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Effects of dexmedetomidine on succinylcholine-induced myalgia in the early postoperative period

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ABSTRACT

الأهداف: تحديد التأثيرات لدى ديكسميديتوميدين على نسبة حدوث الإختلاجات والآلام العضلية وكذلك تقييم التغييرات في مستويات كرياتينكيناز الناتجة عن استعمال سوكسينيلكولين.

الطريقة: اشتملت هذه الدراسة على 60 مريضاً خضعوا إلى عملية تنظير الحنجرة المباشر في مستشفى جامعة هاستيب، قسم التخدير والعناية المركزة، أنقرة، تركيا وذلك خلال الفترة يناير 2010م ومارس 2010م. تم عَرضْ المرضى عشوائياً على3 أطباء تخدير. تم تقسيم المرضى عشوائيا إلى مجموعتين. تلقى 30 مريضاً في مجموعة ديكسميديتوميدين (مجموعة D) عقار ديكسميديتوميدين وريدياً بمقدار 1ملغ/كغ ولمدةعشرة دقائق قبل التنبيب الرغامي. بينما تلقى 30 مريضاً في مجموعة التحكم (مجموعة C) المحلول الملحي الطبيعي وبنفس مقادير ديكسميديتوميدين المُعْطاة إلى المجموعة D. تمت المباشرة بالتنبيب الرغامي بعد دقيقة واحدة من تطبيق عقارسوكسينيلكولين على المريض، وبالإضافة إلى ذلك فقد تم الإستمرار بتَسريب ديكسميديتوميدين حتى نهاية العملية الجراحية. تم تقييم الإختلاجات العضلية والآلام العضلية بعد العملية ب30 دقيقة وكذلك تم تقييم مستويات كرياتينكيناز قبل البدء بالتخدير وبعد العملية ب 24 ساعة .

النتائج: إنّ شدَةْ ونسبة ظهورالإختلاجات العضلية في المجموعة D كانت أفضلَ مقارنة بالمجموعة C p=0.025. لوحظ إنّ شروط تنبيب الرغامي كانت أفْضَل في مجموعة ديكسميديتوميدين (p=0.011). في فترة ال30 دقيقة بعد العملية كانت شدَةْ الآلام العضلية ونسبة ظهورها أعلى وبشكل ملحوظ في المجموعة C (p=0.014). كانت المستويات الأساسية لكرياتينكيناز بعد العملية أعلى وبشكل ملحوظ في المجموعتين (p=0.017)، كما كان إرتفاع مستوى كرياتينكيناز أعلى في المجموعة C (p=0.03).

خاتمة: إنَ تسريب ديكسميديتوميدين قبل وبعد استخدام سوكسينيلكولين قد يكون مُفيداً في التَقليل من نسبة ظهور الآلام العضلية في المرحلة المبكرة بعد العملية الجراحية والناتجة عن إعطاء عقار سوكسينيلكولين.

Objectives: To determine the effects of dexmedetomidine on the incidence of fasciculation and myalgia, and to evaluate changes in creatine kinase levels due to succinylcholine administration.

Methods: Sixty patients undergoing direct laryngoscopy were enrolled in this study carried out in the Department of Anesthesiology and Reanimation, Hacettepe University, Ankara, Turkey between January and March 2010. Patients were allocated blindly to 3 anesthesiologists. In the dexmedetomidine group (group D) (n=30), dexmedetomidine 1μg/kg was administered intravenously over 10 minutes before the intubation. In the control group (group C) (n=30), the same volume of normal saline was administered. Laryngoscopy was performed one minute after administration of succinylcholine. Dexmedetomidine infusion was continued until the end of surgery. Fasciculation and myalgia at the postoperative thirtieth minute, and creatine kinase levels before the induction of anesthesia and at the postoperative 24th hour, and adequacy of relaxation for intubation were recorded.

Results: The severity and incidence of fasciculation were better in group D than group C (p=0.025). Intubating conditions were better in the dexmedetomidine group (p=0.011). At the thirtieth minute, the incidence and severity of myalgia were significantly higher in group C (p=0.014). Postoperative creatine kinase levels increased significantly compared with their base-line levels in both groups (p=0.022 in group D and p=0.017 in group C). Creatine kinase level elevation was higher in group C (p=0.03).

Conclusion: Dexmedetomidine infusion before and after succinylcholine administration may be useful in diminishing the incidence of succinylcholine-induced myalgia in the early postoperative period. Routine use of dexmedetomidine cannot be recommended, but further research is needed with a larger number of patients.

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Succinylcholine possesses the unique properties of rapid onset and short duration of action, and is still the accepted standard for rapid sequence intubation.[1] It also seems to be a popular muscle relaxant of ambulatory anesthesia, short surgical procedures, and emergency situations.[2] However, it has some disadvantages, such as fasciculation, postoperative myalgia and increased serum creatine kinase (CK).[3] The mechanism of succinylcholine-induced myalgia is not fully understood. In some of the previous studies, non-steroidal anti-inflammatory drugs were found effective in reducing postoperative myalgia.[4] The α2-receptor agonist dexmedetomidine, which has been recently introduced for sedation in the ICU setting, has analgesic-sparing properties and inhibits the inflammatory response.[5-7] These anti-inflammatory effects of dexmedetomidine may diminish the succinylcholine-induced myalgia. We therefore designed a study to determine the effects of dexmedetomidine on succinylcholine-induced myalgia in the early postoperative period, and to evaluate changes in CK levels following succinylcholine administration.

Methods. This was a randomized, placebo-controlled, double-blind study. Sixty American Society of Anesthesiology (ASA) grade I or II patients undergoing direct laryngoscopy were studied after their informed consent at Hacettepe University, Ankara, Turkey between January and March 2010. Approval of the Hacettepe University Human Ethics Committee was obtained. Preoperative exclusion criteria were cardiovascular pathologies (such as coronary artery disease, valvular heart disease, arrhythmia, hypotension or hypertension), hepatic/renal impairment, neuromuscular disease, increased intraocular and intracranial pressure, malignant hyperthermia, hyperkalemia, dehydration, and the use of medications known to interact with neuromuscular function. An ECG, non-invasive blood pressure, peripheral oxygen saturation, and capnography were monitored routinely perioperatively. During the surgery, blood pressure, and heart rate were also measured every 5 minutes. The rapid administration of dexmedetomidine may cause hemodynamic changes, therefore mean blood pressure and heart rate data were recorded (before anesthesia induction, after anesthesia induction, 15/min and 45/min into surgery). Atropine (intravenous [IV]/0.5 mg) was planned to be administered in case of bradycardia (heart rate <40 bpm) and ephedrine in case of hypotension (mean arterial pressure <60 mm Hg).

Patients were randomly assigned to one of 2 groups via a computer generated random number sequence. In group D (n=30), dexmedetomidine 1μg/kg was administered intravenously over 10 minutes (Precedex, Abbot Laboratories Inc., Abbott park, IL, USA). In group C (n=30), the same volume of normal saline was administered intravenously. After the bolus doses of study drugs, thiopental 5 mg/kg, succinylcholine 1 mg/kg, and fentanyl 1 μg/kg were administered for induction of anesthesia, 0.1 μg/kg/min dexmedetomidine infusion was continued until the end of surgery. Laryngoscopy was performed one minute after administration of succinylcholine. After the intubation, direct laryngoscopy was performed by an ENT surgeon. Maintenance was with 2% sevoflurane in nitrous oxide (50%) and oxygen supplemented with bolus doses of succinylcholine (10 mg) as needed.

Fasciculation was graded according to a scale developed by Mingus et al.[8] The adequacy of relaxation for intubation was evaluated as follows: well relaxed, no patient movement during intubation, vocal cords not moving = satisfactory; minor patient movement or vocal cords moving = fair; and obvious patient movement, bucking, or coughing during intubation = poor.[9]

Patients were allocated blindly to 3 anesthesiologists. The first anesthesiologist applied the infusing drugs such as saline or dexmedetomidine, the second anesthesiologist applied the drugs to the patients in the operating room, and the third one questioned the patients before and after the surgery. They were asked regarding muscle pain at the postoperative thirtieth minute. Muscle pain not related to surgical intervention was graded according to Harvey et al:[9] absence of muscle pain = no myalgia; minor stiffness limited to one area of the body = mild; muscle pain or stiffness noticed spontaneously by the patient, which may require analgesic therapy = moderate; and generalized, severe, or incapacitating discomfort = severe. No intramuscular injections were performed during the pre or postoperative period. Blood samples to determine CK levels were obtained before the induction of anesthesia and at the 24th hour postoperatively. Postoperative care was standardized for all patients.

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA) version 11.0 for Windows. Heart rate and mean blood pressure were analyzed using

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2-way ANOVA (between groups). One-Way ANOVA and post Hoc Bonferroni multiple comparison test were used for comparison within groups. Fasciculation score, postoperative myalgia score, and adequacy of relaxation for intubation was analyzed using the chi-square test. The Fisher's Exact test was used to compare the severity of fasciculation and myalgia between the groups. Mann-Whitney U and Wilcoxon tests were used to analyze CK levels between the groups. A value of $p<0.05$ was considered statistically significant.

Results. There were no significant differences between the 2 groups with respect to age, weight, gender, duration of surgery, and additional succinylcholine doses (**Table 1**). In both groups, the base-line heart rate and mean blood pressure was similar. Bolus infusion of dexmedetomidine did not decrease heart rate and mean blood pressure significantly (**Figures 1 & 2**). Atropine or ephedrine was not required in any patient. In both groups after intubation, the mean blood pressure increased significantly from base-line ($p=0.009$), but the increase in heart rate was not significant in both groups. In the dexmedetomidine group, the increase in mean blood pressure was greater, but there was no significant difference between the groups.

The severity and incidence of fasciculation were better in group D than group C ($p=0.025$) (**Table 2**). Intubating conditions were better in the dexmedetomidine group ($p=0.011$) (**Table 2**). At the thirtieth minute, none of the patients in either group suffered from moderate or severe myalgia. In group D, only one patient suffered from mild myalgia, and 29 patients had no myalgia. In group C, 10 patients suffered from mild myalgia, and 20 patients had no myalgia. The incidence and severity of myalgia were significantly higher in group C ($p=0.014$) (**Table 3**).

The postoperative CK levels increased significantly compared with their base-line levels in both groups ($p=0.022$ in group D and p=0.017 in group C). The CK level elevation was higher in group C ($p=0.03$) (**Figure 3**). The normal levels for CK in our laboratory are 30-170 IU.

Table 1 - Demographic data of study participants (mean±SD, or number of patients).

Variable	Group D, n=30	Group C, n=30
Age (years)	46.9±9.4	49.6±9.8
Weight (kg)	75.5±9.3	78.9±14.4
Gender (M/F)	23/7	25/5
Duration of surgery	25±5	23±4
Additional succinylcholine doses	34.3±34.7	36.6±34.2

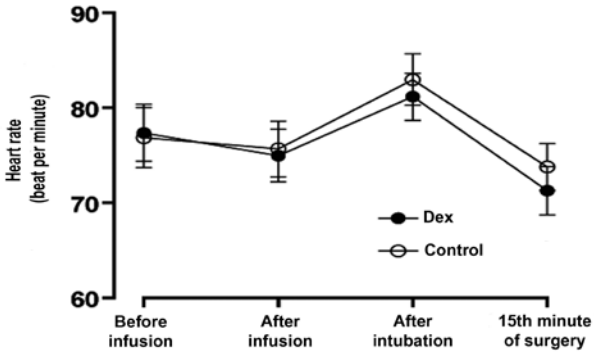

Figure 1 - Heart rates of the dexmedetomidine and control groups.

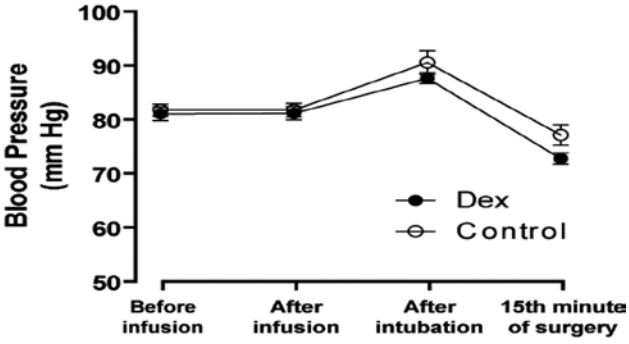

Figure 2 - Blood pressure measurements of the dexmedetomidine and control groups.

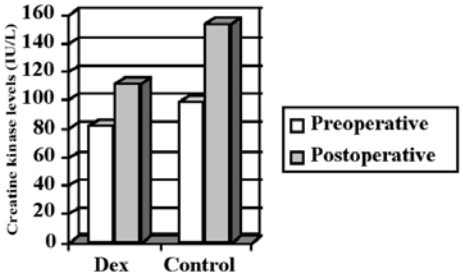

Figure 3 - Preoperative and postoperative creatine kinase levels of the dexmedetomidine (Dex) and control groups.

Discussion. In an attempt to correlate succinylcholine-induced fasciculation with muscle injury and the ensuing muscular pain and stiffness, changes in serum creatine phosphokinase after succinylcholine administration were studied. Hartman et al[10] showed that antidromically conducted axonal depolarization initiated by succinylcholine binding on

Table 2 - Fasciculations and intubation conditions among the study participants.

Variable	Group D, n=30	Group C, n=30
	n (%)	
Fasciculations		
Grade 0	5 (17)*	2 (6)
Grade 1	13 (43)	5 (17)
Grade 2	8 (27)	18 (60)
Grade 3	4 (13)	5 (17)
Intubating conditions		
Satisfactory	25 (83)*	15 (50)
Fair	4 (13)	12 (40)
Poor	1 (4)	3 (10)

*p<0.05 compared with Group C

Table 3 - Incidence and severity of postoperative myalgia among the study participants.

Postoperative thirtieth minute	Group D, n=30	Group C, n=30
	n (%)	
No myalgia	29 (97)*	20 (67)
Mild	1 (3)	10 (33)
Moderate	0	0
Severe	0	0

*p<0.05 compared with Group D

prejunctional nicotinic cholinergic receptors caused fasciculation. There was no correlation between the incidence of myalgia and creatinine kinase elevation.[11] In our study, postoperative CK levels increased significantly compared with their base-line levels in both groups (p<0.05). Also, the CK level elevation was higher in group C (p<0.05). Dexmedetomidine infusion was effective in reducing fasciculations after succinylcholine (p<0.05). The mechanism of the dexmedetomidine's inhibitory effect on fasciculation and CK is unclear. This effect may be mediated by stimulation of α2 adrenoreceptors in the spinal cord.

Group D had better intubating conditions, and this effect could have been caused by the antinociceptive properties of dexmedetomidine.[12] Under dexmedetomidine sedation, awake intubation did not cause discomfort, and dexmedetomidine sedation provided a good intraoral view and reduced airway responses for intubation.[13] Dexmedetomidine is a α2 adrenoreceptor agonist and a new sedative agent that has been used in intensive care units for sedation.[14] It is a novel lipophilic imidazole derivative with a higher affinity for α2-adrenoreceptors than the prototype drug clonidine.[15] Administration of an α2 adrenoreceptor agonist can decrease heart rate and increase mean blood pressure and systemic vascular resistance. Dexmedetomidine suppresses the cardiovascular responses to laryngoscopy and tracheal intubation.[16,17] After anesthesia induction and tracheal intubation, heart rate and mean blood pressure increased, but to a lower extent than the control group (p>0.05). The reason for this could be the stress of fasciculation pain occurring in ASA I-II noncardiac patients. In addition, dexmedetomidine (1 μg/kg) significantly decreased hemodynamic response when compared with the control group in cases of endotracheal intubation.[18]

Dexmedetomidine administration inhibits the inflammatory response.[7] Anti-inflammatory drugs were shown to be effective in fasciculation-induced pain. The anti-inflammatory effect of dexmedetomidine may be the mechanism behind the lower incidence and severity of myalgia in the dexmedetomidine group in our study. The other mechanism at play may be the analgesic effect of dexmedetomidine. Centrally active α-adrenergic agonists exert a powerful analgesic action, which may be due to the inhibition of substance P release in the dorsal root neuron.

Postoperative myalgia following the use of succinylcholine is a common, troublesome clinical problem. Unfortunately, it is associated with postoperative muscle pain in 5-83% of patients.[19] To solve this myalgia, many techniques and alternative agents have been employed, but the exact underlying pathophysiology has not been clarified completely.[3] It has been reported that increased myoplasmic calcium concentrations, membrane phospholipid degradation, released free fatty acids, and free radicals may be responsible for muscle damage and postoperative myalgia.[20] These findings have led to the use of several agents including non-steroidal anti-inflammatory drugs (NSAID), non-depolarizing neuromuscular blockers and pretreatment with lidocaine, diazepam, diphenylhydantoin, propofol, and gabapentin to minimize postoperative muscle pain. There is some evidence that NSAIDs reduce the incidence and severity of succinylcholine induced myalgia.[4] The use of NSAIDs may interrupt the prostaglandin-mediated destructive cycle, and this may provide a rationale for their use in preventing postoperative myalgia.[3] In our study, the incidence of myalgia was significantly lower at the thirtieth minute in the dexmedetomidine group (3%) (p<0.05). Additionally, a previous study showed that dexmedetomidine decreased postoperative analgesic requirements.[21] Unlugenc et al[21] reported that a single IV dose of dexmedetomidine (1 μg /kg) reduced

postoperative morphine consumption at identical pain scores compared with control. Moreover, Yildiz et al[16] reported that preoperative administration of a single dose of dexmedetomidine increased the hemodynamic responses during laryngoscopy and reduced opioid and anesthetic requirements. In our study, we also used 1 μg/kg dexmedetomidine for these effects.

There are some limitations to our study. First, all of our patients were not hospitalized, so we could not assess occurrence and severity of postoperative 24 hour myalgia of 23 patients (15 of 23 in group D). Therefore, we did not analyze the results. We only had data of CK levels. Another limitation was the small sample size and heterogeneity of the population. In future studies, these problems can be resolved.

We conclude that dexmedetomidine infusion before and after succinylcholine administration may be useful in diminishing the incidence of succinylcholine-induced myalgia in the early postoperative period. Routine use of dexmedetomidine cannot be recommended, and further research is required with a larger number of patients.

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