Effects of dexmedetomidine on inflammatory responses in patients undergoing major abdominal surgeries

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Abstract

Background: Surgical injury to tissue as in major abdominal surgeries causes a variety of profound inflammatory response which may lead to postoperative complicationswith significant co morbidity.Dexmedetomidine, a highly selective α2-adrenoceptor agonist, is widely used in clinical anaesthesia, and intensive care unit.The aim of this study is to evaluate the anti-inflammatory effect of dexmedetomidine in major abdominal surgeries.

Patients and methods:40 patients for radical cystectomy in the age range of 40 – 65 years participated in thisprospective, randomized, double blinded, placebo controlled clinical study.Patients were randomly assigned to receive either Dexmeditomidine (Dex group) or normal saline (0.9%) (Control group).Serum tumor necrosis factor (TNF-α), Interleukin-6 (IL-6), and C-reactive protein (CRP) were analyzedbefore the start of the study drug infusion, after complete recovery and the day one postoperatively.

Results: inflammatory markers were significantly higher in both groups compared to baseline measurements. TNF-α, IL-6 measurements were less in Dex group in postoperative period.

Conclusion: Dexmedetomidine is effective in attenuating the postoperative rise of the proinflammatory cytokine interleukin-6 and tumor necrosis factor (TNF-α).

Introduction:-

Surgical injury to tissue as in major abdominal surgeries causes a variety of profound physiologic reactions which are essential to the restoration of an organisms' homeostasis. The response involves the release of stress hormones (i.e. C - reactive protein (CRP), cortisol, catecholamines), stimulation of the complement system, directioning of leukocytes to the site of injury, the release of cytokines (e.g. interleukins, tumour necrosis factor) in addition to other cellular products (i.e. superoxide radicals, proteases, growth factors). **(1)**

Inflammatory response may be a cause of postoperative complications in patients with significant co morbidity. **(2)**

Dexmedetomidine, a highly selective α2-adrenoceptor agonist, is widely used in clinical anesthesia, intensive care unit (ICU) management and pain treatment as a sedative agent**. (3)**

It is well known that dexmedetomidine (DEX) inhibits both neuroendocrine and inflammatory response in different experimental and clinical settings. **(4)**

Aim of the study:-

This study aimed to evaluate the anti inflammatory effect of dexmedetomidine in major abdominal or pelvi abdominal surgeries**.**

Patients and methods:

This prospective, randomized, double blinded, placebo controlled clinical study was approved by the Ethics and Research Committee of Sohag Faculty of Medicine, Sohag University. It was done at Sohag University Hospital between August 2015 and December 2016. Written informed consent was assigned by each patient preoperatively. The study included 40 patients between 40 – 65 years.

The Inclusion criteria were as follows:-

Patients with an American Society of Anesthesiologists (ASA) physical status of I or II and scheduled for major abdominal or pelvi-abdominal surgery under general anesthesia were included in this study.

Exclusion criteria included the followings:-

A history of drug or alcohol abuse , allergy to any of the study medications , 2nd or 3rd degree heart block , treatment with α 2 agonists or antagonists, chronic use of anti-psychotic medications, chronic use of anti-inflammatory drugs , labile hypertension, cardiac dysrhythmias, coronary artery disease, renal, hepatic or cognitive impairment.

Patients were randomly assigned to receive either Dexmeditomidine (Dex group) or normal saline (0.9%) (Control group).Randomization and enrollment were done using sequentially numbered closed envelops. All patients assessment were performed by an anesthetist blinded to the drug used for the study and to reduce the selection and pretest biases another anesthetist prepared the study drug and covered the syringe pumps and infusion system

All patients were premeditated with atropine (0.02 mg IM) and midazolam 5mg IM. Standard moniroring were applied to all patients.Two large bore intravenous cannulas were inserted in the right and left forearms.

After complete aseptic conditions central venous line was inserted in the right internal jugular or subclavian vein using Seldinger's technique for rapid infusion of fluids if needed. Radial artery on either side was cannulated after doing Allen's test (to make sure that there is adequate blood supply for the wrist and hand by the ulnar artery) for continuous monitoring of blood pressure.

Patients were randomly assigned into two groups:-

Patients in the dexmedetomidine group (Dex group) were infused by dexmedetomidine at 1 µg/kg in 20 ml of 0.9 saline infused IV over 10 minutes as a loading dose then a maintenance dose of 0.5 µg/kg/h was infused along the course of the surgery, and patients in the control group received 20 ml of normal saline infused IV over 10 minutes followed by a maintenance infusion of normal saline till the end of surgery.

General anesthesia was induced in both groups by propofol (1.5-2 mg/kg) and fentanyl (2-5 µg/kg). Rocuronium (1 mg/kg) was used for endotracheal intubation. Patients were mechanically ventilated with a mixture of oxygen - air (FiO_2 = 0.4) with $EtCO_2$ stabilized at 30-35 mmHg.

Anesthesia was maintained by inhalational route with Sevoflourane in both groups. All patients in each group were injected with ondansetron 4 mg prior to the end of surgery.

Patients were completely reversed and extubated on table and were transferred to the PACU after following commands.

Data collection and measurements:-

Patient characteristics including age , sex , weight, ASA physical status , volume of blood loss and volume of blood transfused in addition to duration of anesthesia (time from the start of induction of anesthesia till discontinuation of inhalational anesthesia, reversal of muscle relaxant and tracheal extubation). And duration of surgery (time from the skin incision till the end of skin closure) were recorded.

Laboratory investigations:

About 10 ml venous blood was withdrawn before the start of the study drug infusion, after complete recovery and the day one postoperatively at 8 am from patients and control by a clean venipuncture and immediately delivered into3 serum separator tubes.

The following investigations were performed:

1- Serum IL-6 and TNF-α concentrations were determined by commercially available enzyme –linked immunosorbant assay (ELISA)(Assay Max Human)

.This assay employs a quantitative sandwatwish enzyme immunoassay technique that measured IL-6 and TNF-α murine monoclonal antibody specific for IL-6 and TNF-α has been precoated onto microplate . IL-6 and TNF-α IL-6 and TNF-α standards and samples is sandwiched by the immobilized antibody specific for human IL-6 and TNF-α which is recognized by streptavidin-peroxidase conjugate .All unbound material washed away and peroxidase enzyme substrate is added. The color developed stopped and intensity of the color is measured at 450nm.

Minimal detection limit < 10pg/ml

2- C-reactive protein was tested by semiquntitative latex agglutination test (Omega Diagnostic Kit UK) according to manufactures guide

Data are presented as mean±standard deviation or number (%). Independent t-test and Mann Whitney tests were used to compare between study groups. Categorical data were compared by chi squared and fisher exact tests. P-value less than 0.05 was considered significant

Results:-

A total of forty patients were involved in this prospective study; twenty patients received the study drug, dexmedetomidine, and twenty patients as control.

All patients performed radical cystectomy with orthotopic diversion. Patients' demographic data, duration of anesthesia and surgery, volume of blood loss, and volume of blood transfusion did not differ between the two groups (Table 1).

Table (1): Patients demographic data, duration of anesthesia and surgery, volume of blood loss, and volume of blood transfusion.

	Dex group (N=20)	Control group (N=20)	*P-value
Age (years)	54.45±8.9	54.65± 8.5	0.94
Sex: Male Female	 18 (90) 2 (10%)	 17(85%) 3 (15%)	0.4
Weight (kg)	78± 10.05	79.5± 7.76	0.6
Physical status (ASA): I II	 8(40%) 12(60%)	 9(45%) 11(55%)	0.23
Duration of anesthesia (hours)	5.1±1.65	5.28±1.45	0.45
Duration of surgery (hours)	4.71 ±1.03	4.91±1.35	0.57
Volume of blood loss (ml)	1237.5±884.6	1030±542	0.36
Volume of blood transfusion (ml)	940±857.4	975.25±1070.6	0.91

Data are presented as mean ± standard deviation or number (%).

Dex group = dexmedetomidine group.

*P-value denotes statistical significance.
The plasma level of TNF-α, IL-6, and C-reactive protein before the start of the study drug infusion, after complete recovery and the day one postoperatively at 8 am were written in tables 2,3,4,5,6 and shown in figures 1,2,3,4,5 respectively.
Tumor necrosis factor –α (TNF-α) (pg/ml): Dex group than control group at recovery and the day one postoperatively at 8 am.
TNF-α was significantly lower at complete recovery when compared with the baseline value in both groups.
TNF-α was significantly lower in the day one postoperatively at 8 am when compared with the baseline value in the control group.
Table (2): Tumor necrosis factor –α (TNF-α).

	Dex group N=20	Control group N=20	P-value
TNF-α before the start of the study drug infusion (baseline)	16.4 ± 2.1	17.4 ± 2.6	0.184
Table 2 and figure 1 showed that tumour necrotic factor was significantly lower in TNF-α at recovery	ŧ23 ± 3.4	# 36 ± 5.3	<0.001*
TNF-α the day one postoperatively at 8 am	13.8 ± 3.1	# 24.3 ± 3.8	<0.001*

Data are presented as mean ± standard deviation.
Dex group = dexmedetomidine group.
*P-value denotes statistical significance versus the control group.
ŧ P-value denotes statistical significance with the base line value in the Dex group.
p-value denotes statistical significance with the base line value in the control group.

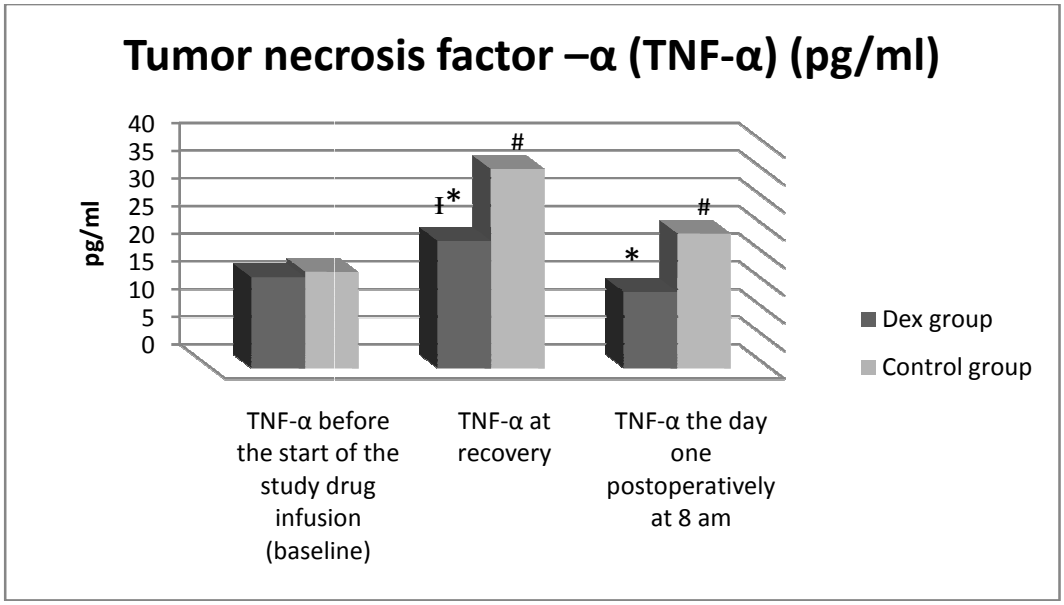

Figure (1): Tumor necrosis factor –α (TNF-α).
Data are presented as mean.
Dex group = dexmedetomidine group.

*P-value < 0.05 denotes statistical significance versus the control group.
† P-value denotes statistical significance with the base line value in the Dex group.
# P-value denotes statistical significance with the base line value in the control group.

Serum Interleukine-6 (IL-6) (pg/ml):

Serum Interleukine-6 was significantly lower in Dex group than control group at recovery and the day one postoperatively at 8 am and serum IL-6was significantly lower at complete recovery and in day one postoperatively at 8 am when compared with the baseline value in the control group as shown in table (3) and figure (2).

Table (3): Serum Interleukine-6 (IL-6).

	Dex group N=20	Control group N=20	P-value
IL-6 before the start of the study drug infusion (baseline)	8.4± 1	8.7 ±1.2	0.441
IL-6 at recovery	9.3± 1	# 38.1± 8.8	<0.001*
IL-6 the day one postoperatively at 8 am	9.6 ±1.2	# 57.1± 11.5	<0.001*

Data are presented as mean ± standard deviation.
Dex group = dexmedetomidine group.
*P-value denotes statistical significance versus the control group.
P-value denotes statistical significance with the baseline value in the control group.

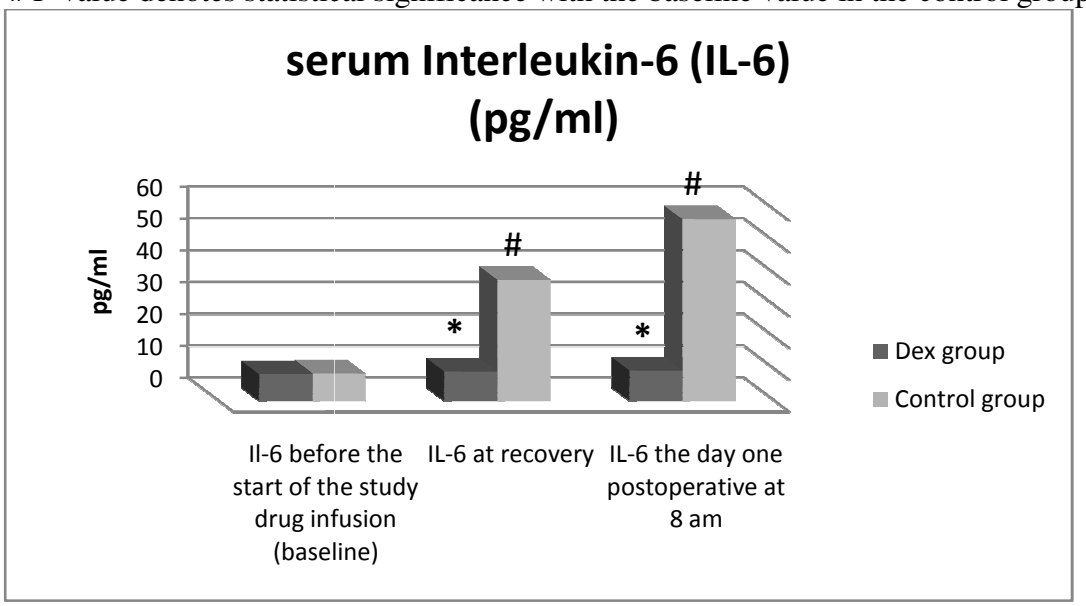

Figure (2): Serum Interleukine-6 (IL-6).

Data are presented as mean.
Dex group = dexmedetomidine group.
*P-value < 0.05 denotes statistical significance versus the control group.
P-value denotes statistical significance with the base line value in the control group.

C- Reactive protein (CRP) (mg/l):

No significant difference in CRP between both groups, while C-reactive protein was significantly lower in day one postoperatively at 8 am when compared with the baseline value in either groups as shown in table (6) and figure (5).

Table (6): C- reactive protein (CRP)

	Dex group N=20	Control group N=20	P-value
CRP before the start of the study drug infusion (baseline).	3.2± 6.2	3.3± 3.9	0.980
CRP at recovery.	2.5 ±5.4	3.2 ±3.9	0.673
CRP the day one postoperative at 8 am.	☨ 12.4± 8.7	# 15.3 ±7.6	0.259

Data are presented as mean ± standard deviation.
Dex group = dexmedetomidine group.
*P-value denotes statistical significance versus the control group.
☨ P-value denotes statistical significance with the base line value in the Dexl group.
P-value denotes statistical significance with the base line value in the control group.

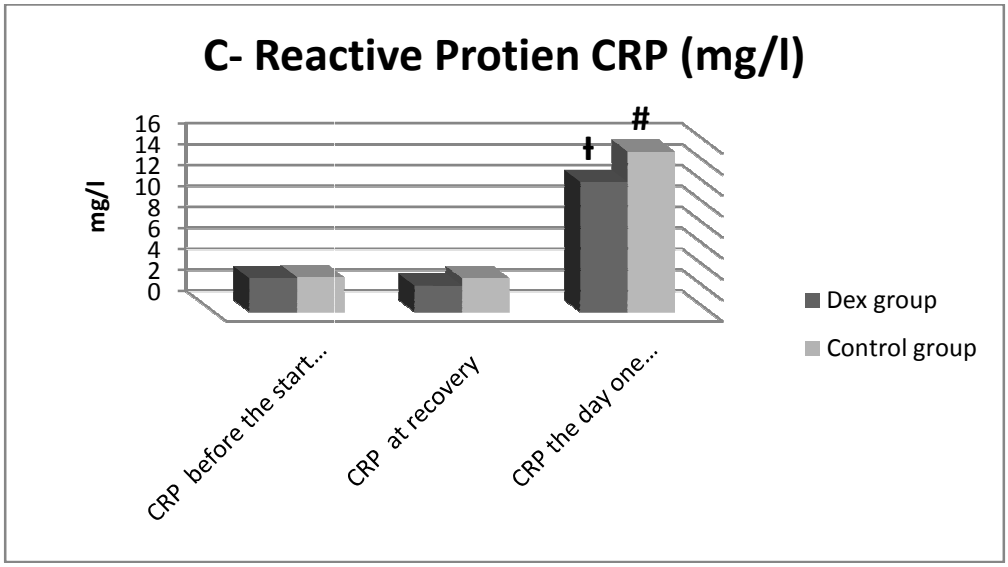

Figure (5): C-reactive protein (CRP).
Data are presented as mean.
Dex group = dexmedetomidine group.
*P-value < 0.05 denotes statistical significance versus the control group.
☨ P-value denotes statistical significance with the base line value in the Dex group.
P-value denotes statistical significance with the base line value in the control group.

Discussion:-

Dexmedetomidine is a centrally acting α2-adrenergic agonist decreasing norepinephrine turnover and reducing central sympathetic outflow. Different mechanisms of dexmedetomidine action have been illustrated including the modulation of cytokine production by macrophages and monocytes during the stress response which may also be stimulated via the α 2-adrenoceptors, inhibition of apoptosis, central sympatholytic effects including the stimulation of cholinergic anti-inflammatory pathway, and anti nociceptive action involving interactions between pain and immune factors such as proinflammatory cytokines.**(5)**

The surgical stress response is a neuroendocrine and cytokine response to surgical trauma. Which involves increase in catecholamine and steroid hormones, with metabolic sequences**. (6)**

This stress response is considered as the physiological homeostatic defence mechanism, important for the body for adaptation and developing resistance to the noxious insults. If such exaggerated physiological changes are prolonged, that may result in exhaustion of essential components of the body increasing morbidity and mortality**.(7)**

We found no significant difference in CRP between both groups in post-operative period. When compared to saline, Ueki et al found no significant difference in CRP with patients received dexmedetomidine after cardiopulmonary bypass.**(8)**

Intraoperative Infusion of dexmedetomidine did not reduce CRP significantly following major spinal surgery**.(9)**

While in laparoscopic cholecystectomy, CRP were significantly less in patients received dexmedetomidine in postoperative day one.**(5)**

Interleukin-6 is a proinflammatory cytokine that has both local and systemic effects for decreasing tissue injury and minimizing infections while stimulating tissue healing and repair. (**10**)

It is the main interleukin released following surgery and has a reliable indicator role of the inflammatory response to surgical trauma.**(11)**

We found that Patients received dexmedetomidine had lower serum IL-6 level at recovery and one day after surgery. These results agree with Yacout et al. who worked in patients performing major abdominal surgeries**. (12)**

In patients received dexmedetomidine, IL-6 concentrations declined significantly after laparoscopic cholecystectomy.**(9)**

After cardiopulmonary bypass, plasma IL-6 levels were higher in the saline group than the dexmedetomidine group. **(8)**

Dexmedetomidinedid not differentially modulate levels of IL-6 after major spinal surgery.**(9)**

Tumor necrosis factor-α is also a proinflammatory cytokine that regulates several other cytokines. (**13**)

TNF was significantly lower in Patients received dexmedetomidine at recovery and one day after surgery.Perioperative use of dexmedetomidine as an adjunct to general anesthesia was found to cause significant decreases TNF-α within a period of 24 hours postoperatively. (**14)**

Tasdogan et al. showed that intravenous dexmedetomidine infusion decreases serum TNF after abdominal surgery. (**15)**

Conclusion:

Dexmedetomidine is effective in attenuating the postoperative rise of the proinflammatory cytokine interleukin-6 and tumor necrosis factor (TNF-α) and resulted in lower levels of markers of stress response to surgery as cortisol and blood glucose.

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تأثيرات استخدام عقار ديكسميديتوميدين على الاستجابات الالتهابية فى مرضى عمليات البطن الكبرى
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المقدمه

تسببإلاصابة الجراحية للأنسجة كما هو الحال في جراحات البطن الكبرى مجموعة متنوعة من ردود الفعل الفسيولوجية العميقة التي تعتبر ضرورية لاستعادة التوازن في الكائنات الحية . تتضمن الاستجابة زيادة هرمونات التوتر، الكورتيزول ، الكاتيكولامينات والهجرة من الكريات البيض إلى موقع الإصابة ، والإفراج عن السيتوكينات فضلا عن المنتجات الخلوية الأخرى.وسطاء الالتهاب يمكن أن تسبب التعب و إطالة فترة النقاهة في المرضى الأصحاء. وبالتالي ، تعديل الاستجابة المناعية قد يقلل من حدوث مضاعفات ما بعد الجراحة وتحسين النقاهه.

ديكساميديتوميدين له تأثيره المضاد للالتهابات عن طريق خفض مستويات [وجدت الدراسات الحديثة أن عقار المصل من العوامل الالتهابية.و مما تم توثيقه جيدا أن هذا العقاريثبط الغدد الصماء العصبية ويمنع الاستجابة الالتهابية في العديد من تاتجارب المعمليه و الاكلنيكيه.

وتشير الأدلة مؤخرا أن هذا العقار يقلل إنتاج السيتوكينات الالتهابية في حين يخفض الضغط داخل البطن في المرضى ذوي الحالات الحرجة . تشير الدراسات على الحيوانات أيضا أن هذا العقار خفف من زيادة مستويات البلازما خلوى بعد حقن الذيفان الداخلي ويقلل من معدل الوفيات من الحيوانات المصابة بشكل كبير . وتشير هذه النتائج دور للعقارفي منع استجابات التوتر غيرالمرغوب فيها ، والتعجيل من النقاهة بعد العمليات الجراحية وربما خفض معدل حدوث مضاعفات أثناء فترة النقاهة.

الهدف من الدراسة:-

تهدف هذه الدراسه إلى توضيح الدور المضاد للالتهاب الذى يلعبه عقار ديكساميديتوميدين فى جراحات البطن الكبرى وتأثير ذلك على مستوى الافاقه بعد العمليات.

المرضى و طرق البحث:-

جرت هذه الدراسة العشوائية المستقبلية بقسم التخدير و العناية المركزة الجراحية فى مستشفى سوهاج الجامعى و بعد الحصول على الموافقة الكتابية المبنية على المعرفة من المرضى الذين شملتهم هذه الدراسة و البالغ عددهم أربعون شخصا تتراوح اعمارهم بين اربعين عاما و خمسة و ستين عاما ممن خضعوا لجراحات كبرى فى البطن او الحوض خلال الفترة من اغسطس ٢٠١٥ و حتى ديسمبر ٢٠١٦. حيث سيتم تقسيمهم الى مجموعتين:-

المجموعة الأولى:- شملت عشرين مريضا و هي المجموعة التي استخدم فيها تقنية حقن العقار محل البحث عن طريق الوريد

المجموعة الثانية :- شملت عشرين مريضا و هى مجموعة المقارنه التى تلقت محلول ملحى عادى.

و المرضى الذين شملتم الدراسة يجب أن تنطبق عليهم الشروط الآتية:-

ان يكون المرضى من الفئة الاولى و الثانيه طبق تصنيف الجمعية الامريكيه لاطباء التخدير والمحضرين لاجراء عمليات كبرى فى البطن او الحوض تحت مخدر عام.

و المرضى الذين لم تشملهم هذه الدراسة :-

- الاستخدام المزمن للكحوليات و الادويه - الحساسيه لعقار الديكسميديتوميدين - استخدام ادويه مجموعة الفا - ٢ المحفزة او المثبطة - مرضى الضغط و اضطراب نبضات القلبو مرضى قصور الشرايين التاجيه - مرضى اضطراب وظائف الكلى و الكبد - الاستخدام المزمن للعقاقير المضادة للالتهابات (أي المنشطات، و المسكنات، وما إلى ذلك)

جميع المرضى في كلا المجموعتين تلقت التخدير العام. ونم اعطاؤهم اتروبين عن طريق الحقن العضلى بتركيز ٠.٠٢ ملللى جرام وكذلك الميدازولام بتركيز ٥ ملللى جرام قبل الدخول لغرفة العمليات وسوف يكون ذلك حافزا بالتخدير العام مع الفنتانيل ٢-٥ ميكروغرام / كغ، البروبوفول ٢-٥.١ ملللى جرام / كغ (الجرعة) ورواكرونيوم ١ ملللى جرام / كغ جرعة عن طريق الوريد. سيتم الحفاظ على التخدير مع تقنية متوازن مخدر، وتتألف من المخدر المتطايرة) ((سيفوفلوران ٠،٧-١)وخليط من الهواء والأكسجين .

شارك بالدراسة اربعون مريضا خضعوا لعملية استئصال كامل للمثانة البولية. أظهرت النتائج ارتفاع الاستجابات الالتهابية بصورة ملحوظة فى كلا المجموعتين، ولكن بدرجة أقل وذات دلالة إحصائية فى مجموعة الديكسميديتوميدين. كما أظهرت النتائج أن مرضى مجموعة الديكسميديتوميدين قد اشتكوا من درجة أقل من الألم وتلقوا كميات أقل من المورفين فى فترة بعد العملية وكان ذلك كله مع ثبات المعدلات الحيوي فى كلا المجموعتين.

الاستنتاج:

عقار الديكسميديتوميدين فعال في تخفيف ارتفاع ما بعد الجراحة من السيتوكينات انترلوكين -٦ وعامل نخر الورم الفا.