Oral Clonidine Pretreatment Prior to Venous Cannulation

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Clonidine is a preferential alpha-2 agonist drug that has been used for over 35 years to treat hypertension. Recently, it has also been used as a preoperative medication and as a sedative/anxiolytic drug. This randomized, double-blind, placebo-controlled crossover clinical trial characterized the effects of oral clonidine pretreatment on intravenous catheter placement in 13 patients. Parameters measured included the bispectral index (BIS), Observer's Assessment of Alertness/Sedation Scale (OAA/S), frontal temporal electromyogram (EMG), 30-Second Blink Count (Blink), Digit Symbol Substitution Test (DSST), State Anxiety Inventory (SAI), fingertip versus forearm skin temperatures, and multiple questionnaires. Oral clonidine significantly decreased SAI scores, OAA/S, EMG, and Blink, but did not cause statistically significant BIS or DSST reductions. Subjects preferred oral clonidine pretreatment prior to venipuncture compared to placebo. Questionnaires also indicated that clonidine provided minimal sedation, considerable anxiolysis, and some analgesia. Fingertip versus forearm skin temperature differentials were decreased. Reduced fingertip versus forearm temperature differentials suggest increased peripheral cutaneous blood flow prior to venous cannulation. Oral clonidine pretreatment not only helped control patient anxiety and pain but also provided cardiovascular stability.

Key Words: Clonidine; Venous cannulation; BIS; SAI; DSST.

Intravenous (IV) catheters have become the accepted standard of care for general anesthesia and IV sedation.[1] Catheterization of peripheral veins can be made more comfortable using a variety of techniques, including local anesthesia infiltration,[2,3] nitrous oxide inhalation,[2,4,5] ethyl chloride topical,[4,6] eutectic mixture of local anesthetics (lidocaine-prilocaine) cream,[7,8] tetracaine patches,[9] and even midazolam nasal spray.[10] The goals of these methods are pain and anxiety reduction with minimal invasiveness and lack of significant complications. An additional benefit of some cannulation pretreatments is cutaneous vasodilation.

Previous medical anesthesia/sedation studies have indicated that clonidine administration prior to surgery decreases pain[11,12] and anxiety[12] and also stabilizes blood pressure and heart rate by reduction of central sympathetic outflow.[13–15] Additional investigations have shown that clonidine pretreatment also increases skin temperature[16] and decreases the difference between fingertip and forearm temperatures.[17] These results suggest an increase in cutaneous blood flow.[18]

The purpose of this randomized, double-blind, placebo-controlled crossover clinical trial was to characterize the sedative/anxiolytic effects and changes in skin temperatures of oral clonidine pretreatment prior to IV catheter placement.

METHODS

The study protocol and informed consent form were approved by The Ohio State University Institutional Review Board. Inclusion criteria were (a) adults with American Society of Anesthesiologists ASA1 or ASA2 health status, (b) severe chronic periodontal disease and/or the

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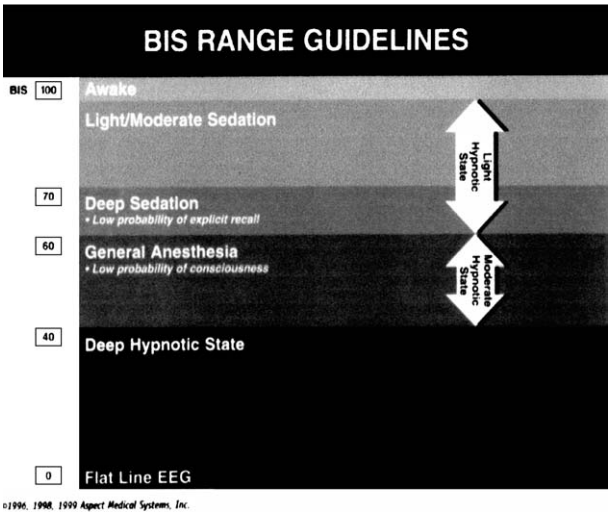

Figure 1. Bispectral index study range guidelines.

need for dental implant(s), and (c) treatment plan including at least 2 periodontal surgical procedures requiring IV sedation of at least 2 hours duration. Exclusion criteria were (a) neurological or psychiatric disease, (b) sleep disorders, (c) severe asthma, (d) uncontrolled hypertension, (e) insulin-dependent diabetes, (f) relative or absolute contraindication to local anesthesia, diazepam, meperidine, or clonidine, including pregnancy, and (g) a history of substance abuse. Sixteen volunteer periodontal surgery patients aged 20–60 years were recruited. The number of subjects required for this study (N = 13) was determined by power analysis of data from a previous bispectral index (BIS) study.[19] Each subject took nothing by mouth for 8–12 hours and was accompanied and transported by a responsible adult.

All subjects arrived 1 hour prior to scheduled periodontal surgery (time = 0) and were seated in a semisupine position in a standard dental chair. Baseline skin temperatures (T1, finger, and T2, forearm), BIS (Figure 1), Observer's Assessment of Alertness/Sedation Scale (OAA/S; Table 1), frontal temporal electromyography (EMG), 30-Second Blink Count (Blink), Digit Symbol Substitution Test (DSST), and Spielberger State Anxiety Inventory Scores (SAI) were recorded. The DSST asks subjects to decode, digit-associate, and write as many simple geometric symbols as possible within 90 seconds. The DSST was initially administered 2–4 times to minimize learning effects, and the final score was recorded. The SAI is a 20-question inventory with responses rated on a 1 to 4 scale. SAI scores range from 20 (low anxiety state) to 80 (high anxiety state). Subjects were also shown a photograph of a simple object for 5 seconds to remember. Each patient then swallowed 1 capsule of clonidine (0.1 mg/35 kg body weight) or 1 placebo capsule. An Aspect A-1050 BIS monitor (As-

Table 1. Observer's Assessment of Alertness/Sedation Scale

Responsiveness	*Speech*	*Facial Expression*	*Eyes*	*Composite Score*
Responds readily to name spoken in normal tone	Normal	Normal	Clear, no ptosis	5 (alert)
Lethargic response to name spoken in normal tone	Mild slowing or thickening	Mild relaxation	Glazed or mild ptosis (less than half the eye)	4
Responds only after name is called loudly and/or repeatedly	Slurring or prominent slowing	Marked relaxation (slack jaw)	Glazed and marked ptosis (half the eye or more)	3
Responds only after mild prodding or shaking	Few recognizable words			2
Does not respond to mild prodding or shaking				1 (asleep)

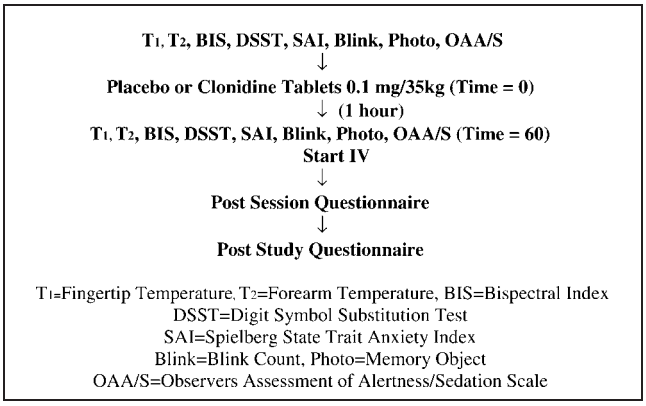

Figure 2. Clonidine study design flow diagram.

pect Medical Systems, Newton, Mass) was used with default settings including a 30-second smoothing time. A standard frontal temporal montage was recorded using BIS sensor electrodes applied to the scalp–left temple after mild cotton 2 × 2 abrasion resulting in contact impedance under 5 kΩ. Frontal temporal EMG logarithmic decibel values were rounded to the nearest 5 db (30, 35, 40, 45, 50, 55, 60, 65, or 70). Immediate access to the blinded list of drug assignments was available in case of emergency.

One hour after oral premedication with clonidine or placebo (time = 60), all baseline measurements were repeated. A 20-gauge, 2.54-cm (1-in) Jelco (Ethicon Inc., Arlington, Tex) intravenous catheter was then placed in each subject's arm or hand. IV lines were maintained with 5% dextrose and normal saline at a rate of 100 mL/h. The same sedationist performed intravenous cannulation for each patient at both of the patient's sessions using identical techniques. A corresponding site on the same or opposite arm or hand was catheterized at the second session. During all sessions, talking and background noise were minimized because patients sedated with clonidine are easy to arouse.[20] Patients were encouraged to use restroom facilities prior to sedation sessions because clonidine can exert a mild diuretic effect.[21] Patients breathed 4 L/min of 100% O_2 via nasal cannula during venipuncture.

Recall and recognition were tested following at least 2 hours of intravenous conscious sedation and approximately 20 minutes of recovery (time = 200) via a postsession follow-up questionnaire and all original baseline measurements repeated. The sedationist and surgeon also completed postsession questionnaires. All subjects also completed a poststudy questionnaire immediately following the second session (Figure 2). Although the study design included evaluation of vital signs and responses during sedation, the present report is limited to the effects of clonidine administration on venipuncture.

Quantitative changes in BIS were compared using a Friedman test with $P \leq .05$ considered significant. Parametric data including fingertip and forearm skin temperatures were analyzed using paired and unpaired 2-tailed t tests with $|t| < 0.05$ significant. Each subject participated in 2 test sessions in randomized order with clonidine (clonidine sessions) and with placebo (control sessions) and acted as his or her own control. Postsession and poststudy questionnaires along with amnesia results were assessed and validated by comparison to a previous study[19] including nonsedated controls. Questionnaire and amnesia results were also correlated with objective data from this study (OAA/S, BIS, EMG, SAI, Blink, and DSST). Simple yes/no memory percentage correct amnesia data and survey responses were evaluated by chi-square likelihood ratios, with $P \leq .05$ considered significant. OAA/S, EMG, Blink, DSST, SAI, and survey score differences were analyzed using paired 2-tailed t tests ($|t| \leq 0.05$ considered significant) or Wilcoxon signed-rank tests ($|z| \leq 0.05$ considered significant).

RESULTS

Three of 16 subjects did not complete their second sessions. A statistically significant majority of subjects (9) preferred clonidine pretreatment prior to venipuncture over intravenous cannulation with placebo ($P < .05$). Four subjects expressed no preference and no subject favored placebo pretreatment. No statistically significant correlations were observed between the order of the 2 sessions, venipuncture site, surgical procedure(s) performed, surgeon, sedationist (venipuncturist), date and time of treatment, and any other variables measured in this study.

Tables 2 and 3 list fingertip versus forearm skin temperatures before (time = 0) and 1 hour after (time = 60) pretreatment with clonidine (Table 3) versus placebo (Table 2). Fingertip skin temperatures after clonidine pretreatment were elevated significantly compared to pretreatment baselines ($|t| < 0.05$). Differences between forearm and fingertip temperatures in individual subjects were significantly decreased by clonidine pretreatment ($|t| < 0.05$).

Tables 4 and 5 show BIS, OAA/S, EMG, DSST, SAI, and Blink values before (time = 0) and 1 hour after (time = 60) oral clonidine (Table 5) and placebo administration (Table 4). Clonidine pretreatment significantly reduced OAA/S, EMG, SAI, and Blink ($P < .05$) at time = 60 compared to time = 0. DSST results did not detect significant impairment compared to baseline after oral clonidine (time = 60). BIS readings were reduced following clonidine administration, but the reductions were not statistically significant.

Table 2. Differences in Skin Temperatures (°C) for 13 Subjects Before and After Venipuncture With Oral Placebo Pretreatment (Control Sessions)*

Skin Temperature	*Time = 0 (SD)*	*Time = 60 (SD)*	*Difference, Time = 0 vs Time = 60 (t test)†*
T2 (forearm)	31.9 (2.7)	31.8 (2.9)	0.1 (NS)
T1 (fingertip)	28.5 (3.7)	28.7 (3.5)	−0.2 (NS)
Difference, T2 − T1	3.4‡ (4.3)	3.1‡ (4.2)	0.3 (NS)

* Time = 0 is baseline, and time = 60 is 1 hour after placebo administration. T2 indicates forearm skin temperature; NS, not significant; and T1, fingertip skin temperature.

† Probability of difference between time = 0 and time = 60 according to a paired 2-tailed Student *t* test (|t|) is given in parentheses.

‡ Statistically significant difference between T2 and T1 ($P < .05$).

Table 6 summarizes surgeon, sedationist, and subject responses to questionnaires. All 3 respondents favored clonidine over placebo, but the results were statistically significant for subjects only.

Table 7 lists amnesia results for clonidine and placebo groups. All subjects remembered intravenous catheterization both with clonidine and with placebo pretreatment. Oral clonidine pretreatment did not significantly change picture memory percentage correct.

No study subject experienced or reported any untoward reactions or complications including rebound hypertension from oral clonidine. No subject required emergency treatment. One subject did go through a brief syncopal episode during venipuncture after placebo pretreatment. This episode was preceded by a drop in BIS below 70. There was no significant difference in the number of subjects needing to urinate during study sessions with clonidine or with placebo. The ''blinded list of drug assignments'' were not revealed until the study was completed.

DISCUSSION

Clonidine (Catapres), an imidazoline compound, was introduced 35 years ago, first as a treatment for nasal congestion and then for hypertension.[22–24] Clonidine has also been used to treat and/or prevent diarrhea,[25] manic and bipolar symptoms,[26] muscle rigidity and spasticity,[27] hyperactivity and attention deficit disorder in children,[28] withdrawal states,[29–32] congestive heart failure,[33] new-onset rapid atrial fibrillation,[34] angina pectoris,[35] myocardial infarction,[36] post–general anesthesia shivering[37] and agitation,[38–41] glaucoma,[42] chronic pain,[43] and syncope.[44] It can also supplement peribulbar,[45] epidural,[46] and intrathecal anesthesia.[47] Recently, clonidine has been utilized as a preoperative medication providing anxiolysis,[12,48] sedation,[49] analgesia,[11,50,51] hemodynamic stability,[13,50–53] saliva control,[23,54] and antiemetic effects.[55] It also possesses sedative-,[56,57] anesthetic-,[58,59] and analgesic-sparing[13,53] properties. Clonidine exhibits anxiolytic effects independent of sedation[60] and also reduces perioperative plasma catecholamine[53] and prolactin[61] concentrations. Optimal oral premedication dosage has been established at 0.2 mg for an average 70-kg adult.[62] Clonidine is a relatively nontoxic drug, as indicated by case reports of 50- to 1000-fold overdoses resulting in no permanent injuries.[63–66] A single 0.2-mg dose of clonidine exhibits its maximal hypotensive effect 60–90 minutes after oral administration. Single doses do not cause rebound hypertensive effects occasionally associated with discontinuation of long-term treatment. When used as an oral premedication, clonidine rarely causes significant bradycardia and/or hypotension requiring treatment with IV fluids, atropine, or other medications.[49,67,68] The small decreases in heart rate and in systolic, diastolic, and mean ar-

Table 3. Differences in Skin Temperatures (°C) for 13 Subjects Before and After Venipuncture With Oral Clonidine Pretreatment (Clonidine Sessions)*

Skin Temperature	*Time = 0 (SD)*	*Time = 60 (SD)*	*Difference, Time = 0 vs Time = 60 (t Test)†*
T2 (forearm)	33.3 (2.2)	32.0 (1.5)	1.3 (NS)
T1 (finger tip)	27.8 (3.2)	30.6 (3.1)	−2.8 (|t| < 0.05)
Difference, T2 − T1	5.5‡ (1.7)	1.4‡ (2.0)	4.1 (|t| < 0.05)

* Time = 0 is baseline, and time = 60 is 1 hour after clonidine administration. T2 indicates forearm skin temperature; NS, not significant; and T1, fingertip skin temperature.

† Probability of difference between time = 0 and time = 60 according to a paired 2-tailed Student *t* test (|t|) is given in parentheses.

‡ Statistically significant difference between T2 and T1 ($P < .05$).

Table 4. Differences in Sedation Parameters for 13 Subjects Before and After Venipuncture With Oral Placebo Pretreatment (Control Sessions)*

Sedation Parameter (Range)	*Time = 0 (SD)*	*Time = 60 (SD)*	*Difference, Time = 0 vs Time = 60 (Test)†*
BIS (0–100)	96 (1.6)	97 (1.9)	−1 (NS)
OAA/S (1–5)	5.0 (0.07)	5.0 (0.09)	0 (NS)
EMG (30–70)	50 (6)	48 (5)	2 (NS)
Blink	7.7 (7.0)	8.4 (6.8)	−0.7 (NS)
DSST (0–100)	56.2 (13.9)	56.2 (13.5)	0 (NS)
SAI (20–80)	39.1 (5.2)	41.8 (8.6)	−(2.7) (NS)

* Time = 0 is baseline, and time = 60 is 1 hour after placebo administration. BIS indicates bispectral index; NS, not significant; OAA/S, Observer's Assessment of Alertness/Sedation Scale EMG, frontal temporal electromyograph; Blink, 30-second blink count; DSST, Digit Symbol Substitution Test; and SAI, Speilberger State Anxiety Inventory. BIS values are 90–100 = awake, 80–90 = light sedation, 70–80 = moderate sedation, 60–70 = deep sedation and 40–60 = general anesthesia; OAA/S values range from 1 = asleep, to 5 = totally awake. EMG readings are logarithmic decibel values rounded to the nearest 5 decibels. SAI scores range from 20 = low anxiety state to 80 = high anxiety state.

† Probability of difference between time = 0 and time = 60 according to a paired 2-tailed Student *t* test (|t|) or a Wilcoxon signed-rank test (|z|) is given in parentheses.

Table 5. Differences in Sedation Parameters for 13 Subjects Before and After Venipuncture With Oral Clonidine Pretreatment (Clonidine Sessions)*

Sedation Parameter (Range)	*Time = 0 (SD)*	*Time = 60 (SD)*	*Difference, Time = 0 vs Time = 60 (Test)†*
BIS (0–100)	97 (1.3)	96 (1.8)	1 (NS)
OAA/S (1–5)	4.9 (0.1)	4.6 (0.54)	0.3 ($\|z\| < 0.05$)
EMG (30–70)	50 (4)	45 (4)	5 ($\|z\| < 0.05$)
Blink	8.1 (5.7)	4.7 (4.1)	3.4 ($\|t\| < 0.05$)
DSST (0–100)	57.2 (15.8)	57.5 (16.7)	−0.3 (NS)
SAI (20–80)	42.4 (8.3)	36.7 (9.2)	5.7 ($\|z\| < 0.05$)

* Time = 0 is baseline, and time = 60 is 1 hour after clonidine administration. BIS indicates bispectral index; NS, not significant; OAA/S, Observer's Assessment of Alertness/Sedation Scale; EMG, frontal temporal electromyograph; Blink, 30-second blink count; DSST, Digit Symbol Substitution Test; and SAI, Speilberger State Anxiety Inventory. BIS values are 90–100 = awake, 80–90 = light sedation, 70–80 = moderate sedation, 60–70 = deep sedation, and 40–60 = general anesthesia. OAA/S values range from 1 = asleep, to 5 = totally awake. EMG readings are logarithmic decibel values rounded to the nearest 5 decibels. SAI scores range from 20 = low anxiety state to 80 = high anxiety state.

† Probability of difference between time = 0 and time = 60 according to a paired 2-tailed Student *t* test (|t|) or a Wilcoxon signed-rank test (|z|) is given in parentheses.

terial blood pressures following oral clonidine administration generally have no harmful clinical consequences and cause no clinical symptoms or apparent problems. These findings are confirmed and reinforced by a large body of literature.[12,13,15,49–53,55–58,67,69,70] Clonidine is a mixed alpha agonist drug possessing peripheral $\alpha 1$ and $\alpha 2$ activity as well as imidazoline agonist effects. In low doses it primarily produces central $\alpha 2$ effects.[70] Clonidine exhibits an $\alpha 2 : \alpha 1$ selectivity ratio of 200 : 1 and an $\alpha 2$a to imidazoline activity ratio of 16.[71] Even though various $\alpha 2$ antagonists, including atipamezole, have experimentally reversed clonidine in humans, they are currently approved for veterinary applications only.[72]

The results of this study are consistent with the known properties of clonidine. Clonidine-induced anxiolysis prior to venipuncture was indicated by statistically significant 13% reductions in SAI and validated by subject surveys. The SAI has been utilized for decades in countless studies and recently has been used to evaluate the anxiolytic properties of clonidine.[48,73–75] Significant decreases in OAA/S and EMG values at time 60 after clonidine administration indicated mild sedation. Statistically insignificant decreases in BIS were also observed 1 hour after oral clonidine administration (Table 5). Malinovsky et al[76] reported small but statistically significant BIS depression following large doses of intrathecal clo-

Table 6. Differences in Questionnaire Responses After Venipuncture for 13 Study Subjects With Clonidine vs Placebo Oral Pretreatments*

Questionnaire Responses Scored 0–5 With Higher Score Indicating Favorable Preference	*Average of Responses With Placebo (± SD)*	*Average of Responses With Clonidine (± SD)*	*Difference With Placebo vs With Clonidine (Signed-Rank)†*
Sedationist postsession tolerance to IV placement	3.7 (1.2)	4.4 (0.77)	0.7 (NS)
Surgeon postsession tolerance to IV placement	3.5 (1.0)	4.1 (0.86)	0.6 (NS)
Subject postsession tolerance to IV placement	2.9 (1.2)	3.8 (.90)	0.9 ($\|z\| < 0.05$)

* IV indicates intravenous catheter; NS, not significant.

† Probability of difference between placebo and clonidine according to a Wilcoxon signed-rank test (|z|) is given in parentheses.

Table 7. Amnesia Results for 13 Study Subjects With Clonidine and With Placebo Oral Pretreatment*

Amnesia/Memory Loss Event or Picture (Time Shown)	*Correct Responses With Placebo*	*Correct Responses With Clonidine*	*Difference With Clonidine vs With Placebo (Chi-Square)†*
Number of subjects recalling venipuncture	13	13	0 (NS)
Number of subjects recalling memory picture (time = 0)	13	13	0 (NS)
Number of subjects recognizing memory picture (time = 0)	13	13	0 (NS)
Number of subjects recalling memory picture (time = 60)	9	11	2 (NS)
Number of subjects recognizing memory picture (time = 60)	10	12	2 (NS)

* Time = 0 is baseline, and time = 60 is 1 hour after clonidine administration. NS indicates not significant.

† Probability of difference between placebo and clonidine according to a chi-square likelihood ratio is given in parentheses.

nidine. Recent studies have used BIS to evaluate dental sedation.[19,77]

DSST is a measure of cognitive and psychomotor impairment that has been used to evaluate recovery from various sedation agents.[78,79] Blink counts have also been utilized to assess sedation, impairment, and recovery.[80–82] Both Blink and DSST measurements decrease during sedation and return to normal baselines after recovery. Significant decreases in Blink were seen 1 hour after clonidine pretreatment versus placebo. DSST results in this study did not detect significant impairment because of clonidine pretreatment at time 60 compared to time 0.

Nine of 13 (69%) of subjects reported that oral clonidine pretreatment reduced discomfort of intravenous catheter placement compared to pretreatment with placebo ($P < .05$). Clonidine also significantly reduced fingertip versus forearm skin temperature differentials, suggesting an increase in cutaneous blood flow. This could be an additional advantage to enable easier intravenous access, especially when anxious patients exhibit high sympathetic tone and increased peripheral vascular constriction. One subject experienced a brief syncopal episode preceded by a significant drop in BIS[83] during venipuncture with placebo pretreatment. This subject did not faint during catheter placement with clonidine pretreatment.

The limitations of this study include the relatively low number of subjects ($N = 13$), the difficulty in maintaining blinding because of obvious signs after clonidine administration in some patients, and the inherent difficulties in making subjective evaluations of sedation levels.[84] Although oral clonidine pretreatment seems to be purely beneficial, negative effects, including prolonged recovery, hypotension, and bradycardia could be discovered with further investigations and larger sample sizes. The next generation of more potent, more receptor-specific central $\alpha 2$ agonists such as dexmedetomidine[43,71,85] is already available in the United States. Perhaps increased utilization of $\alpha 2$ drugs will lead to FDA approval of atipamezole as a reversal agent.[72] The apparent advantages of oral clonidine prior to venipuncture may also be of value in oral sedation[86] of mildly anxious patients prior to routine dental injections and minor dental procedures. Additional research is needed, especially for possible benefits to dental patients who are hypertensive and/or exhibit cardiovascular instability.

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REFERENCES

1. Weaver JM. The steel-needle butterfly—an outdated intravenous lifeline technology in modern anesthesiology. *Anesth Prog.* 2000;47:117–118.

2. Solomowitz BH. Intravenous cannulation: a different approach. *Anesth Prog.* 1993;40:20–22.

3. Langham BT, Harrison DA. Local anesthetic: does it really reduce the pain of insertion of all sizes of venous cannula? *Anaesthesia.* 1992;47:890–891.

4. Crecelius C, Rouhfar L, Beirne OR. Venous cannulation and topical ethyl chloride in patients receiving nitrous oxide. *Anesth Prog.* 1999;46:100–103.

5. Henderson JM, Spence DG, Komocar LM, Bonn GE, Stenstrom R. Administration of nitrous oxide to pediatric patients provides analgesia for venous cannulation. *Anesthesiology.* 1990;72:269–271.

6. Armstrong P, Young C, McKeown D. Ethyl chloride and venipuncture pain: a comparison with intradermal lidocaine. *Can J Anaesth.* 1990;37:656–658.

7. Selby IR, Bowles BJM. Analgesia for venous cannulation: a comparison of EMLA (5 minutes application), lignocaine, ethyl chloride and nothing. *J R Soc Med.* 1995;88: 264–267.

8. Hallen B, Carlsson P, Uppfeldt A. Clinical study of lignocaine-prilocaine cream to relieve the pain of venipuncture. *Br J Anaesth.* 1985;57:326–328.

9. Long CP, McCafferty DF, Sittlington NM, Halliday HL, Woolfson AD, Jones DS. Randomized trial of novel tetracaine patch to provide local anesthesia in neonates undergoing venipuncture. *Br J Anaesth.* 2003;91:514–518.

10. Ljungman G, Kreuger A, Andreasson S, Gordh T, Sorensen S. Midazolam nasal spray reduces procedural anxiety in children. *Pediatrics.* 2000:105:73–78.

11. Yoshikawa T, Wajima Z, Ogura A, Inoue T, Ogawa R. Orally administered clonidine significantly reduces pain during injection of propofol. *Br J Anaesth.* 2001;86:874–876.

12. Beer GM, Spicher I, Seifert B, Emanuel B, Kompatscher P, Meyer VE. Oral premedication for operations on the face under local anesthesia: a placebo-controlled double-blind trial. *Plast Reconstr Surg.* 2001;108:637–643.

13. Laisalmi M, Koivusalo AM, Valta P, Tikkanen I, Lindgren L. Clonidine provides opioid-sparing effect, stable hemodynamics, and renal integrity during laparoscopic cholecystectomy. *Surg Endosc.* 2001;15:1331–1335.

14. Kulka PJ, Tryba M, Zenz M. Dose-response effects of intravenous clonidine on stress response during induction of anesthesia in coronary artery bypass graft patients. *Anesth Analg.* 1995;80:263–268.

15. Nishina K, Mikawa K, Uesugi T, et al. Efficacy of clonidine for prevention of perioperative myocardial ischemia: a critical appraisal and meta-analysis of the literature. *Anesthesiology.* 2002;96:323–329.

16. Kanto J, Allonen H, Hiltunen R, Marvola M, Mãntylã R. Bioavailability and clinical effects of three brands of clonidine: the relationship between plasma level and effect. *Int J Clin Pharmacol.* 1982;20:118–121.

17. Delaunay L, Bonnet F, Liu N, Beydon L, Catoire P, Sessler DI. Clonidine comparably decreases the thermoregulatory thresholds for vasoconstriction and shivering in humans. *Anesthesiology.* 1993;79:470–474.

18. Talke PO, Caldwell JE, Richardson CA, Heier T. The effects of clonidine on human digital vasculature. *Anesth Analg.* 2000;91:793–797.

19. Hall DL, Weaver JM, Ganzberg S, Rashid R, Wilson S. Bispectral EEG index monitoring of high dose nitrous oxide and low dose sevoflurane sedation. *Anesth Prog.* 2002;49: 56–62.

20. Hall JE, Uhrich TD, Ebert TJ. Sedative, analgesic and cognitive effects of clonidine infusions in humans. *Br J Anaesth.* 2001;86:5–11.

21. Hamaya Y, Nishikawa T, Dohi S. Diuretic effect of clonidine during isoflurane, nitrous-oxide, and oxygen anesthesia. *Anesthesiology.* 1994;81:811–819.

22. Gavras I, Mangolis AJ, Gavras H. The alpha2-adrenergic receptors in hypertension and heart failure: experimental and clinical studies. *J Hypertens.* 2001;29:2115–2124.

23. Reid JL, Wing LMH, Miathias CJ, Frankel HI, Neill E. The clinical pharmacology of clonidine and related central antihypertensive agents. *Br J Clin Pharmacol.* 1981;12:295–302.

24. Barnett AJ, Cantor S. Observations on the hypertensive action of Catapres (ST155) in man. *Med J Aust.* 1968; 1:87–91.

25. McArthur KE, Anderson DS, Durbin TE, Orloff MJ, Dharmsathaphorn K. Clonidine and lidamidine to inhibit watery diarrhea in a patient with lung cancer. *Ann Intern Med.* 1982;96:323–325.

26. Zubenko GS, Cohen BM, Lipinski JF, Jonas JM. Clonidine in the treatment of mania and mixed bipolar disorder. *Am J Psychiatry.* 1984;141:1617–1618.

27. Jerussi TP, Capacchione JF, Benvenga MJ. Reversal of opioid-induced muscle rigidity in rats. Evidence for α-2adrenergic involvement. *Pharmacol Biochem Behav.* 1987;28: 283–289.

28. Hunt RB, Minderaa RB, Cohen DJ. Clonidine benefits children with attention deficit disorder and hyperactivity. Report of double-blind placebo-crossover therapeutic trial. *J Am Acad Child Adolesc Psychiatry.* 1985;24:617–629.

29. Gold MS, Pottash AL, Sweeny DR, Kleber HD. Efficacy of clonidine in opiate withdrawal: a study of thirty patients. *Drug Alcohol Depend.* 1980;6:201–208.

30. Ashton H. Benzodiazepine withdrawal. Outcome in 50 patients. *Br J Addict.* 1987;82:665–671.

31. Cushman P Jr, Sowers JR. Alcohol withdrawal syndrome: clinical and hormonal responses to α2-adrenergic treatment. *Alcoholism.* 1989;13:361–364.

32. Davison R, Kaplan K, Fintel D, Parker M, Anderson L, Haring O. The effect of clonidine and the cessation of cigarette smoking. *Clin Pharmacol Ther.* 1988;44:265–267.

33. Hermiller JB, Margorien RD, Leithe ME, Unverferth DV, Leier CV. Clonidine in congestive heart failure: a vasodilator drug with negative inotropic effects. *Am J Cardiology.* 1983;51:791–795.

34. Simpson CS, Ghali WA, Sanfilippo AJ, Moritz S, Abdollah H. Clinical assessment of clonidine in the treatment of new-onset rapid atrial fibrillation: a prospective, randomized clinical trial. *Am Heart J.* 2001;142:93–98.

35. Thomas MG, Quiroz AC, Rice JC, Sander GE, Giles TD. Antianginal effects of clonidine. *J Cardiovasc Pharmacol.* 1986;8:S69–S75.

36. Foresti A, Massari FM, Lotto A. Hemodynamic effects of clonidine in patients with acute myocardial infarction complicated by hypertension. *J Cardiovasc Pharmacol.* 1986;54: S30–S32.

37. Goldfarb G, Ang ET, Debaene B, Khon S, Jolis P. Effect of clonidine on postoperative shivering in man: a double blind study [abstract]. *Anesthesiology.* 1989;54:650.

38. Kulka PJ, Bressem M, Tryba M. Clonidine prevents sev-

oflurane-induced agitation in children. *Anesth Analg.* 2001; 93:335–338.

39. Mikawa K, Nishina K, Shiga M. Prevention of sevoflurane-induced agitation with oral clonidine premedication. *Anesth Analg.* 2002;94:1675–1676.

40. Bock M, Kunz P, Schreckenberger R, Graf BM, Martin E, Motsch J. Comparison of caudal and intravenous clonidine in the prevention of agitation after sevoflurane in children. *Br J Anaesth.* 2002;88:790–796.

41. Verner L, Hartmann M, Seitz W. Clonidine supplemented analgesia and sedation in prevention of postoperative delirium. *Anaesthesiol Intensivther Notfallmed.* 1990;25: 274–280.

42. Krieglstein GK, Langham ME, Leydhecker W. The peripheral and central neural actions of clonidine in normal and glaucomatous eyes. *Invest Ophthalmol Vis Sci.* 1978;54: 149–158.

43. Puke MJC, Wiesenfeld-Hallin Z. The differential effects of morphine and the 2-adrenoceptor agonists clonidine and dexmedetomidine on the prevention and treatment of experimental neuropathic pain. *Anesth Analg.* 1993;54:104–109.

44. Hilz MJ, Marthol H, Neundorfer B. Syncope—a systematic overview of classification, pathogenesis, diagnosis and management. *Fortschr Neurol Psychiatr.* 2002;70:95–107.

45. Madan R, Bharti N, Shende D, Khokhar SK, Kaul HL. A dose response study of clonidine with local anesthetic mixture for peribulbar block: a comparison of three doses. *Anesth Analg.* 2001;93:1593–1597.

46. Nishikawa T, Dohi S. Clinical evaluation of clonidine added to lidocaine solution for epidural anesthesia. *Anesthesiology.* 1990;73:853–859.

47. Klimscha W, Chiari A, Krafft P, et al. Hemodynamic and analgesic effects of clonidine added repetitively to continuous epidural and spinal blocks. *Anesth Analg.* 1995;54: 322–327.

48. Frank T, Wehner M, Heinke W, Schmadicke I. Clonidine vs. midazolam for premedication comparison of the anxiolytic effect by using the STAI-test. *Anaesthesiol Intensivmed Notfallmed Schmerzther.* 2002;37:89–93.

49. Ramesh VJ, Bhardwaj N, Batra YK. Comparative study of oral clonidine and diazepam as premedicants in children. *Int J Clin Pharmacol Ther.* 1997;35:218–221.

50. Ise T, Yamashiro M, Furuya H. Clonidine as a drug for intravenous conscious sedation. *Odontology.* 2002;90:57–63.

51. Siiba S, Nakanishi O, Ishikawa T, Hirakawa T, Kawahara H, Imamura Y. Increase in the threshold of pain and touch sensation in the human face with clonidine plus 30% nitrous oxide. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod.* 1999;87:294–298.

52. Kulka PJ, Tryba M, Zenz M. Dose-response effects of intravenous clonidine on stress response during induction of anesthesia in coronary artery bypass graft patients. *Anesth Analg.* 1995;80:263–268.

53. Flacke JW, Bloor BC, Flacke WE, et al. Reduced narcotic requirement by clonidine with improved hemodynamic and adrenergic stability in patients undergoing coronary bypass surgery. *Anesthesiology.* 1987;67:909–917.

54. Arya DK, Langley RW, Szabadi E, Bradshaw CM. Comparison of the effects of high ambient temperature and clonidine on autonomic functions in man. *Naunyn Schmiedebergs Arch Pharmacol.* 1997;355:376–383.

55. Frank T, Thieme V, Olthoff D. Preoperative clonidine comedication within the scope of balanced inhalation anesthesia with sevoflurane in oral surgery procedures. *Anaesthesiol Reanim.* 1999;24:65–70.

56. Murai T, Kyoda N, Misaki T, Takada K, Sawada S, Machida T. Effects of clonidine on intravenous sedation with midazolam. *Anesth Prog.* 1995;42:135–138.

57. Fehr SB, Zalunardo MP, Siefert B, et al. Clonidine decreases propofol requirements during anaesthesia: effect on bispectral index. *Br J Anaesth.* 2001;86:627–632.

58. DeDeyne C, Struys M, Heylen R, et al. Influence of intravenous clonidine pretreatment on anesthetic requirements during bispectral EEG-guided sevoflurane anesthesia. *J Clin Anesth.* 2000;12:52–57.

59. Clacysoone K, DeDeyne C, Struys M, Rolly G, Heylen R. Influence of dosage of intravenous clonidine pretreatment on anesthetic requirements in a bis-guided sevoflurane monoanesthesia [abstract]. *Br J Anaesth.* 1999;82:454.

60. Handley SL, Mithani S. Effects of alpha-adrenoceptor agonists and antagonists in a maze-exploration model of fear-motivated behavior. *Naunyn Schmiedebergs Arch Pharmacol.* 1984;327:1–5.

61. Samso E, Valles J, Pol O, Gallart L, Puig MM. Comparative assessment of the anaesthetic and analgesic effects of intramuscular and epidural clonidine in humans. *Can J Anaesth.* 1996;43:1195–1202.

62. Carabine UA, Wright PMC, Moore J. Preanesthetic medication with clonidine: a dose-response study. *Br J Anaesth.* 1991;67:79–83.

63. Kappagoda C, Schell DN, Hanson RM, Hutchins P. Clonidine overdose in childhood: implications of increased prescribing. *J Paediatr Child Health.* 1998;34:508–512.

64. Heidemann SM, Sarnaik AP. Clonidine poisoning in children. *Crit Care Med.* 1990;18:618–620.

65. Nichols MH, King WD, James LP. Clonidine poisoning in Jefferson County, Alabama. *Ann Emerg Med.* 1997;29: 511–517.

66. Romano M, Dinh A. A 1000-fold overdose of clonidine caused by a compounding error in a 5 year old child with attention-deficit/hyperactivity disorder. *Pediatrics.* 2001;108: 471–472.

67. Mikawa K, Maekawa N, Nishina K, Takao Y, Yaku H, Obara H. Efficacy of oral clonidine premedication in children. *Anesthesiology.* 1993;79:926–931.

68. Carabine UA, Wright PMC, Howe JP, Moore J. Cardiovascular effects of intravenous clonidine. Partial attenuation of the pressor response to intubation by clonidine. *Anaesthesia.* 1991;46:634–637.

69. Prause A, Wappler F, Scholz J, Bause H, Schulte J. Respiratory depression under long-term sedation with sufentanil, midazolam and clonidine has no clinical significance. *Intensive Care Med.* 2000;26:1454–1461.

70. Jarvis DA, Duncan SR, Segal IS, Maze M. Ventilatory

effects of clonidine alone and in the presence of alfentanyl, in human volunteers. *Anesthesiology.* 1992;76:899–905.

71. Khan ZP, Ferguson CN, Jones RM. Alpha-2 and imidazoline receptor agonists. *Anaesthesia.* 1999;54:146–165.

72. Karhuvaara S, Kallio A, Salonen M, Tuominen J, Scheinin M. Rapid reversal of α2-adrenoceptor agonist effects by atipamezole in human volunteers. *Br J Pharmacol.* 1991; 31:160–165.

73. Mizuki Y, Suetsugi M, Ushijima I, Yamada M. Differential effects of noradrenergic drugs on anxiety and arousal in healthy volunteers with high and low anxiety. *Prog Neuropsychopharmacol Biol Psychiatry.* 1996;20:1353–1367.

74. Osborn TM, Sandler NA. The effects of preoperative anxiety on intravenous sedation. *Anesth Prog.* 2004;51:46–51.

75. Spielberger C. *Stait-Trait Anxiety Inventory for Adults.* Redwood City, Calif: Mind Garden; 1983:4–12.

76. Malinovsky JM, Blanche E, Malinge M, Lepage JY, Pinaud M. BIS and sedation after spinal clonidine [abstract]. *Anesthesiology.* 1998;89:873.

77. Matsuzaki S, Tananka H. The feasibility of bispectral index monitoring for intravenous sedation during dental treatment. *Anesth Prog.* 2004;51:52–55.

78. Ibrahim AE, Ghoneim MM, Kharasch ED, et al. Speed of recovery and side-effect profile of sevoflurane sedation compared with midazolam. *Anesthesiology.* 2001;94:87–94.

79. Zhi JG, Massarella JW, Melia AT, et al. The pharmacokinetic-pharmacodynamic (digit-symbol-substitution-test) relationship of flumazenil in a midazolam steady-state model in healthy-volunteers. *Clin Pharmacol Ther.* 1994;56:530–536.

80. Nouraei SA, DePennington N, Jones JG, Carpenter RH. Dose-related effect of sevoflurane sedation on higher control of eye movements and decision making. *Br J Anaesth.* 2003;91:175–183.

81. Jandziol AK, Prabhu M, Carpenter RH, Jones JG. Blink duration as a measure of low-level anaesthetic sedation. *Eur J Anaesthesiol.* 2001;18:476–484.

82. Carpenter RH, Descamps CH, Morley CH, Leary TS, Jones JG. The effect of low dose sevoflurane on saccadic eye movement latency. *Anaesthesia.* 2002;57:855.

83. Win NN, Kohase H, Miyamoto T, Umino M. Decreased bispectral index as an indicator of syncope before hypotension and bradycardia in two patients with needle phobia. *Br J Anaesth.* 2003;91:749–752.

84. Chernik DA, Gillings D, Laine H, et al. Validity and reliability of the observer's assessment of alertness sedation scale—study with intravenous midazolam. *J Clin Psychopharmacol.* 1990;10:244–251.

85. Khan ZP, Munday IT, Jones RM, Thornton C, Mant TG, Amin D. Effects of dexmedetomidine on isoflurane requirements in healthy volunteers. 1: Pharmacodynamic and pharmacokinetic interactions. *Br J Anaesth.* 1999;83:372–380.

86. Fanini D, Poglio M, Marci MC, Iovinelli G, Antenucci F. Oral premedication with clonidine as an alternative in dental practice. The effects on the pain threshold, blood pressure and saliva flow. *Minerva Stomatol.* 1998;47:453–464.