Effects of Preanesthetic Administration of Dexmedetomidine on Propofol-Fentanyl Induction

Preanestezik Uygulanan Deksmedetomidinin Propofol-Fentanil Indüksiyonuna Etkileri

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Geliş Tarihi/*Received:* 10.10.2007
Kabul Tarihi/*Accepted:* 15.04.2008

Bu çalışmanın bir bölümü 2006 yılı Avrupa Anestezi Birliği (ESA)'nin Madrid'deki kongresinde sunulmuştur.

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ABSTRACT Objective: Premedication is often required for anxiolysis and to lessen the psychological impact of hospitalisation or procedures. Dexmedetomidine is an α2-agonist which has anxiolytic, sedative and analgesic effects. In this study the premedication charactheristics of dexmedetomidine were assessed followed by propofol and propofol-fentanyl induction. **Material and Methods:** Sixty patients ASA I-II, aged 18–59 years, scheduled for elective surgery under general anesthesia, were randomly distributed into three groups of 20 patients each. Dexmedetomidine ($0.5\mu g \cdot kg^{-1}$) was given in 10 minutes as infusion to Group D and Group DF, 30 minutes before induction while Group C (control) received equal volume of saline as infusion. After propofol induction which was used in the dosage up to the eye-lash reflex abolishment, fentanyl ($1\mu g \cdot kg^{-1}$) was given to Groups C and DF. Before induction, the levels of sedation (Ramsay Sedation Score:1-6) and anxiety (Visuel Analogue Scale:0-100) scores were recorded. After induction; hemodynamic parameters, quality of induction (4-point scale), propofol consumption, additional anesthetic requirement, and side effects were compared among the groups. **Results:** The anxiety and sedation scores were significantly lower in Groups D and DF than in Group C ($p<0.05$). Quality of induction and additional anesthetic requirement were similar in all groups ($p>0.05$). Tympanic temperatures were significantly lower in Group D and DF than in Group C ($p<0.05$). Five patients in Group DF and two in Group D developed hypotension. Six patients in Group DF and one patient in Group D developed bradycardia. **Conclusion:** Dexmedetomidine premedication provided a satisfactory sedation and anxiolysis with decreased tympanic temperature and hemodynamic stability with propofol induction. Fentanyl can be used with careful management to avoid undesirable hemodynamic side effects.

Key Words: Dexmedetomidine; fentanyl; premedication; propofol; adverse effects

ÖZET Amaç: Hastanede yatışın veya müdahalelerin etkisini azaltabilmek ve anksiyoliz amacıyla sıklıkla premedikasyon gerekir. Deksmedetomidin anksiyolitik, sedatif ve analjezik etkileri olan bir α2-agonisttir. Bu çalışmada propofol ve propofol-fentanil indüksiyonu öncesi deksmedetomidin premedikasyonunun özellikleri değerlendirildi. **Gereç ve Yöntemler:** Elektif cerrahi girişimler için genel anestezi planlanan ASA I-II, 18-59 yaş aralığında, 60 hasta çalışmaya alındı. Hastalar randomize olarak her grupta 20 kişi olacak şekilde üç gruba ayrıldı. İndüksiyondan 30 dk önce Grup D ve Grup DF'ye $0.5\mu g\ kg^{-1}$ deksmedetomidin 10 dakika içinde infüzyon şeklinde uygulandı. Grup C (kontrol)'ye eşdeğer hacimde salin infüzyon şeklinde verildi. Kirpik refleksini ortadan kaldıracak dozda propofol indüksiyonundan sonra Grup C ve Grup DF'ye $1\mu g\ kg^{-1}$ fentanil verildi. İndüksiyondan önce, sedasyon (Ramsay sedasyon skoru;0-6) ve anksiyete düzeyleri (Vizüel analog skala; 0-100) kaydedildi. İndüksiyon sonrası hemodinamik parametreler, indüksiyon kalitesi (4-puan skala), ST segment analizi, timpanik ısı, ek anestezik gereksinimi ve yan etkiler karşılaştırıldı. **Bulgular:** Anksiyete ve sedasyon skorları Grup D ve DF'de Group C'ye göre anlamlı düşüktü ($p<0.05$). İndüksiyon kalitesi ve ek anestezik gereksinimi bütün gruplarda benzerdi ($p>0.05$). Timpanik ısı Grup D ve DF'de Grup C'den anlamlı düşüktü ($p<0.05$). Grup DF'de 5 ve Grup D'de 2 hastada hipotansiyon gelişti. Grup DF'de 6 ve Grup D'de bir hastada bradikardi gelişti. **Sonuç:** Deksmedetomidin premedikasyonu propofol indüksiyonunda azalmış timpanik ısı ve hemodinamik stabilite ile birlikte yeterli sedasyon ve anksiyoliz sağladı. Fentanil, istenmeyen hemodinamik yan etkilerden kaçınmak için, dikkatle kullanılabilir.

Anahtar Kelimeler: Deksmedetomidin; fentanyl; premedikasyon; propofol; yan etkiler

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Turkiye Klinikleri J Anest Reanim 2008, 6:59-64

Premedication is the administration of drugs in the period 1–2 h before the induction of anesthesia. The objectives of premedication are to allay anxiety and fear, reduce secretions, enhance the hypnotic effect of general anesthetic agents, reduce postoperative nausea and vomiting, produce amnesia, reduce the volume and increase the pH of the gastric contents, attenuate the vagal reflex and sympathoadrenal response, facilitate the smooth induction of anesthesia, and protect against allergic reactions.[1,2] Benzodiazepines, opioid analgesics, butyrophenones, phenothiazines, anticholinergic agents, β-blockers, and α_2- agonists like clonidine and dexmedetomidine are the alternatives which are useful for premedication. Of those dexmedetomidine has been considered for preoperative use to attenuate intraoperative sympathoadrenal responses. It is more specific for the α_2-receptor and probably has greater potential for premedication. These agents may also have a role in attenuating the sympathoadrenal responses during the induction of anesthesia.[1]

In this study our aims were to assess;

1. Premedication charactheristics of dexmedetomidine used 30 minutes before propofol induction.

2. Dexmedetomidine effects on propofol consumption and interaction with fentanyl.

MATERIAL AND METHODS

After obtaining approval from the hospital scientific and ethics board and patients' written informed consent, 60 consecutive ASA physical status I and II patients, aged 18–59 years, scheduled for elective surgery (laparoscopic cholecystectomy) under general anesthesia, were randomly distributed into three groups of 20 patients in each. Patients with hearing difficulty, a history of neurological or psychiatric disorders, contraindications for one of the drugs that were to be used, chronic alcoholism, cardiac, renal, hepatic, or respiratory disorders, obesity, or pregnancy, or were taking cerebrally active medications were excluded from the study. An intravenous cannula (20 Gauge) was inserted in the nondominant hand and 0.9% NaCl was infused at 8 $ml \cdot kg^{-1} \cdot h^{-1}$. Monitoring included an electrocardiogram, noninvasive blood pressure measurement, and pulse oximetry. As premedication, Group C received saline (1 $\mu g \cdot kg^{-1}$ fentanyl bolus in induction), Group D received dexmedetomidine (0.5 $\mu g \cdot kg^{-1}$) within 10 min intravenously, and Group DF received dexmedetomidine (0.5$\mu g \cdot kg^{-1}$) within 10 min intravenously (1$\mu g \cdot kg^{-1}$ fentanyl bolus in induction). Dexmedetomidine (0.5$\mu g \cdot kg^{-1}$) was infused within 10 min using an injector pump (ASCOR AP22 Warsaw, Poland) into patients in Groups D and DF. The same volume of saline was infused in Group C (control group). The patients were moved to the operating theatre from the premedication room 30 min after the dexmedetomidine infusion. The blinded surgeon assessed the anxiety score (Visuel Analogue Scale: 0–100) and Ramsay sedation score (1: anxious, agitated, 2: cooperative, relaxed, 3: responds to commands, 4: drowsy, responds to verbal commands, 5: sleepy, responds to touch, 6: asleep, no response to command). In addition to routine monitoring (non-invasive blood pressure, heart rate, SpO_2, $ETCO_2$), ST segment analysis and tympanic temperature were recorded at 5-min intervals for the first 30 min following induction. The patients' tympanic temperature values were maintained in normal range by an external heater, after 30 minutes of induction. In induction, the patients in Group C and Group DF were given fentanyl bolus (1$\mu g \cdot kg^{-1}$) first. Propofol was administered until the eyelash reflex disappeared and the amount of propofol was recorded. Endotracheal intubation was performed after injecting vecuronium (0.1$mg \cdot kg^{-1}$) by an anesthetist who was unaware of the study drugs. The quality of the anesthetic induction was assessed by the same anesthesiologist on a 4-point scale:1 = poor (slow onset, hypotension and tachycardia lasting 3–6 min), 2 = fair (transient hypotension and/or tachycardia lasting 1–2 min), 3 = good (15–25% changes in MAP or HR values), and 4 = excellent (rapid onset, ≤15% changes in MAP or HR values).[3] Before induction, the levels of sedation, and anxiety were recorded. After induction, hemodynamic parameters, quality of induction, induction propofol requirement, and possible side effects were recorded. Anesthesia was maintained with 1 MAC sevoflurane (in 50-50% O_2-N_2O) adjusted according to the age of the patient.

Clinically relevant hypotension was defined as a decrease in systolic blood pressure (SBP) of 20% below baseline levels or to less than 80 mmHg. Patients were to be treated for hypotension with 5 to 10 mg intravenous ephedrine. Bradycardia was defined as a pulse rate lower than 50 bpm and were planned to treat with 0.5 to 1 mg intravenous atropine sulfate.

All data were analysed using SPSS (Version 10.1, SPSS, Chicago, IL, USA). Tests of normality were found as p>0.05. The patient characteristics (age, body weight and height) were compared between groups using ANOVA and Student's *t*-test. Hemodynamic data, ST segment analysis, tympanic temperatures were compared among three groups using two-way repeated factor ANOVA with one repeated factor. Paired- t-test were used within each group. The anxiety, sedation scores, induction quality, and side effects were analysed using chi-square test. Statistical significance was accepted as p<0.05.

RESULTS

Patient charactheristics were similar in all groups (p>0.05).

The Ramsay sedation scores were significantly higher in Group D and Group DF than in the control group ($P < 0.05$) (Figure 1).

The anxiety scores (VAS) were significantly lower in Groups D and DF than in the control group ($P < 0.05$) (Figure 2). After premedication the mean VAS were 48.4 ± 15.9 in Group C, 26 ± 8.8 in Group D, and 23.7 ± 10.1 in Group DF. Baseline anxiety scores were 48.2 ± 15.9 in Group C, 49.7 ± 16.7 in Group D, and 49.2 ± 14.8 in Group DF ($P>0.05$). Induction quality and additional aneshetic requirement were found similar [3 (good)] in all groups (p>0.05). The induction quality scores were similar in all three groups ($P > 0.05$). The propofol requirement for induction decreased significantly in both Groups D and DF compared to the control group (1.1, 1.1, and 2.3 $mg \cdot kg^{-1}$, respectively) (Figure 3). Five patients in Group DF and two in Group D developed hypotension which responded to ephedrine treatment; six patients in Group DF and one in Group D developed bradycardia which was responsive atropine treatment (p<0.05) (Figure 4, 5).

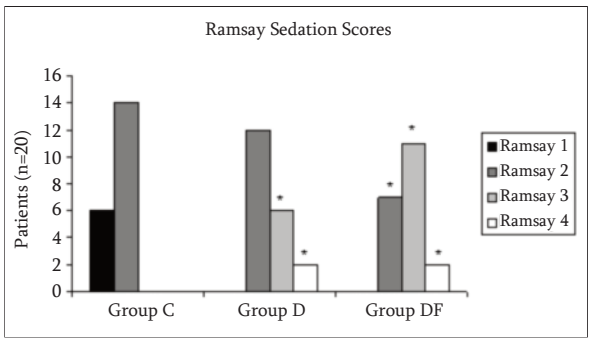

FIGURE 1: The sedation scores of the groups.
*p<0.05 between Group C and Group D.
*p<0.05 between Group C and DF.

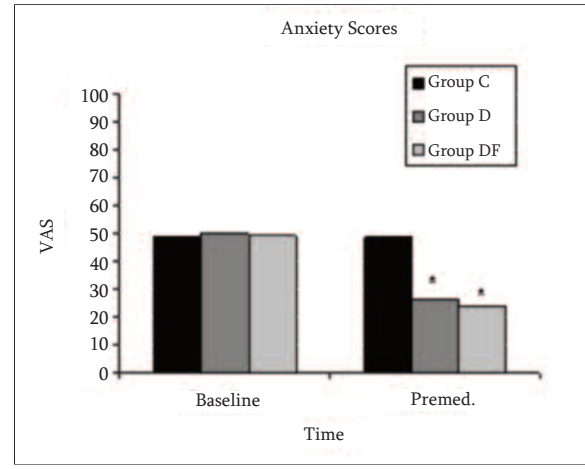

FIGURE 2: The anxiety scores of the groups.
*p<0.05 between Group D and Group C.
*p<0.05 between Group DF and Group C.

SpO_2, $ETCO_2$, ST segment analysis were similar in all groups ($P > 0.05$).

Tympanic membrane temperatures at 5th min after intubation were found significantly lower in Groups D and DF than in the control group ($P < 0.05$) (Figure 6).

DISCUSSION

The purposes of premedication are to allay anxiety, to establish sedation, and to provide analgesia if required. Barbiturates, benzodiazepines, antihistamines, opioids, and α_2-agonists (clonidine and dexmedetomidine) are all used for premedication. Dexmedetomidine is a highly selective,

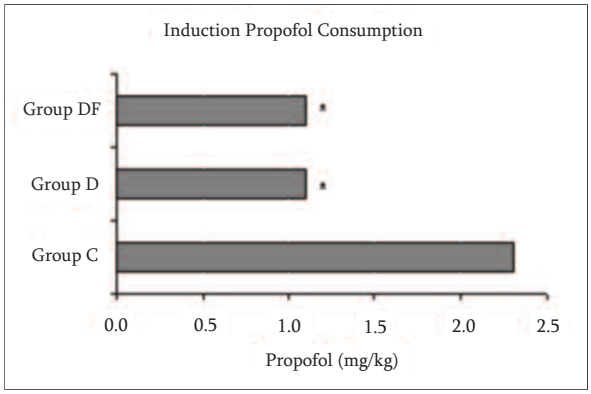

FIGURE 3: Total propofol consumption in the induction of the groups.
*p<0.05 between Group D and Group C.
*p<0.05 between Group DF and Group C.

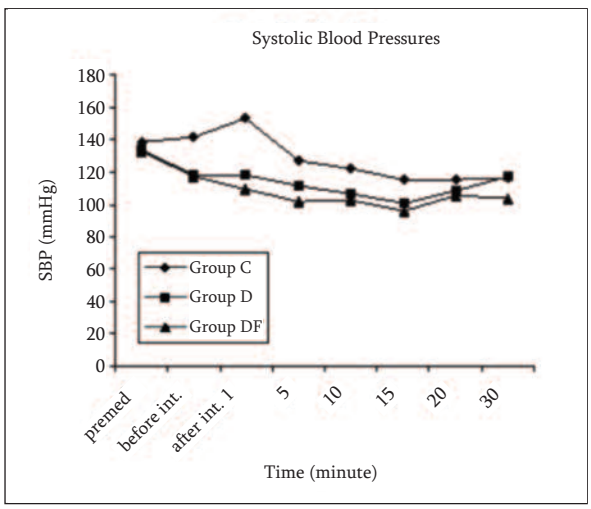

FIGURE 4: The systolic blood pressure (SBP) changes of the groups in 30 minutes of the operation. (Premed: The mean SBP values of the groups before premedication. Before int: The mean SBP values of the groups before intubation. After int. 1. min-30.min: The mean SBP values of the groups at first minute to 30th minute of induction.) (p>0.05)

centrally acting, α_2-adrenergic agonist thought to provide successful sedation without appreciable ventilatory effects.[4] It was reported that the hypnotic response was established via the effect of dexmedetomidine on the locus coeruleus which is an important modulator of wakefulness in the central nervous system.[5,6] Dexmedetomidine has also anxiolytic, analgesic, and antisialogogue effects.[7] In this study, while 30% of the patients in the control group were observed to be nervous and anxious, both groups with dexmedetomidine were relaxed and anxiety free.

Dexmedetomidine was reported to lead to a decrease in anesthetic requirement.[8] Mendes reported a decrease in propofol consumption in cats, similar to our results with dexmedetomidine.[9] Similarly Peden and coworkers reported decreased propofol and alfentanil consumption with 0.63 $\mu g \cdot kg^{-1}$ intravenous dexmedetomidine premedication.[10] Ozturk and coworkers reported lower propofol consumption both induction and maintenance of anesthesia with dexmedetomidine.[11] In this study, the propofol consumption during induction was found approximately 50% lower in the dexmedetomidine groups than in the control group. It is likely due of the effect of dexmedetomidine on the locus coeruleus and central neuro-adrenergic transmission.

Propofol consumption according to produce loss of consciousness resulted with similar induction quality in all groups. Propofol consumption in induction in the control group was found approximately two times more than as in the dexmedetomidine groups. Peden et al. similarly reported a reduction in the overall concentration and dose of propofol with intravenous dexmedetomidine premedication.[10] Therefore it is conceivable that we could observe the difference in induction quality with a constant dosage of propofol in all groups,

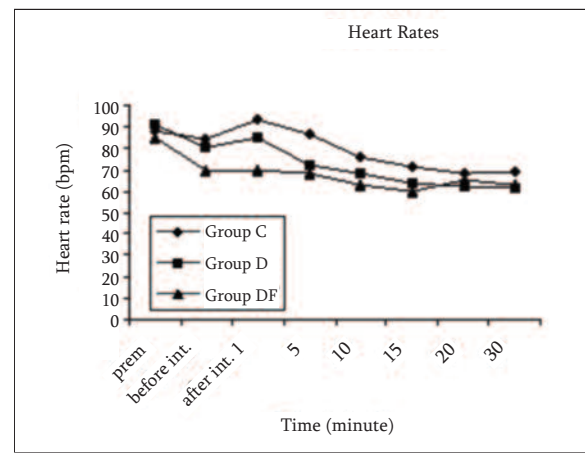

FIGURE 5: The mean heart rate (HR) changes of the groups in 30 minutes of the operation. (Premed: The mean HR values of the groups before premedication. Beforeint: The mean HR values of the groups before intubation. 1. min-30.min: The mean HR values of the groups at first minute to 30th minute of induction.)(p>0.05)

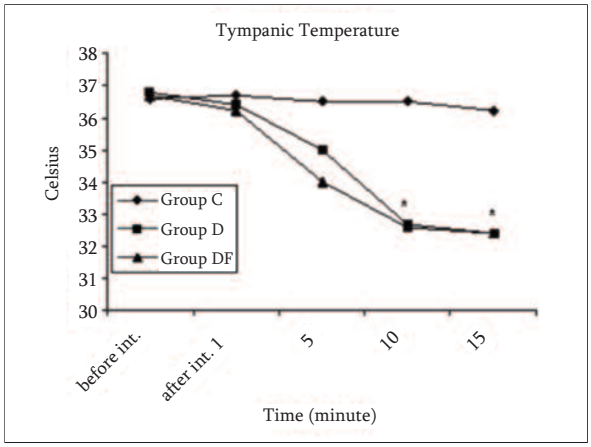

FIGURE 6: The mean tympanic membrane temperatures of the groups at first 30 minutes of induction. *p<0.05 in Groups D and DF compared to Group C.

Bradycardia and hypotension is a potential side effect of α_2-agonist administration.[1] Dexmedetomidine is eight times more selective than clonidine for the α_2- adrenergic receptor. It is 1620 times more potent as an α_2-agonist than as an α_1-adrenergic receptor agonist.[12] Dexmedetomidine induced bradycardia relates to its cental sympatholytic action with unopposed vagal tone, reduction of noradrenaline release, or direct vagotonic effect and usually reversed by anticholinergics.[9,13] Some authors have successfully used dexmedetomidine to prevent the increased blood pressure response to laryngoscopy and intubation.[13] Taittonen and coworkers reported both decreased blood pressures (11%) and heart rates (18%) compared to baseline values with dexmedetomidine administration and placebo, respectively.[14] In this study, dexmedetomidine was found effective in terms of the hemodynamic response to laryngoscopy and intubation, although hypotension and bradycardia which responded atropine treatment, were observed in Groups D and DF. Since those effects were more frequent in Group DF than in Group D, we concluded that the undesired hemodynamic effects of dexmedetomidine were augmented by fentanyl supplement. Similarly Jaakola and coworkers suggested decreased fentanyl requirement peroperatively in patients premedicated with dexmedetomidine intramuscularly.[15] As dexmedetomidine was given 30 minutes before fentanyl, it was expected to be slightly interaction with fentanyl. Fentanyl might reveal more compromised hemodynamic effects, if it was used as a coinduction agent with dexmedetomidine.

Dexmedetomidine affects thermogenesis by several mechanisms. It causes profound hypothermia which was found a result from the activation of α_2-ARs in the hypothalamus.[9,16,17] The postsynaptic effect of dexmedetomidine on α_2-AR inhibits lipolysis. In adults, dexmedetomidine dose dependently decreases thermoregulatory vasoconstriction and shivering thresholds.[18] All α_2-Agonists can decrease the set point of the thermoregulatory centre by over 0.5°C. In this study we observed significant decrease in tympanic temperature at 5th minute of induction and it became profound at 30th minute which required exogenous heating. In conclusion, careful monitoring and expeditiously control of body temperature with the use of exogenous heat sources in adults (specially in the elderly, childhood and infants) receiving dexmedetomidine are imperative.

The ST segments of the electrocardiogram become elevated within 20 to 30 seconds after the onset of acute coronary occlusion and, when persistent, such changes offer a possible indirect marker of the extent and severity of myocardial ischemic injury. An ST-segment deviation of ≥ 1mm (0.1 mV) lasting for at least 1 minute is accepted to be an indicator of myocardial infarction. Systemic infusion of dexmedetomidine confers complex direct and indirect cardiovascular responses that affect myocardial perfusion. Low and high concentration of dexmedetomidine (0,5 ng/ml vs 5 ng/ml) were reported reduced myocardial perfusion in parallel with a reduction in myocardial oxygen demand without evident myocardial ischemia in healthy subjects.[19,20] Our study also suggested that dexmedetomidine infusion was found safe according to ST-segment analysis at the dose used.

In conclusion, dexmedetomidine was found to be an anxiolytic and sedative at the dosage studied, and it decreased propofol consumption during induction. Therefore, dexmedetomidine may be considered as a reliable premedication agent. However, opioids should be used with caution following dexmedetomidine to prevent serious side effects like hypothermia and bradycardia.

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