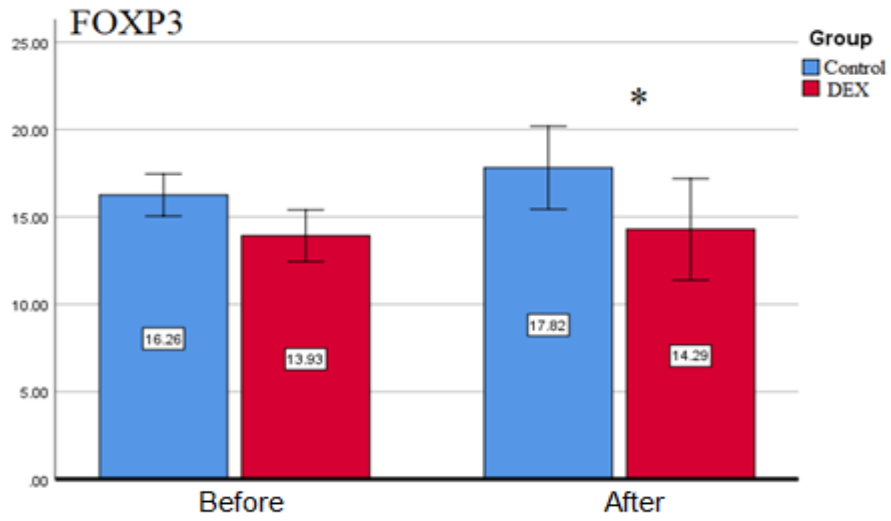

Figure 6. Foxp3 level before and after surgery in control and experimental group.

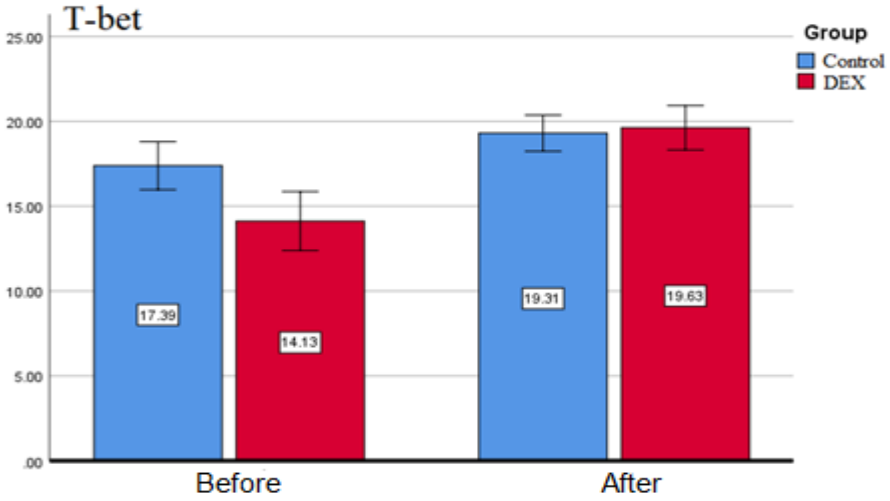

Figure 7. T-bet level before and after surgery in control and experimental group.

Overall, the results showed that the expression of inflammatory cytokine genes and transcription factors were significantly reduced in all patients except mRNA T-bet after surgery in the dexmedetomidine group.

Studies have shown that aortic clamping causes the release of catecholamines during AAAR, followed by an increase in systemic vasospasm, resulting in arterial stenosis and a decrease in venous capacity (10). This rapid decrease in blood flow leads to an increase in the rate of anaerobic metabolic reactions, lactic acidosis, and also, decreased glycogen, increased inflammatory molecules levels, oxygen-free radicals, and disorders of the complement system. (7, 11)

On the other hand, clamping significantly reduces blood pressure and causes hypoxia-induced vasodilation of peripheral arteries and the excessive secretion of vasodilator metabolites from tissues distal to the clamping site. On the other hand, following the clamping and blood flow retention, various inflammatory pathways are activated and biochemical changes happen, and reestablishing oxygen flow causes ischemia-reperfusion injury. These results in the formation of oxygen-free radicals, the activation of

Table 1: Comparison of demographic characteristics of patients in control and experimental group.

Variable		Control Group	Experimental Group	P-value
Age		69.83±10.8	75.75±7.1	0.10
Gender	Male	10	5	0.29
	Female	2	3	
Blood Group	A+	4	1	0.302
	AB+	1	0	
	B+	3	3	
	O-	2	0	
	O+	2	4	
Diabetes mellitus		2	2	0.53
Hypertension		10	8	0.34
History of Cardiac Disease		10	8	0.34

Table 2: Comparison of Biochemical variables, crystalloid and blood products of two groups during surgery.

Variable		Control Group	Experimental Group	P-value
Hemoglobin		12.52±1.3	12.54±1.6	0.97
Platelet		174.58±74.9	195.00±84.3	0.62
Blood Sugar		102.0±15.7	106.00±18.0	0.49
INR		1.15±0.1	1.03±0.0	0.06
Duration of Surgery (Hour)		3.97±0.4	3.86±0.4	0.48
Urine Output (cc)		700 ±286.6	1061.25±520.7	0.11
Normal Saline (L)		3.4±0.3	3.5±0.3	0.51
Ringer Lactate (L)		0.92±1.3	0.19±0.5	0.02
Length of ICU Stay		2.33±0.8	1.88±0.8	0.27
Length of Hospital Stay		2.33±0.6	3.25±1.1	0.06
Packed Red Blood Cell	1	1	0	0.34
	2	0	2	
	3	1	0	
	4	1	1	
Plasma	1	2	4	0.10
	2	4	4	
	3	2	0	
Days till expiration of Packed Red Blood Cell		9.75±7.9	16.00±4.0	0.06

the complement system, platelet aggregation, and the activation of white blood cells, leading to microvascular dysfunction in the tissues and organs distal to the clamping site (12-19).

Dexmedetomidine is a highly selective alpha-2 adrenergic agonist with a sedative and analgesic effect and is administrated as a sedative and short-term sleep-inducing drug in the clinic (30). Although many studies

Table 3: Comparison of expression of inflammatory cytokines Before and after surgery in both groups.

	Variable	Before Surgery	After Surgery	P-Value
Control	mRNA IL-1	0.22±0.4	0.20±0.03	0.002*
	mRNA IL-6	1.89±0.09	1.84±0.08	0.002*
	mRNA TNF-α	15.51±0.08	15.32±0.15	0.002*
	mRNA GATA-3	18.12±3.2	20.99±5.35	0.002*
	mRNA RORγ-T	18.28±3.3	23.40±3.3	0.028*
	mRNA Foxp3	16.25±1.6	17.81±4.6	0.09
	mRNA T-bet	17.39±2.9	19.30±1.6	0.05
Experimental	mRNA IL-1	0.22±0.2	0.15±0.02	0.011*
	mRNA IL-6	1.91±0.03	1.46±0.07	0.012*
	mRNA TNF-α	15.48±0.22	13.10±0.13	0.012*
	mRNA GATA-3	15.43±2.2	16.38±1.15	0.205
	mRNA RORγ-T	18.01±3.9	18.06±1.02	0.67
	mRNA Foxp3	13.92±2.3	14.28±2.17	0.15
	mRNA T-bet	14.12±0.6	19.62±1.92	0.01*

Table 4: Comparison of studied gene expression after surgery in both groups.

Variable	Control Group	Experimental Group	P-value
mRNA IL-1	0.20±0.03	0.15±0.02	0.007*
mRNA IL-6	1.84±0.08	1.46±0.07	<0.001*
mRNA TNF-α	15.32±0.15	13.10±0.13	<0.001*
mRNA GATA-3	20.99±5.35	16.38±1.15	0.022*
mRNA RORγ-T	23.40±3.3	18.06±1.02	0.004*
mRNA Foxp3	17.81±4.6	14.28±2.17	0.033*
mRNA T-bet	19.30±1.6	19.62±1.92	0.064

have been performed on the effect of dexmedetomidine in various surgeries, there has been still no study on its effect on vascular surgery, including AAAR and its effects on controlling inflammatory reactions following clamping and declamping. One of the reasons for the absence of studies on the effect of dexmedetomidine in this surgery is hypotension and hemodynamic instability during surgery. Therefore, hemodynamic stability was maintained through continuous monitoring of patients, and the patient was excluded in the case of hemodynamic instability.

The importance of this issue is that in addition to the need to maintain the patient's hemodynamic stability during AAR, and avoid unwanted hypotension, the clamps increase the complications of ischemic-reperfusion injury (IRI) in patients.

The results of the present study showed that the intraoperative dexmedetomidine administration, clamping, and declamping maintained the hemodynamic stability of patients and prevented severe intraoperative hypotension in patients compared to the control group.

Previous studies have proved the effect of dexmedetomidine on the hemodynamic system. Dexmedetomidine causes temporary vasoconstriction, followed by an increase in mean arterial blood pressure, and physiologically a decrease in heart rate by stimulating alpha-2 receptors on vascular smooth muscles. In addition to its effects on peripheral arteries, dexmedetomidine induces a sedative effect by affecting the central nervous system, decreases the number of circulating catecholamines which cause; these effects suppress the surgical stress and minimize hemodynamic fluctuations (31, 32).

In a study, Jalkanen et al. (2016) measured the severity of the response to systemic inflammation in patients undergoing open AAAR by measuring inflammatory factors. To investigate the serum level of inflammatory factors in their study, blood samples were taken from 6 patients undergoing aortic clamping in AAAR and 6 patients undergoing joint femoral surgery before and 24 hours after surgery. In this study,

48 different types of cytokines were evaluated in blood samples. The results of this study showed the highest increase in Il-6 and growth hormone after surgery (P = 0.016). HIF-1 levels also increased significantly in all patients except patients who had undergone blood transfusion during surgery. On the other hand, despite the significant increase in HIF-1 level after clamping, the CD39 and CD73 levels were significantly reduced. Jalkanen et al. concluded that aortic clamping induced a strong systemic inflammatory response and that appropriate drug therapy strategies should be used to reduce the complications of postoperative systemic inflammation (33).

In another study on the pattern of inflammatory cytokines levels before and after AAAR, Otterhag et al. (2014) investigated inflammatory mediators such as soluble urokinase-type plasminogen activator receptor (suPAR), endothelin, TNF-α, Il-6, and IgM antibodies against phosphorylcholine in 21 patients undergoing AAAR before and after surgery. The found that the serum suPAR, endothelin, and IL-6 levels were significantly increased after surgery. In contrast, IgM antibodies against phosphorylcholine levels were significantly reduced. The results of this study indicated that AAAR is associated with increased serum levels of inflammatory biomarkers, which may be affected by reconstructive surgery. It was also stated in this study that the serum IL-6 level can be used as one of the predictors of short-term surgical complications in patients living with aortic aneurysms (34).

Talke et al. (1995) conducted the first study on the role of dexmedetomidine in vascular surgery. In this study, they assessed the dose-dependent hemodynamic effects associated with dexmedetomidine infusion with different targeted plasma concentrations before the surgery in at-risk coronary artery disease patients. They concluded that dexmedetomidine reduced heart rate and systolic blood pressure in a dose-dependent manner (35). In a subsequent study on the effect of dexmedetomidine on the adrenergic and hemodynamic systems of patients undergoing vascular surgery, Talke et al. showed that dexmedetomidine infusion reduced the rate of increase in heart rate and plasma norepinephrine when anesthetizing patients undergoing vascular surgery (32).

In two meta-analyses on the effect of dexmedetomidine on vascular surgery, Vigisundra et al. showed that α-2 -adrenergic agonists reduced overall mortality, mortality from cardiac disease, and myocardial infarction during major vascular surgeries. These Meta-analyses reviewed 23 studies (n=3395 patients) and 31 studies (n=4578 patients) in 2003 and 2009, respectively (36, 37).

Soleyman & Zahri found fewer cases of hypertension and hypotension, lower demands for antihypertensive drugs in the aortic closure phase, as well as vasopressors in the declamping phase, and crystalloids, sevoflurane, and fentanyl in dexmedetomidine recipient patients undergoing AAAR. However, the most interesting finding of this study was the cardioprotective effect of dexmedetomidine, as evidenced by decreased postoperative plasma concentrations of troponin I, fewer cases of ischemia and myocardial infarction, and fewer cases of rhythm disturbances on echocardiography (38).

In another study on patients undergoing vascular surgery, Nair et al. showed that dexmedetomidine maintained hemodynamic stability during induction, surgery, and extubation in patients undergoing carotid endarterectomy (39). Bekker et al. also found that dexmedetomidine significantly reduced the need for beta-blockers and antihypertensive drugs and minimized hemodynamic fluctuations in awake patients undergoing carotid endarterectomy (40).

In recent years, many studies have investigated inflammatory activities induced by environmental stresses such as surgery and its effect on the body's inflammatory activity and the cells responsible for these processes. These studies have shown that the activity of T cells as one of the most important cells involved in inflammatory processes is controlled by a group of transcription factors such as Runx1 and Runx3, which are themselves directly affected by the T-bet gene, GATA-3, and RORγts expression (24, 25). Regulatory T cells (Tregs), on the other hand, play an important role in immune tolerance and stability, which is controlled by the Foxp3 transcription factor. Balance or imbalance between T helper 1 and 2 as well as T helper 1 and Tregs has been shown to play an important role in many pathological processes (such as stress caused by surgery or ischemic-reperfusion

processes). The inflammatory response to different stresses can be easily measured by measuring the expression of T-bet, GATA-3, RORγt, and Foxp3 genes (instead of measuring the amount of each cell alone) (26, 27).

Results of the present study showed that dexmedetomidine was effective in reducing the expression of genes involved in inflammatory activities of T cells. As explained, the decrease in the expression of the genes measured in the present study indicates a decrease in inflammatory cell differentiation and thus modulation of inflammatory processes, which leads to a decrease in the production of inflammatory cytokines such as IL- 1, IL- 6, and IFN-α. The importance of reduced T cell inflammatory activity during surgery is that inflammatory activity modulation occurring following the ischemic-reperfusion process during surgical procedures that require clamping and declamping processes can lead to a reduction in reactive oxygen species (ROS) production and subsequent cell survival (41).

Consistent with the results of the present study, two clinical trials have shown that intraoperative dexmedetomidine administration can inhibit the ischemic-reperfusion-induced inflammatory response during cardiopulmonary bypass. The first trial was carried out on patients undergoing coronary artery bypass grafting (CABG) or valve replacement surgery, and dexmedetomidine was administered as a bolus (1 μg/kg) within 10 minutes, followed by 0.5 μg / kg infusion per hour. In this study, the inflammatory response was measured using plasma concentrations of high-mobility group box protein (HMGB) and IL-6 as well as activation of nuclear factor KB (NF-κB) in neutrophils (42). In the second trial, CABG patients were examined who underwent partial cardiopulmonary bypass and dexmedetomidine (0.3 μg / kg / h) was started before the induction of anesthesia without loading doses. In this second trial, IL-1 and IL-6, TNF-α, and INF-γ were measured as indicators of the inflammatory response (43). As mentioned above, the results of the two clinical trials confirmed the significant reduction in inflammatory factors in the dexmedetomidine group as compared with the control group, which are consistent with the results of the present study suggesting the effective role of this drug in controlling inflammatory activities in vascular surgery requiring clamping and declamping.

Basic science studies have been performed to justify the anti-inflammatory effects of dexmedetomidine, and the results showed that dexmedetomidine prevents apoptosis of cardiomyocytes following IRI by inhibiting endoplasmic reticulum stress and reducing the production of reactive oxygen species (ROS) (44). In the central nervous system, dexmedetomidine can activate HIF-1α and suppress neuronal autophagy after cerebral ischemia (45). At the same time, dexmedetomidine inhibits activation of Toll-Like Receptor 4 (TLR4) and NF-κB pathways and microglia, leading to neuroprotection and the protection of neurons against inflammatory injury (46). The beneficial effect of dexmedetomidine on renal tissue has also been observed. dexmedetomidine treatment reduces neuroinflammation and oxidative stress following ischemic-reperfusion and increases renal cell survival by activating the extracellular-signal-regulated kinases (ERK) and Protein kinase B (PKB, also known as Akt) signaling pathways (41, 47). It has also been reported that dexmedetomidine activates phosphoinositide 3-kinases (PI3K), AKT, and HIF-1α pathways following IRI in the lung tissue, thus stimulating angiogenesis, maintaining glucose-metabolism, and ultimately facilitating ischemic preconditioning and cell survival (48).

Dexmedetomidine also has antioxidant and anti-inflammatory effects, which have a protective effect against surgical stress by inhibiting the production of pro-inflammatory cytokines and lipid peroxidation (8, 49, 50). Clinical evidence suggests that dexmedetomidine-induced sedation suppresses the inflammatory response caused by TNF-α, IL-1b, and IL-6 (51, 52). Animal studies have also shown that dexmedetomidine is effective in inhibiting the release of cytokines during inflammatory responses and thus reducing mortality, and in protecting organs and tissues considering its anti-inflammatory properties (53, 54).

Conclusion

Overall, the results of clinical and laboratory studies have shown that intraoperative dexmedetomidine administration in patients undergoing AAAR can significantly reduce complications caused by clamping-declamping processes, which can lead to

impaired hemodynamic stability as well as IRI. However, further studies with higher sample size and measurement of other inflammatory and anti-inflammatory factors are recommended.

Acknowledgment

The authors would like to acknowledge the kind support of all physicians and nurses, Shohada-e Tajrish Hospital, Tehran, Iran. Besides, the kind cooperation of the Anesthesiology Research Center, SBMU is highly appreciated.

Conflicts of Interest

The authors declare that they have no conflict of interest.

References

1. Moll FL, Powell JT, Fraedrich G, Verzini F, Haulon S, Waltham M, et al. Management of abdominal aortic aneurysms clinical practice guidelines of the European society for vascular surgery. Eur J Vasc Endovasc Surg. 2011;41 Suppl 1:S1-S58.
2. Bengtsson H, Bergqvist D. Ruptured abdominal aortic aneurysm: a population-based study. J Vasc Surg. 1993;18(1):74-80.
3. Johansson G, Swedenborg J. Ruptured abdominal aortic aneurysms: a study of incidence and mortality. Br J Surg. 1986;73(2):101-3.
4. Mealy K, Salman A. The true incidence of ruptured abdominal aortic aneurysms. Eur J Vasc Surg. 1988;2(6):405-8.
5. Aivatidi C, Vourliotakis G, Georgopoulos S, Sigala F, Bastounis E, Papalambros E. Oxidative stress during abdominal aortic aneurysm repair--biomarkers and antioxidant's protective effect: a review. Eur Rev Med Pharmacol Sci. 2011;15(3):245-52.
6. Eltzschig HK. Targeting purinergic signaling for perioperative organ protection. Anesthesiology. 2013;118(5):1001-4.
7. Moris DN, Kontos MI, Mantonakis EI, Athanasiou AK, Spartalis ED, Bakoyiannis CN, et al. Concept of the aortic aneurysm repair-related surgical stress: a review of the literature. Int J Clin Exp Med. 2014;7(9):2402-12.
8. Brady AR, Fowkes FG, Greenhalgh RM, Powell JT, Ruckley CV, Thompson SG. Risk factors for postoperative death following elective surgical repair of abdominal aortic aneurysm: results from the UK Small Aneurysm Trial. On behalf of the UK Small Aneurysm Trial participants. Br J Surg. 2000;87(6):742-9.
9. Papia G, Klein D, Lindsay TF. Intensive care of the patient following open abdominal aortic surgery. Curr Opin Crit Care. 2006;12(4):340-5.
10. Norwood MG, Bown MJ, Sayers RD. Ischaemia-reperfusion injury and regional inflammatory responses in abdominal aortic aneurysm repair. Eur J Vasc Endovasc Surg. 2004;28(3):234-45.
11. Gelman S, MD, PhD. The Pathophysiology of Aortic Cross-clamping and Unclamping. Anesthesiology. 1995;82(4):1026-57.
12. Lindsay TF, Luo XP, Lehotay DC, Rubin BB, Anderson M, Walker PM, et al. Ruptured abdominal aortic aneurysm, a "two-hit" ischemia/reperfusion injury: evidence from an analysis of oxidative products. J Vasc Surg. 1999;30(2):219-28..
13. Sadeghi M, Dogan EM, Karlsson C, Jansson K, Seilitz J, Skoog P, et al. Total resuscitative endovascular balloon occlusion of the aorta causes inflammatory activation and organ damage within 30 minutes of occlusion in normovolemic pigs. BMC Surg. 2020;20(1):43.
14. Eide TO, Aasland J, Romundstad P, Stenseth R, Saether OD, Aadahl P, et al. Changes in hemodynamics and acid-base balance during cross-clamping of the descending thoracic aorta. A study in patients operated on for thoracic and thoracoabdominal aortic aneurysm. Eur Surg Res. 2005;37(6):330-4.
15. Kieffer E, Chiche L, Godet G, Koskas F, Bahnini A, Bertrand M, et al. Type IV thoracoabdominal aneurysm repair: predictors of postoperative mortality, spinal cord injury, and acute intestinal ischemia. Ann Vasc Surg. 2008;22(6):822-8.
16. Carr GE, Yuen TC, McConville JF, Kress JP, VandenHoek TL, Hall JB, et al. Early cardiac arrest in patients hospitalized with pneumonia: a report from the American Heart Association's Get With The Guidelines-Resuscitation Program. Chest. 2012;141(6):1528-36.
17. Coba V, Jaehne AK, Suarez A, Dagher GA, Brown SC, Yang JJ, et al. The incidence and significance of bacteremia in out of hospital cardiac arrest. Resuscitation. 2014;85(2):196-202.
18. O'Connor CJ, Rothenberg DM. Anesthetic considerations for descending thoracic aortic surgery: part II. J Cardiothorac Vasc Anesth. 1995;9(6):734-47.
19. Wahlberg E, Dimuzio PJ, Stoney RJ. Aortic clamping during elective operations for infrarenal disease: The influence of clamping time on renal function. J Vasc Surg. 2002;36(1):13-8.
20. Grenz A, Zhang H, Eckle T, Mittelbronn M, Wehrmann M, Köhle C, et al. Protective Role of Ecto-5′-Nucleotidase (CD73) in Renal Ischemia. J Am Soc Nephrol. 2007;18(3):833-45.
21. Galle C, De Maertelaer V, Motte S, Zhou L, Stordeur P, Delville JP, et al. Early inflammatory response after elective abdominal aortic aneurysm repair: a comparison between endovascular procedure and conventional surgery. J Vasc Surg. 2000;32(2):234-46.
22. Kiss J, Yegutkin GG, Koskinen K, Savunen T, Jalkanen S, Salmi M. IFN-beta protects from vascular leakage via up-regulation of CD73. Eur J Immunol. 2007;37(12):3334-8.
23. Taniguchi T, Kidani Y, Kanakura H, Takemoto Y, Yamamoto K. Effects of dexmedetomidine on mortality rate and inflammatory responses to endotoxin-induced shock in rats. Crit Care Med. 2004;32(6):1322-6.
24. Saito S, Nakashima A, Shima T, Ito M. Th1/Th2/Th17 and regulatory T-cell paradigm in pregnancy. Am J Reprod Immunol. 2010;63(6):601-10.
25. Wong WF, Kohu K, Chiba T, Sato T, Satake M. Interplay of transcription factors in T-cell differentiation and function: the role of Runx. Immunology. 2011;132(2):157-64.
26. Chakir H, Wang H, Lefebvre DE, Webb J, Scott FW. T-bet/GATA-3 ratio as a measure of the Th1/Th2 cytokine profile in mixed cell populations: predominant role of GATA-3. J Immunol Methods. 2003;278(1-2):157-69.
27. Lee WC, Wang HC, Hung CF, Huang PF, Lia CR, Chen MF. Vaccination of advanced hepatocellular carcinoma patients with tumor lysate-pulsed dendritic cells: a clinical trial. J Immunother. 2005;28(5):496-504.
28. Qiao H, Sanders RD, Ma D, Wu X, Maze M. Sedation improves early outcome in severely septic Sprague Dawley rats. Crit Care. 2009;13(4):R136.
29. Sanders RD, Hussell T, Maze M. Sedation & immunomodulation. Crit Care Clin. 2009;25(3):551-70, ix.
30. Gertler R, Brown HC, Mitchell DH, Silvius EN. Dexmedetomidine: a novel sedative-analgesic agent. Proc (Bayl Univ Med Cent). 2001;14(1):13-21.
31. Ommi D, Teymourian H, Zali A, Ashrafi F, Jabbary Moghaddam M, Mirkheshti A. Effects of Clonidine Premedication on Intraoperative Blood Loss in Patients With and Without Opium Addiction During Elective Femoral Fracture Surgeries. Anesth Pain Med. 2015;5(4):e23626.
32. Talke P, Chen R, Thomas B, Aggarwall A, Gottlieb A, Thorborg P, et al. The hemodynamic and adrenergic effects of perioperative

dexmedetomidine infusion after vascular surgery. Anesth Analg. 2000;90(4):834-9.
33. Jalkanen J, Maksimow M, Jalkanen S, Hakovirta H. Hypoxia-induced inflammation and purinergic signaling in cross clamping the human aorta. Springerplus. 2016;5:2.
34. Otterhag SN, Gottsäter A, Acosta S, Palmqvist B, Lindblad B. Inflammatory mediators after endovascular aortic aneurysm repair. Cytokine. 2014;70(2):151-5.
35. Talke P, Li J, Jain U, Leung J, Drasner K, Hollenberg M, et al. Effects of perioperative dexmedetomidine infusion in patients undergoing vascular surgery. The Study of Perioperative Ischemia Research Group. Anesthesiology. 1995;82(3):620-33.
36. Wijeysundera DN, Bender JS, Beattie WS. Alpha-2 adrenergic agonists for the prevention of cardiac complications among patients undergoing surgery. Cochrane Database Syst Rev. 2009;(4):CD004126.
37. Wijeysundera DN, Naik JS, Beattie WS. Alpha-2 adrenergic agonists to prevent perioperative cardiovascular complications: a meta-analysis. Am J Med. 2003;114(9):742-52.
38. Soliman R, Zohry G. The myocardial protective effect of dexmedetomidine in high-risk patients undergoing aortic vascular surgery. Ann Card Anaesth. 2016;19(4):606-13.
39. Nair AS. Benefits of using dexmedetomidine during carotid endarterectomy: A review. Saudi J Anaesth. 2014;8(2):264-7.
40. Bekker AY, Basile J, Gold M, Riles T, Adelman M, Cuff G, et al. Dexmedetomidine for Awake Carotid Endarterectomy: Efficacy, Hemodynamic Profile, and Side Effects. J Neurosurg Anesthesiol. 2004;16(2):126-35.
41. Kim SH, Jun JH, Oh JE, Shin EJ, Oh YJ, Choi YS. Renoprotective effects of dexmedetomidine against ischemia-reperfusion injury in streptozotocin-induced diabetic rats. PLoS One. 2018;13(8):e0198307.
42. Ueki M, Kawasaki T, Habe K, Hamada K, Kawasaki C, Sata T. The effects of dexmedetomidine on inflammatory mediators after cardiopulmonary bypass. Anaesthesia. 2014;69(7):693-700.
43. Bulow NM, Colpo E, Pereira RP, Correa EF, Waczuk EP, Duarte MF, et al. Dexmedetomidine decreases the inflammatory response to myocardial surgery under mini-cardiopulmonary bypass. Braz J Med Biol Res. 2016;49(4):e4646.
44. Liu C, Fu Q, Mu R, Wang F, Zhou C, Zhang L, et al. Dexmedetomidine alleviates cerebral ischemia-reperfusion injury by inhibiting endoplasmic reticulum stress dependent apoptosis through the PERK-CHOP-Caspase-11 pathway. Brain Res. 2018;1701:246-54.
45. Luo C, Ouyang MW, Fang YY, Li SJ, Zhou Q, Fan J, et al. Dexmedetomidine Protects Mouse Brain from Ischemia-Reperfusion Injury via Inhibiting Neuronal Autophagy through Up-Regulating HIF-1alpha. Front Cell Neurosci. 2017;11:197.
46. Sun Z, Zhao T, Lv S, Gao Y, Masters J, Weng H. Dexmedetomidine attenuates spinal cord ischemia-reperfusion injury through both anti-inflammation and anti-apoptosis mechanisms in rabbits. J Transl Med. 2018;16(1):209.
47. Ma J, Chen Q, Li J, Zhao H, Mi E, Chen Y, et al. Dexmedetomidine-Mediated Prevention of Renal Ischemia-Reperfusion Injury Depends in Part on Cholinergic Anti-Inflammatory Mechanisms. Anesth Analg. 2020;130(4):1054-62.
48. Liang S, Wang Y, Liu Y. Dexmedetomidine alleviates lung ischemia-reperfusion injury in rats by activating PI3K/Akt pathway. Eur Rev Med Pharmacol Sci. 2019;23(1):370-7.
49. Geze S, Cekic B, Imamoglu M, Yoruk MF, Yulug E, Alver A, et al. Use of dexmedetomidine to prevent pulmonary injury after pneumoperitoneum in ventilated rats. Eur Rev Med Pharmacol Sci. 2019;23(1):370-7.
50. Kip G, Celik A, Bilge M, Alkan M, Kiraz HA, Ozer A, et al. Dexmedetomidine protects from post-myocardial ischaemia reperfusion lung damage in diabetic rats. Libyan J Med. 2015;10(1):27828.
51. Gu J, Sun P, Zhao H, Watts HR, Sanders RD, Terrando N, et al. Dexmedetomidine provides renoprotection against ischemia-reperfusion injury in mice. Crit Care. 2011;15(3):R153.
52. Sen V, Guzel A, Sen HS, Ece A, Uluca U, Soker S, et al. Preventive effects of dexmedetomidine on the liver in a rat model of acid-induced acute lung injury. Biomed Res Int. 2014;2014:621827.
53. Taniguchi T, Kurita A, Kobayashi K, Yamamoto K, Inaba H. Dose- and time-related effects of dexmedetomidine on mortality and inflammatory responses to endotoxin-induced shock in rats. J Anesth. 2008;22(3):221-8.
54. Zhang J, Wang Z, Wang Y, Zhou G, Li H. The effect of dexmedetomidine on inflammatory response of septic rats. BMC Anesthesiol. 2015;15:68.