Analgesic, Sedative and Hemodynamic Effects of Dexmedetomidine Following Major Abdominal Surgeries: A Randomized, Double-Blinded Comparative Study with Morphine

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Abstract

This was a randomized double-blinded study; in which 60 ASAI-II adult patients scheduled for major abdominal surgeries (colostomy, radical cystectomy, major gynecological surgery, and abdominal vascular surgery) were received standard general anesthesia. Twenty minutes before the anticipated end of surgery, patients were randomized into two equal groups: dexmedetomidine group (group D) and morphine group (group M). Group D received dexmedetomidine IV infusion 4µg/kg/h for 15 minutes (1µg/Kg) followed by 0.4µg/kg/h for 3h. Group M received morphine sulfate IV (0.07mg/kg). All patients were given a morphine patient controlled analgesia (PCA) pump in the post anesthesia care unit (PACU), delivering IV morphine 2mg with a lockout time of 5 minutes if pain score assessed through visual analog scale (VAS) was more than 5 at any given 5-min assessment. During the PACU recovery period, morphine consumption; pain and sedation scores; hemodynamic variables (heart rate, mean arterial blood pressure, oxygen saturation and respiratory rate); and postoperative nausea, retching and vomiting (PONV) were recorded every 30 min for 3h (study period) by a member of staff blinded to the treatment. The study demonstrated that the use of dexmedetomidine led to significant decrease in the total amount of morphine consumed throughout the entire PACU recovery period (P<0.05). This was associated with reasonable pain and sedation scores; significant slowing in heart rate (P<0.05); significant decrease in mean arterial pressure (P<0.05); less incidence of PONV (P<0.05); without any significant changes in oxygen saturation (P>0.05) or respiratory rate (P>0.05). In conclusion, dexmedetomidine exhibited both analgesic and sedative properties. The associated cardiovascular protective pharmacological profile and the lack of respiratory depression made it potentially extremely interesting for postoperative analgesia after major abdominal surgeries.

Introduction:

Dexmedetomidine is a potent alpha-2 adrenoceptor agonist with an alpha-2 to alpha-ratio more than 7times that of clonidine [1]. Because of its potency, it can be safely administered as an infusion (not as a bolus). Dexmedetomidine has analgesic and sedative properties [2, 3]. Its use is not associated with respiratory depression despite profound levels of sedation [3]. Because of analgesia sparing, sedation and lack of respiratory depression, dexmedetomidine may prove useful in the postoperative period for patients having major surgical procedures that are associated with significant pain.

Aim of the Work

The aim of this study was to assess the analgesic, sedative and hemodynamic effects of dexmedetomidine and to compare it to morphine in early postoperative period following major abdominal surgeries.

Patients and Methods

The study was approved by the hospital ethical committee. A written informed consent was obtained from all patients to participate in this study. Sixty adult patients ASA physical status class I and II scheduled to undergo major abdominal surgeries under general anesthesia were enrolled in the study. Exclusion criteria

included patients with body weight greater than 100 kg, patients receiving any alpha-2 agonists or antagonists or patients on chronic use of opioids in the last 4 weeks of the study.

On the eve of the surgery, patients were instructed on the proper use of the visual analog scale for assessing pain and sedation (10-point scale) and the patient-controlled analgesia (PCA) apparatus. An independent observer administered the visual analog scales in the postoperative period.

The general anesthesia regimen consisted of premedication with midazolam 3mg IV given prior to surgery. Induction was with fentanyl 1.5µg/kg IV and propofol 2mg/kg IV. Atracurium 0.6mg/kg was used to facilitate endotracheal intubation. Anesthesia was maintained with 66% nitrous oxide in oxygen and isoflurane to achieve an end-tidal isoflurane concentration of about 1%. Intraoperative analgesia was provided by increments of fentanyl. Ventilation was controlled mechanically and adjusted to maintain end-tidal carbon dioxide at 38 mm Hg throughout the surgery. Atracurium was supplemented during general anesthesia guided by nerve stimulator (TOF). Fluid replacement was in the form of crystalloids, colloids and blood according to the fasting hours, duration of surgery and amount of blood loss. Monitoring of vital signs (heart rate, blood pressure, electrocardiogram tracing, oxygen saturation and end-tidal CO_2) was done using Datex cardioscope.

Twenty minutes before the anticipated end of surgery, patients were randomized into two equal groups: dexmedetomidine group (group D) and morphine group (group M). Group D (30 patients) received dexmedetomidine by IV infusion, initial loading dose 1µg/kg given over 15 min at rate of 4µg/kg/h, followed by a titrated maintenance dose (0.4µg/kg/h) given for 3h. Group M (30 patients) received morphine sulphate IV (0.07 mg/kg), followed by normal saline via infusion pump by the same technique like group D for blinding purposes.

At the end of surgery, residual neuro-muscular blockade was antagonized by neostigimine (0.04 mg/kg IV) and atropine (0.02mg/kg IV). All patients were extubated in the operative room. The time of cessation of anesthetic administration and the time of recovery from anesthesia (defined as patient's first response to spoken command) were recorded. From that, the awakening time (emergence and recovery from anesthesia) was calculated.

The patients were transferred to the post anesthesia care unit (PACU). In the PACU continuous monitoring of vital signs was done. An observer blinded to the research recorded heart rate (HR), mean arterial blood pressure (MAP), respiratory rate and oxygen saturation every 30 min for 3h (study period).

Postoperative morphine therapy was titrated per standard PACU criteria by a nurse blinded to the research. Postoperative pain was assessed using a 10-point visual analog scale (VAS). Patients with pain score more than 5 at any given 5-min assessment were considered to have severe pain and morphine was given via PCA pump providing 2mg IV bolus with a 5-minute lockout. Total morphine consumption in the PACU was calculated and recorded by a member of staff blinded to the treatment. Sedation in PACU was also assessed every 30 min for 3h using sedation score (graduated from 0-10). Postoperative nausea retching and vomiting (PONV) in the PACU were recorded. The number of patients in each group felt nauseated or had an emetic episode (single vomit or retch) or received a rescue antiemetic were calculated.

All values were expressed as mean (SD) or number (%). Results were compared using the unpaired Student's t test and Mann-Whitney U test. Categorical variables were examined by the chi-square test and Fisher's exact test. All tests were considered significant at P<0.05.

Results

Patient's demographics and intraoperative data were summarized in (table 1). The studied groups were similar in age, sex, weight, height and ASA physical status. The type and duration of

surgical procedures were similar in the studied groups. No significant differences between the groups in the intraoperative doses of fentanyl, intraoperative HR, intraoperative MAP, duration of anesthesia, awakening time, (P>0.05).

The cardiovascular and respiratory effects of the studied drugs were shown in (tables 2-5). The results in (table 2 and 3) showed that the use of dexmedetomidine was associated with significant slowing in HR (P<0.05) and decrease in MAP (P<0.05) during the entire PACU recovery period.

The results in (tables 4 and 5) showed no significant differences between the studied groups in respiratory rate (P>0.05) or oxygen saturation (P>0.05) throughout the entire PACU recovery period.

The level of sedation (table 6) was similar in both groups during the PACU recovery period. No significant differences in sedation score between the group throughout the entire PACU recovery period (P>0.05).

The results in (table 7) showed that the mean morphine consumption in PACU in group D (3.5 mg) was significantly lower than that in group M (10.5 mg). Patients who received dexmedetomidine required significantly less morphine to control postoperative pain during the entire PACU recovery period (P<0.05).

The results in (table 8) showed less incidence of PONV in the dexmedetomidine group (P<0.05)

Table (1): Patients' demographics and operations' details. Values are expressed as mean (SD) except number (%).

	Group-D (n=30)	Group-M (n=30)
Age (yr)	47(12)	49(11)
Sex (m/f)	13/17	12/18
Weight (Kg)	69(8)	68(9)
Height (Cm)	167(11)	165(12)
Physical status (n)		
ASAI	14(47)	15(50)
ASA II	16(53)	15(50)
Operation type (n)		
Colostomy	12(40)	13(43)
Radical cystectomy	7(23)	6(20)
Major gynecological surgery	9(30)	8(27)
Vascular abdominal surgery	2(7)	3(10)
Intraoperative fentanyl (µg)	315(98)	320(90)
Intraoperative HR (beats/min)	67(9)	66(8)
Intraoperative MAP (mm Hg)	83(7)	84(9)
Duration of surgery (min)	202(88)	229(93)
Duration of anesthesia (min)	238(75)	245(82)
Awakening time (min)	11.5(1.7)	11.8(1.5)

No significant differences between groups.

Table (2): HR in PACU. Values are expressed as mean (SD).

Time in PACU (min)	HR (beats/min)	
	Group-D (n=30)	Group-M (n=30)
30	65 (2)	74 (3)
60	66 (1)	76 (2)
90	67 (1)	75 (1)
120	64 (2)	75 (2)
150	68 (1)	77 (1)
180	63 (3)	73 (2)

The use of dexmedetomidine was associated with significant slowing in HR throughout the entire PACU recovery period (P<0.05).

Table (3): MAP in PACU. Values are expressed as mean (SD).

Time in PACU (min)	MAP (mm Hg)	
	Group-D (n=30)	Group-M (n=30)
30	85 (6)	97 (4)
60	87 (7)	96 (6)
90	84 (8)	95 (3)
120	86 (5)	94 (5)
150	85 (2)	95 (8)
180	83 (4)	94 (6)

The use of dexmedetomidine was associated with significant decrease in MAP throughout the entire PACU recovery period (P<0.05).

Table (4): Respiratory rate in PACU.Values are expressed as mean (SD).

Time in PACU (min)	Respiratory rate (breaths/min)	
	Group-D (n=30)	Group-M (n=30)
30	14 (1)	13 (2)
60	13 (2)	13 (1)
90	15 (2)	14 (2)
120	13 (1)	14 (1)
150	14 (2)	14 (2)
180	13 (1)	14 (1)

No Significant differences in respiratory rate between groups throughout the entire PACU recovery period (P>0.05).

Table (5): Oxygen saturation (%) in PACU. Values are expressed as mean (SD).

Time in PACU (min)	O2 saturation (%)	
	Group-D (n=30)	Group-M (n=30)
30	96 (1)	97 (1)
60	98 (1)	98 (2)
90	97 (2)	97 (1)
120	98 (1)	98 (2)
150	97 (1)	98 (1)
180	98 (1)	97 (1)

No significant differences in O2 saturation between groups throughout the entire PACU recovery period (P>0.05).

Table (6): Sedation score (graduated from 0-10) in PACU (0=asleep and 10=wide awake). Values are expressed as mean (SD).

Time in PACU (min)	Sedation score	
	Group-D (n=30)	Group-M (n=30)
30	5.1(0.1)	5.1(0.2)
60	5.5 (0.3)	5.4 (0.2)
90	4.9 (0.2)	5.2 (0.1)
120	5.1 (0.3)	5.2 (0.1)
150	5.1 (0.2)	5.2 (0.1)
180	5.6 (0.2)	5.5 (0.3)

No significant differences in sedation score between groups throughout the entire PACU recovery period (P>0.05).

Table (7): Total morphine consumption (mg) in PACU (study period). Values are expressed as mean (SD).

Group-D (n=30)	Group-M (n=30)
3.5 (1.2)	10.5 (1.4)

Patients receiving dexmedetomidine required significantly less morphine to control postoperative pain (P<0.05).

Table (8): Incidence of PONV in the studied groups: number (%) of patients felt nauseated or had an emetic episode (single vomit or retch) or received a rescue antiemetic in PACU (study period).

Group-D (n=30)	Group-M (n=30)
12(40)	18 (60)

The incidence of PONV was significantly less in the dexmedetomidine group (P<0.05).

Discussion

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 anesthesia and surgery [4-6]. They also reduce anesthetic and opioid requirements [7,8], and cause sedation and analgesia [9]. They allow psychomotor function to be preserved while letting the patient rest comfortably [10,11]. With these combination of effects, alpha-2 adrenoceptor agonists may offer benefits in the prophylaxis and adjuvant treatment of perioperative myocardial ischemia [12]. Furthermore, their roles in pain management and regional anesthesia are expanding [13].

Several reports supported the use of dexmedetomidine as a novel drug for sedation and analgesia in the intensive care units especially for those intubated and mechanically ventilated patients [14-17].

The present study was focused on evaluation of the efficacy of dexmedetomidine to control postoperative pain following major abdominal surgeries. The analgesic property of dexmedetomidine was assessed as a primary target. The safety and the associated hemodynamic effects of this drug were also assessed and compared to those of the standard postoperative analgesic opioid (morphine).

In this study dexmedetomidine was administered 20 minutes before the anticipated end of surgery in an attempt to attain a therapeutic analgesic level before completion of surgery [4].

No significant differences were observed between the studied groups in the time taken to wake up from anesthesia, the time spent in the PACU. Patients who received dexmedetomidine required significantly less amounts of morphine (P<0.05) to achieve equivalent analgesia and reasonnable pain and sedation scores (tables 6-7). Because of its sedative and analgesic effects, there was a significant reduction in the amount of morphine given through PCA apparatus during the entire PACU recovery period. The mean morphine consumption in the dexmedetomidine group (3.5mg) was significantly lower than that in the morphine group (10.5mg), which meant that the total PACU morphine consumption in the dexmedetomidine treated group was decreased by 2/3 to achieve reasonable and equivalent analgesia. The activation of the alpha-2 adrenoceptor located on the spinal terminals of the primary sensory neurons leading to suppression of release of the pain neurotransmitters might explain the analgesic property of dexmedetomidine [18-20].

Besides being an analgesic drug on its own merits, dexmedetomidine was found to have the ability to enhance in a synergistic way opioids-induced analgesia[21,22].

The use of dexmedetomidine was associated with significant ($P<0.05$) slowing in HR (table 2) and decrease in MAP (table 3) throughout the entire PACU recovery period. Respiratory rate and oxygen saturation were maintained and not changed (tables 4-5).

The cardiovascular effects of dexmedetomidine could be part of the therapeutic goals in surgical patients at risk of adverse cardiovascular events. Indeed, activation of the sympathetic nervous system in the perioperative period increases cardiovascular morbidity and mortality in patients with ischemic or non-ischemic heart diseases. Perioperative therapy with alpha-2 adrenoceptor agonists or beta-blockers decreases both the incidence of myocardial infarction and mortality in the perioperative period[12,23]. It was the reduction of heart rate, and not the beta-adrenergic receptor blockade per se that was beneficial in terms of improvement of cardiovascular morbidity in the perioperative setting[24]. By slowing the HR, dexmedetomidine contributes to increase coronary blood supply to the left ventricle through prolongation of diastole and a decrease in the myocardial oxygen consumption. In addition, after load is decreased especially in high risk hypertensive patients. Therefore, dexmedetomidine could be useful adjunct to patients with cardiovascular problems providing protective pharmacological profile with moderate sympathetic depression which is quite useful in cardiac surgery and general surgery for patients with heart diseases.

PONV are accepted side-effects after major abdominal surgeries especially in patients receiving morphine PCA[25-28]. The present study revealed less incidence of PONV in the dexmedetomidine group through the entire PACU recovery period ($P<0.05$). This because the amount of morphine consumed through PCA in the dexmedetomidine group was reduced by 2/3 (table 7).

In conclusion, dexmedetomidine exhibited both analgesic and sedative properties. The associated cardiovascular protective profile and the lack of respiratory depression made it potentially extremely interesting for postoperative analgesia after major abdominal surgeries.

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تأثير عقار الديكسميدتوميدن على الدوران والتنفس وفاعليته كعقار مهدئ ومزيل للألم عقب الجراحات الكبرى للبطن : دراسة مقارنة مع المورفين بإستخدام الطريقة العشوائية عمياء الطرفين

خالد طه عطيه ندا
قسم التخدير بطب عين شمس

تكونت عينة البحث من عدد (60) مريضاً بالغاً من الدرجة الأولى والثانية الصحية على حسب تصنيف جمعية التخدير الأمريكية ، والذين كان مقرراً لهم إجراء جراحات كبرى فى البطن ، هذا وقد تم تخدير المرضى تخديراً كلياً ، وقبل الوقت المتوقع لإنتهاء الجراحة بـ (20) دقيقة ثم تقسيم المرضى بطريق عشوائية إلى مجموعتين متساويتين: مجموعة الديكسميدتوميدن (مجموعة د) ومجموعة المورفين (مجموعة م)، وبإستخدام الطريقة العمياء المزدوجة تم إعطاء مرضى (المجموعة د) عقار الديكسميدتوميدن بالتسريب الوريدى بمعدل (4 ميكروغرام / كغ/ ساعة) لمدة 15 دقيقة (1مكروغرام / كغ) ، ثم بمعدل (0.4 ميكروغرام / كغ / ساعة) لمدة 3 ساعات . هذا وقد تم إعطاء مرضى (المجموعة د) عقار المورفين بالوريد (0.07 ملغ / كغ) .

وقد تم علاج ألم ما بعد الجراحة بإستخدام (مضخة إزالة الألم بواسطة تحكم المريض) فى وحدة العناية بالمرضى بعد التخدير، ولقد تم ضبط المضخة لتعطى 2 ملغ مورفين بالوريد عندما تكون شدة الألم مساوية لخمس درجات على المقياس البصرى المتناظر (مقياس تقييم الألم) .

وفى وحدة العناية بالمرضى بعد التخدير تم تسجيل كل من كمية المورفين المستهلكة، الدرجات المعطاة على المقياس البصرى المتناظر (لقياس كل من شدة الألم ودرجة الهدوء)، العلامات الحيوية للدوران والتنفس (سرعة ضربات القلب ، متوسط ضغط الدم الشريانى ، نسبة تشبع الدم الشريانى بالأوكسجين ، عدد مرات التنفس فى الدقيقة)، وأيضاً تم تسجيل عدد المرضى الذين عانوا من الغثيان والتقيؤ . وقد تم أخذ الملاحظات السابقة وتدوينها كل 30 دقيقة لمدة 3 ساعات (فترة الدراسة) بواسطة أحد العاملين بوحدة العناية بعد التخدير ، والذى كان لا يعلم شيئاً عن هدف وطبيعة الدراسة .

وقد أوضحت الدراسة أن استخدام عقار الديكسميدتوميدن أدى إلى نقص فى كمية المورفين المستهلكة لمرضى الدراسة خلال فترة تواجدهم فى وحدة العناية بعد التخدير وصاحب هذا النقصان وجود درجة معقولة من الهدوء والتسكين ، ووجود نقص ذو دلالة إحصائية فى كل من سرعة ضربات القلب ومتوسط ضغط الدم الشريانى ، وقلة نسبة حدوث غثيان وتقيؤ مابعد الجراحة ،مع عدم وجود أى تغيير فى عدد مرات التنفس أو نسبة تشبع الدم الشريانى بالأوكسجين .

الخلاصة : أظهر عقار الديكسميدتوميدن فاعلية كعقار مهدئ ومزيل للألم ، وساهم إستخدامه فى توفير حماية للقلب والدوران ، ولم يؤدى إستخدامه إلى وجود هبوط فى التنفس ، مما جعله مفيداً كمزيل للألم بعد العمليات الكبرى فى البطن .