EFFECT OF DEXMEDETOMIDINE ON PAIN CAUSED BY INJECTION OF PROPOFOL

Gamze Sarkılar MD,[1] İnci Kara MD,[2] Ateş Duman MD,[1] Feride Aygın MD,[2] Selmin Ökesli MD[1]

[1] Selcuk University, Meram Faculty of Medicine, Department of Anesthesiology and Intensive Care, Konya, Turkey

[2] Meram Education and Research Hospital, Department of Anesthesiology and Intensive Care, Konya, Turkey

ABSTRACT

Objective: *This study was designed to assess the local and systemic effects of two different pre-anesthetic infusion dose of dexmedetomidine in preventing propofol injection pain.*

Material and Method: *Two hundred fifty adults were assigned into five groups. Before injection of propofol, group 1 (placebo n=50) received an infusion of saline solution, group 2 (n=50) received 0.5 μg kg^{-1} of dexmedetomidine and group 3 (n=50) received 1 μg kg^{-1} of dexmedetomidine from the same vein. Group 4 (n=50) received 0.5 μg kg^{-1} of dexmedetomidine and group 5 (n=50) received 1 μg kg^{-1} dexmedetomidine followed by an injection of propofol from a vein located in the opposite hand. Pain assessment was made immediately after propofol injection.*

Results: *Two hundred twenty five patients completed the study. The number of patients who suffered from any degree of pain was significantly high when compared to dexmedetomidine group (p=0.05). When compared with placebo and opposite hand, administering dexmedetomidine from the same vein was more efficient to prevent propofol pain (p=0.003). 1 μg kg^{-1} of dexmedetomidine was similar to 0.5 μg kg^{-1} of dexmedetomidine in preventing propofol pain.*

Conclusion: *Dexmedetomidine infusions in pre-anesthetic sedative doses of 0.5 μg kg^{-1} and 1 μg kg^{-1} decrease the incidence of propofol injection pain compared to placebo.*

Key Words: *Dexmedetomidine, propofol, pain.* ***Nobel Med 2012; 8(1): 83-88***

DEKSMEDETOMİDİNİN PROPOFOL ENJEKSİYON AĞRISINA ETKİSİ

ÖZET

Amaç: Bu çalışma deksmedetomidinin iki farklı pre-anestezik infüzyon dozunun propofol enjeksiyon ağrısının önlenmesindeki lokal ve sistemik etkilerini değerlenmeyi amaçlamaktadır.

Materyal ve Metod: İki yüz elli erişkin hasta 5 gruba ayrıldı. Propofol enjeksiyonundan önce, grup 1'e (plasebo n=50) serum fizyolojik, grup 2'ye (n=50) 0,5 μg kg^{-1} deksmedetomidin ve grup 3'e (n=50) 1 μg kg^{-1} deksmedetomidin aynı venden, grup 4'e (n=50) 0,5 μg kg^{-1} deksmedetomidin ve grup 5'e (n=50) 1 μg kg^{-1} deksmedetomidin diğer eldeki bir venden enjekte edildi. Ağrı değerlendirmeleri propofol enjeksiyonundan hemen sonra yapıldı.

Bulgular: İki yüz yirmi beş hasta çalışmayı tamamladı. Deksmedetomidin verilen tüm hastalar plaseboyla kıyaslandığında; herhangi bir derecede ağrı duyulması placebo grubunda daha fazlaydı (p=0,05). Plasebo ve karşı taraftaki elle kıyaslandığında deksmedetomidinin aynı elden verilmesi propofol ağrısını önlemede daha etkin bulundu (p=0,003). 1 μg kg^{-1} deksmedetomidin propofol ağrısının önlenmesinde 0,5 μg kg^{-1} deksmedetomidin ile benzer bulundu.

Sonuç: Preanestetik sedatif dozlar olan 0,5 μg kg^{-1} ve 1 μg kg^{-1} deksmedetomidin, propofol enjeksiyon ağrısı insidansını plaseboya kıyasla azaltmaktadır.

Anahtar Kelimeler: Deksmedetomidin, propofol, ağrı **Nobel Med 2012; 8(1): 83-88**

INTRODUCTION

Lipid emulsion propofol remains the most common drug used for anesthetic induction. In the absence of treatment regimes, 28% to 90% of patients experience moderate to severe pain when propofol is injected into a peripheral vein.[1] A number of techniques, drugs and even new propofol formulations have been tried to minimize propofol-induced pain with varying success.

Propofol pain is encountered during induction of anesthesia. Unfortunately routine pre-anesthetic premedication does not affect the incidence or severity of pain on injection of propofol.[2] Dexmedetomidine is a highly selective and potent α2-adrenoreceptor agonist drug with sedative and analgesic properties. Dexmedetomidine is sometimes used as pre-anesthetic medication, as an adjuvant drug during anesthetic induction or as a total intravenous anesthetic agent.[3-5] Previous two clinical trials regarding dexmedetomidine for decreasing propofol injection pain have revealed conflicting results.[6,7] Both studies employed dexmedetomidine as bolus administration using a tourniquet. While Ayoglu et al. found 0.25 μg kg^{-1} dexmedetomidine is not effective in reducing injection pain of propofol, Turan et al. claimed that similar dose of dexmedetomidine prevents propofol pain similar to lidocaine.[6,7] Neither study used pre-anesthetic loading infusion of dexmedetomidine in their design. We designed this prospective, double blind, placebo-controlled study to assess the local and systemic effects of two different pre-anesthetic infusion dose of dexmedetomidine in preventing propofol injection pain.

MATERIAL and METHOD

The study was approved by the Human Research Ethics Committee. Written informed consent was obtained from 225 adult patients (American Society of Anesthesiologists categories I-III) scheduled for elective surgery at two teaching hospitals. Exclusion criterion included the patients with communication difficulties. Patients were instructed on the pain evaluation score before entering the room. No patient received pre-anesthetic medication. When the patients arrived in the operating room, routine cardio respiratory monitoring for heart rate (HR), peripheral oxygen saturation (SpO_2) and noninvasive blood pressure was applied.

Patients were randomly allocated (a computer-generated sequence with a sealed envelope method) to one of five study groups: Venous access was obtained on the dorsum of both hands by using 20-G cannula. Two veins of similar size one on the back of each hand was chosen. Patients were excluded from the study if either one of the cannula was not inserted properly at the first attempt. In group 1 (n=50) (placebo) patients received an infusion of 0.9% NaCl solution followed by bolus injection of propofol, from the same vein. Group 2 (n=50) received an infusion of 0.5 μg kg^{-1} dexmedetomidine followed by a bolus injection of propofol from the same vein. Group 3 (n=50) received 1 μg kg^{-1} dexmedetomidine infusion followed by an injection of propofol from the same vein. Group 4 (n=50) received an infusion of 0.5 μg kg^{-1} dexmedetomidine i.v. followed by a bolus injection of propofol from the vein located in the opposite hand. Group 5 (n=50) received 1 μg kg^{-1} dexmedetomidine i.v. followed by a bolus injection of propofol from the vein in the opposite hand. Dexmedetomidine was prepared as 200 μg diluted to 50 mL with 0.9% NaCl (2 mL dexmedetomidine plus 48 mL 0.9% NaCl). Propofol injections were always performed through the cannula in the patient's non-dominant hand. Dexmedetomidine infusion and propofol injection hands were determined by non-blinded anesthesiologist according to the assignment groups. All dexmedetomidine and placebo infusions were performed in ten minutes at ambient operating room temperature (20-22°C). Another anesthesiologist, who was unaware of the study groups, entered the room just after completion of the infusion, first determined the sedation scores of the patient and then administered 4 mL of 1% propofol in 5 sec. and assessed the intensity of pain 30 sec. after propofol injection.

Sedation was evaluated by using the Ramsay sedation scale (1=Patient is anxious and agitated or restless, or both, 2=Patient is co-operative, oriented, and tranquil, 3=Patient responds to commands only, 4=Patient exhibits brisk response to light glabellar tap or loud auditory stimulus, 5=Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus, 6=Patient exhibits no response).[8]

The patients were observed and asked after injection of the propofol if they had pain in the hand or arm. The grading criteria for injection pain were as follows: 0=no pain, 1=mild pain, 2=severe pain without behavioral signs such as grimace or arm withdrawal movement, and 3=severe pain accompanied by behavioral signs. Once the assessment of injection pain was performed, induction of anesthesia continued according to the anesthetist's routine practice. Study was discontinued in patients who showed local signs of extravasation of i.v. fluid infusion or study drug and patients who were deeply sedated (Ramsay score>3).

All adverse effects were recorded. Hypotension was defined as a decrease of systolic blood pressure of 20% or more and bradycardia as a heart rate of < 50 beats per minute. →

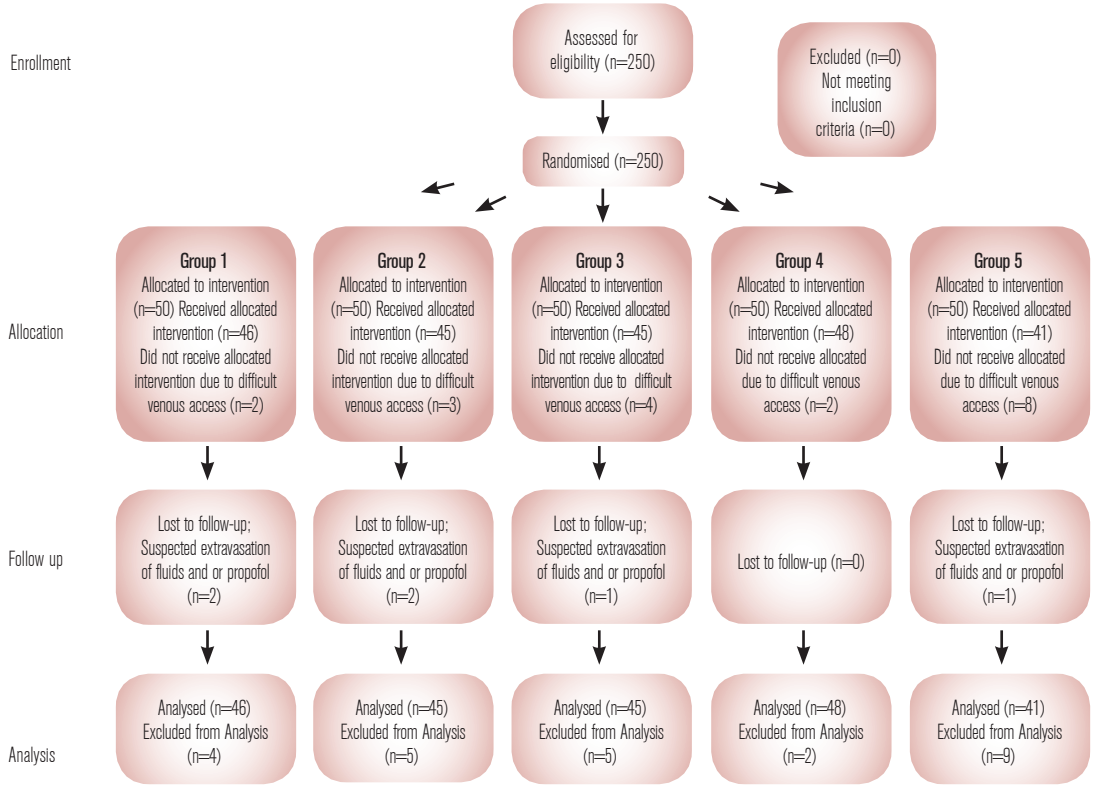

Figure 1. Patient enrollment flowchart

The primary outcome criterion was the incidence and severity of pain during injection of propofol, and secondary outcomes were sedation, hemodynamic parameters and adverse events from i.v. infusion until end of propofol injection.

Assuming prevalence of pain after i.v. propofol is 80% and that this would be reduced to 40% after therapy, with α=0.05 and ß=0.80, 40 patients would need to be included in each group. To allow an exclusion rate of 25% we initially included 250 patients. The results were analyzed with one-way ANOVA, post hoc test (Tukey HSD) and Chi-square tests. Statistical significance was set at a p value of <0.05.

RESULTS

Two hundred twenty five patients completed the study. Main reasons for exclusion were failure to insert venous cannula at the first attempt (n=19) and suspected extravasation of i.v. fluid and/or propofol (n=6) (Figure 1).

The five groups were similar with respect to patient gender and body weight. There were significant differences regarding age and ASA physical status (Table 1). The incidence and severity of pain are presented in Table 2. The number of patients who suffered from any degree of pain was significantly high when compared to dexmedetomidine group (p=0.05). When compared with placebo and opposite hand, administering dexmedetomidine from the same vein was significantly more efficient to prevent propofol pain (p=0.003). 1µg kg of dexmedetomidine was similar to 0.5 µg kg of dexmedetomidine in preventing propofol pain.

No episodes of hypotension, bradycardia or other side effects were recorded during the study period. Sedation scores were also similar (Table 3).

DISCUSSION

The main findings in this study may be summarized as follows: 1- Pre-anesthetic infusion of dexmedetomidine was effective in decreasing the incidence of propofol injection pain compared to placebo; 2- Local effect of dexmedetomidine on the vein used for the injection seem to be superior to the systemic analgesic effect 3-Dose of dexmedetomidine does not significantly alter the results.

Propofol-induced pain is considered to be one of the most important problems of current clinical anesthetic practice. It was rated as the seventh most disturbing patient experience in anesthetic practice by a group of experts.[9] Nature of the vascular pain is expressed by the patients as aching, burning and crushing. A reduction in pain incidence and/or intensity has been reported with various drugs new formulations of propofol but→

Table 1: Patient characteristics

	Group 1 (placebo) (n=46)	Group 2 (0.5μg kg^{-1} dex) (n=45)	Group 3 (1μg kg^{-1} dex) (n=45)	Group 4 (0.5μg kg^{-1} dex) (n=48)	Group 5 (1μg kg^{-1} dex) (n=41)
Gender (M/F)	19/27	25/20	18/27	28/20	23/18
Age (yr)	42.2±14.1	48.8±13.2	51.9±11.0*	44.3±14.1**	50.8±11.5*
Weight (kg)	73.7±13.4	72.8±14.3	73.5±14.9	73.5±13.4	75.6±14.2
ASA (I/II/III)	20/15/11	7/19/19*	4/13/28*	10/25/13	3/18/20*

dex: dexmedetomidine. Data are presented as number of patients±SD. *p<0.05 compared to group 1, **p<0.05 compared to group 3.

Table 2: Pain scores associated with propofol injection

	Same hand			Opposite hand	
Intensity of pain	Group 1 (placebo) (n=46)	Group 2 (0.5μg kg^{-1} dex) (n=45)	Group 3 (1μg kg^{-1} dex) (n=45)	Group 4 (0.5μg kg^{-1}dex) (n=48)	Group 5 (1μg kg^{-1} dex) (n=41)
None [0]	13 (28.3%)	24 (53.3%)	25 (55.6%)*	14 (29.2%)	16 (39.0%)
Mild pain [1]	16 (34.8%)	13 (28.9%)	13 (28.9%)	21 (43.8%)	15 (36.6%)
Moderate pain [2]	8 (17.4%)	4 (8.9%)	2 (4.4%)	8 (16.7%)	4 (9.8%)
Severe pain [3]	9 (19.6%)	4 (8.9%)	5 (11.1%)	5 (10.4%)	6 (14.6%)
Pain [1/2/3]	33 (71.7%)	21 (46.7%)**	20 (44.4%)*	34 (70.8%)	25 (61.0%)
		41/90 (45.5%)§		59/89 (66.3%)	
		100/179 (55.8%)#			

The pain scores are shown in square brackets, data are presented in number of patients with percentage of patients in parentheses, *p=0.01 compared with groups 1, 4 and 5, **p=0.047, compared with groups 1, 4 and 5. §p=0.003, #p=0.05 compared to placebo. dex: dexmedetomidine.

none of the proposed drugs and techniques has been able to prevent propofol injection pain.[10-20]

Dexmedetomidine has the advantage of providing sedation, anxiolysis and analgesia without the risk of respiratory depression.[20-24] There are two previous controlled studies comparing bolus administration of dexmedetomidine with lidocaine in the prevention of propofol injection pain. Both Turan et al. and Ayoglu et al. injected 0.25 μg kg^{-1} bolus of dexmedetomidine with a tourniquet on the forearm.[6,7] Turan et al. used a 4 point pain intensity score and found dexmedetomidine to be effective as lidocaine in decreasing propofol injection pain compared with placebo.[7] Contrary to Turan et al. study, using a similar dose and technique, Ayoglu et al. concluded that pretreatment with dexmedetomidine is not as effective as lidocaine in reducing injection pain of propofol. They failed to show a difference in pain on injection of propofol using a verbal rating scale between dexmedetomidine and placebo.[6] There are important design and dose differences between the above mentioned studies and the present study. When designing the present study, we decided to administer dexmedetomidine in the dose and manner proposed in the insertion of the drug.[25] In the present study, 0.5 μg kg^{-1} and 1 μg kg^{-1} dexmedetomidine were administered i.v. over 10 minutes similar to the regular loading dose without a tourniquet. Slow infusion allows more time for dexmedetomidine to come into contact with the endothelium of the vein to elicit local effects. The above mentioned two previous studies employed a tourniquet for 20 seconds to one minute. Our study design also provides us data to differentiate local effects and systemic effects of dexmedetomidine by injecting propofol through veins pretreated and non-pretreated with dexmedetomidine.

Despite numerous clinical and preclinical studies to date, the mechanisms by which propofol causes injection pain is still not fully understood. Previous work has identified the initial component of propofol injection pain to involve immediate stimulation of nociceptors and free nerve endings.[1,26] The concentration of propofol in the aqueous phase is associated with the intensity of initial component of pain on injection.[11,14] The delayed component of pain, appearing within half a minute is also believed to result from interaction with nociceptors and free nerve endings.[1,13] Better analgesia in patients in which dexmedetomidine was administered from the same vein in our study supports the possible role of dexmedetomidine action on local nociceptors present in peripheral veins. There is evidence on local analgesic effects of dexmedetomidine. Dexmedetomidine has been used successfully to improve the quality of anesthesia when combined with local anesthetics in i.v. regional anesthesia by Memis at al. Dexmedetomidine also has systemic analgesic properties.[27] Centrally active α_2-adrenergic agonists such as dexmedetomidine exert powerful analgesic action that is probably transduced at several levels including the dorsal root neuron and α_2-adrenergic receptors located at nerve endings.[26,27] Effect on peripheral α_2-adrenergic receptors may act by preventing norepinephrine release at the nerve ending.[28]

Although many authors argue that plasma kallikrein-kinin system may also be responsible in the delayed component.[14] Recently Sim et al. have disputed this theory by measuring bradykinin concentrations. Their study showed that micro emulsion propofol produces even more frequent and severe pain on injection than lipid emulsion and there was no evidence that bradykinin generation associated with activation of the plasma kallikrein-kinin system causes propofol induced pain.[11] Previous work shows that dexmedetomidine may also act by rectifying hyper polarization-activated conductance in peripherally mediated antinociception and venous α_1 and α_2 stimulation resulting in release of vasodilator prostaglandins that antagonize vasoconstrictor response. This modulates the sympathetic response of venous smooth muscle and may be important in endothelial dysfunction caused by propofol.[28,29] Our study design does not provide data to comment further on possible mechanisms of propofol pain. →

Our study failed to show a significant difference in effectiveness between the two dexmedetomidine doses. Our lower dexmedetomidine dose which was 0.5 µg kg^{-1} may be a sufficient dose to produce local analgesia in the injected vein. Considering the previous effective dose of Turan et al. was half of our lower dose, we can speculate that 0.5 µg kg^{-1} of dexmedetomidine may be one of the reasons our results are different from Ayoglu et al. study.[6]

There may be concerns regarding the safety of dexmedetomidine. The earlier two studies have administered dexmedetomidine as an i.v. bolus.[6,7] Both studies report stable hemodynamics despite the rapid i.v. bolus administration of 0.25 µg kg^{-1} of dexmedetomidine. When dexmedetomidine is administered as a continuous infusion it is associated with a predictable and stable hemodynamic response.[30,31] Despite being higher than previous studies our study doses (0.5-1 µg kg^{-1}) provided good hemodynamics in our patients.There are limitations for this study. Most notably, it was conducted in two different teaching hospitals with a variety of patients. Besides the subjective rating of different anesthesiologists, the age and physical status differences of our patients may have affected our results. Dexmedetomidine is a potent sedative agent. Deep level of sedation may be misinterpreted as analgesia during propofol injection. Although we excluded the patients with deep level of sedation from the study it is difficult to comment on the effects of lighter levels of sedation on our results.

To conclude, dexmedetomidine infusions in pre-anesthetic sedative doses of 0.5 µg kg^{-1} and 1 µg kg^{-1} decrease the incidence of propofol injection pain compared to placebo. Because of clinical limitations for dexmedetomidine, we cannot advise the routine use of dexmedetomidine for prevention of propofol pain but our results show that patients will suffer from less propofol injection pain if they receive dexmedetomidine infusions from the same vein before induction with propofol compared to patients with no mode of treatment.

Table 3: Hemodynamic data and sedation scores

	Group 1 (placebo) (n=46)	Group 2 (0.5 µg kg^{-1} dex) (n=45)	Group 3 (1 µg kg^{-1} dex) (n=45)	Group 4 (0.5 µg kg^{-1} dex) (n=48)	Group 5 (1 µg kg^{-1} dex) (n=41)
Baseline					
HR	80.6±15.7	83.1±15.8	77.5±17.9	83.4±17.1	79.5±16.3
SAP	132.9±17.8	141.4±25.9	141.4±21.9	138.3±19.5	149.4±20.6
DAP	77.4±10.5	81.2±16.2	74.6±12.4	75.7±12.3	86.5±16.9
MAP	97.6±11.3	102.5±22.0	100.9±17.1	99.2±21.8	112.1±18.0
SpO_2	97.0 ±2.0	96.8 ±2.1	96.7±2.1	96.6±2.2	96.5±2.3
Before propofol injection					
HR	81.7±16.3	75.5±15.2	72.8±17.9	74.2±16.0	68.3±14.4
SAP	132.4±20.5	130.6±22.0	133.8±25.4	126.2±16.6	131.6±22.2
DAP	76.8±10.4	75.2±11.6	72.1±11.4	70.5±11.1	76.5±14.6
MAP	97.2±13.0	94.5±14.0	96.0±18.1	92.7±12.4	97.0±18.4
SpO_2	96.9±2.1	96.2±2.1	95.7±2.0	95.6±2.0	95.2±1.9
Ramsay sedation score (2/3)	45/1	32/13	31/14	34/14	30/11

dex: dexmedetomidine. HR: heart rate, SAP: systolic arterial pressure, DAP: diastolic arterial pressure, MAP: mean arterial pressure, SpO_2: peripheral oxygen saturation. Sedation scores are in brackets. Data are presented in number of patients±SD.

C **CORRESPONDING AUTHOR:** Ateş Duman MD, Selcuk University, Meram Faculty of Medicine, Dept. of Anesthesiology and Intensive Care, Konya, Turkey aduman@selcuk.edu.tr

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REFERENCES

1. Tan CH, Onsiong MK. Pain on injection of propofol. Anaesthesia 1998; 53: 468-476.
2. Zub D, Berkenbosch JW, Tobias JD. Preliminary experience with oral dexmedetomidine for procedural and anesthetic premedication. Paediatr Anaesth 2005; 15: 932-938.
3. Bozkurt P. Premedication of the pediatric patient - anesthesia for the uncooperative child. Curr Opin Anaesthesiol 2007; 20: 211-215.
4. Turgut N, Turkmen A, Gökkaya S, Altan A, Hatiboglu MA. Dexmedetomidine-based versus fentanyl-based total intravenous anesthesia for lumbar laminectomy. Minerva Anestesiol 2008; 74: 469-474
5. Ramsay MA, Luterman DL. Dexmedetomidine as a total intravenous anesthetic agent. Anesthesiology 2004; 101: 787-790.
6. Ayoğlu H, Altunkaya H, Ozer Y, et al. Does dexmedetomidine reduce the injection pain due to propofol and rocuronium? Eur J Anaesthesiol 2007; 24: 541-545.
7. Turan A, Memis D, Kaya G, Karamanlioglu B. The prevention of pain from injection of propofol by dexmedetomidine and comparison with lidocaine. Can J Anesth 2005; 52: 548-549.
8. Ramsay MAE, Savage TM, Simpson BRJ. Controlled sedation with\ alphaxalone-alphadolone. Br Med J 1974; 2: 656-659.
9. Macario A, Weinger M, Truong P, Lee M. Which clinical anesthesia outcomes are both common and important to avoid? The perspective of a panel of expert anesthesiologists. Anesth Analg 1999; 88: 1085-1091.
10. Ishiyama T, Kashimoto S, Oguchi T, et al. Clonidine-ephedrine combination reduces pain on injection of propofol and blunts hemodynamic stress responses during the induction sequence. J Clin Anesth 2006; 18: 211-215.
11. Sim JY, Lee SH, Park DY, et al. Pain on injection with microemulsion propofol. Br J Clin Pharmacol 2009; 67: 316-325.
12. Liljeroth E, Karlsson A, Lagerkranser M, Akeson J. Low-dose propofol reduces the incidence of moderate to severe local pain induced by the main dose. Acta Anaesthesiol Scand 2007; 51: 460-463.
13. Liljeroth E, Akeson J. Less local pain on intravenous infusion of a new propofol emulsion. Acta Anaesthesiol Scand 2005; 49: 248-251.
14. Doenicke AW, Roizen MF, Rau J, Kellermann W, Babl J. Reducing pain during propofol injection: the role of solvent. Anesth Analg 1996; 82: 472-474.
15. Scott RP, Saunders DA, Norman J. Propofol: clinical strategies for preventing the pain of injection Anaesthesia 1988; 43: 492-494.
16. Apiliogullari S, Keles B, Apiliogullari B, et al. Comparison of diphenhydramine and lidocaine for prevention of pain after injection

of propofol: a double-blind, placebo-controlled, randomized study. Eur J Anaesthesiol 2007; 24: 235-238.
17. Sasaki T, Okamura S, Kisara A, et al. Effect of lidocaine on pain caused by injection of propofol: comparison of three methods at two injection rates. J Anesth 1999; 13: 14-16.
18. Grauers A, Liljeroth E, Akeson J. Propofol infusion rate does not affect local pain on injection. Acta Anaesthesiol Scand 2002; 46: 361-363.
19. Sun NC, Wong AY, Irwin MG A. Comparison of pain on intravenous injection between two preparations of propofol. Anesth Analg 2005; 101: 675-678.
20. Klement w, Arndt JO. Pain on injection of propofol: effects of concentration and diluents. Br J Anaesth 1991; 67: 281-284.
21. Carollo DS, Nossaman BD, Ramadhyani U. Dexmedetomidine: a review of clinical applications. Curr Opin Anesthesiol 2008; 21: 457-461.
22. Ngwenyama NE, Anderson J, Hoernschemeyer DG, Tobias JD. Effects of dexmedetomidine on propofol and remifentanil infusion rates during total intravenous anesthesia for spine surgery in adolescents. Paediatr Anaesth 2008; 18: 1190-1195.
23. Basar H, Akpinar S, Doganci N, et al. The effects of preanesthetic, single-dose dexmedetomidine on induction, hemodynamic, and cardiovascular parameters. J Clin Anesth 2008; 20: 431-436.
24. Ohtani N, Kida K, Shoji K, Yasui Y, Masaki E. Recovery profiles from dexmedetomidine as a general anesthetic adjuvant in patients undergoing lower abdominal surgery. Anesth Analg 2008; 107: 1871-1874.
25. PrecedexTM (dexmedetomidine) [package insert].Istanbul, Turkey: Abbott Laboratories 2002.
26. Akeson J. Pain on injection of propofol - why bother? Acta Anaesthesiol Scand 2008; 5: 591-593.
27. Memis D, Turan A, Karamanlioglu B, Pamukcu Z, Kurt I. Adding dexmedetomidine to lidocaine for intravenous regional anesthesia. Anesth Analg 2004; 98: 835-840.
28. Kamibayashi T, Maze M. Clinical uses of alpha2 -adrenergic agonists. Anesthesiology 2000; 93: 1345-1349.
29. Callow ID, Campisi P, Lambert ML, Feng Q, Arnold JM. Enhanced in vivo alpha1- and alpha2-adrenoceptor-mediated venoconstriction with indomethacin in humans. Am J Physiol 1998; 275: 837-843.
30. Dalle C, Schneider M, Clergue F, Bretton C, Jirounek P. Inhibition of the I(h) current in isolated peripheral nerve: a novel mode of peripheral antinociception? Muscle Nerve 2001; 24: 254-261.
31. Antaa R, Kallio A, Virtanen R. Dexmedetomidine, a novel α2-adrenergic agonist: a review of its pharmacodynamic characteristics. Drugs Future 1993; 18: 49-56.

NOBEL MEDICUS

Düzeltmeler

Nobel Medicus 2010; 6(2): 68-74 *künyeli sayımızda basılan "The Diagnostic Accuracy of Endotracheal Aspiration (ETA) and Mini-BAL in The Diagnosis of Ventilator Associated Pneumonia" başlıklı yazıda, orjinaline uygun basılmasına rağmen yazar tarafından hatalı gönderildiği ve düzeltilmesi talebi üzerine, aşağıda belirtilen düzeltmeler yapılmıştır.*

Materyal ve Metod bölümünde geçen "This prospective study was conducted between august 2006- may 2007 in our hospital" cümlesi "This prospective study was conducted between august 2004- August 2005 in our hospital" olacak şekilde düzeltilmiştir.

Nobel Medicus 2011; 7(3): 121-122 *künyeli sayımızda basılan "Baryum Sülfat Aspirasyonu: İki Olgu" başlıklı yazıda aşağıda belirtilen düzeltmeler yapılmıştır.*

Makale yazarlarından Hayati Kandiş'in akademik unvanı Doç. Dr. Hayati Kandiş[1] yerine Yrd. Doç. Dr. Hayati Kandiş[1] olacak şekilde düzeltilmiştir.