Article

Effect of perioperative systemic α2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials

BLAUDSZUN, Grégoire, *et al*.

Abstract

Systemic α2 agonists are believed to reduce pain and opioid requirements after surgery, thus decreasing the incidence of opioid-related adverse effects, including hyperalgesia.

Reference

BLAUDSZUN, Grégoire, *et al*. Effect of perioperative systemic α2 agonists on postoperative morphine consumption and pain intensity: systematic review and meta-analysis of randomized controlled trials. *Anesthesiology*, 2012, vol. 116, no. 6, p. 1312-22

DOI : 10.1097/ALN.0b013e31825681cb
PMID : 22546966

Effect of Perioperative Systemic α2 Agonists on Postoperative Morphine Consumption and Pain Intensity

Systematic Review and Meta-analysis of Randomized Controlled Trials

Grégoire Blaudszun, M.D.,* Christopher Lysakowski, M.D.,† Nadia Elia, M.D., M.Sc.,‡ Martin R. Tramèr, M.D., D.Phil.§

ABSTRACT

Background: Systemic α2 agonists are believed to reduce pain and opioid requirements after surgery, thus decreasing the incidence of opioid-related adverse effects, including hyperalgesia.

Methods: The authors searched for randomized placebo-controlled trials testing systemic α2 agonists administrated in surgical patients and reporting on postoperative cumulative opioid consumption and/or pain intensity. Meta-analyses were performed when data from 5 or more trials and/or 100 or more patients could be combined.

Results: Thirty studies (1,792 patients, 933 received clonidine or dexmedetomidine) were included. There was evidence of postoperative morphine-sparing at 24 h; the weighted mean difference was −4.1 mg (95% confidence interval, −6.0 to −2.2) with clonidine and −14.5 mg (−22.1 to −6.8) with dexmedetomidine. There was also evidence of a decrease in pain intensity at 24 h; the weighted mean difference was −0.7 cm (−1.2 to −0.1) on a 10-cm visual analog scale with clonidine and −0.6 cm (−0.9 to −0.2) with dexmedetomidine. The incidence of early nausea was decreased with both (number needed to treat, approximately nine). Clonidine increased the risk of intraoperative (number needed to harm, approximately nine) and postoperative hypotension (number needed to harm, 20). Dexmedetomidine increased the risk of postoperative bradycardia (number needed to harm, three). Recovery times were not prolonged. No trial reported on chronic pain or hyperalgesia.

What We Already Know about This Topic

- Multiple clinical trials have examined the effect of the systemically administered α2-adrenoceptor agonists clonidine and dexmedetomidine on perioperative outcomes

What This Article Tells Us That Is New

- In this meta-analysis including studies of nearly 1,800 subjects, perioperative systemic α2-adrenoceptor agonist treatment improved analgesia and reduced opioid use and postoperative nausea

* Registrar, † Consultant, Division of Anesthesiology, Geneva University Hospitals, Geneva, Switzerland. ‡ Research Associate, Division of Anesthesiology, Geneva University Hospitals, and Institute of Social and Preventive Medicine, Faculty of Medicine, University of Geneva, Geneva, Switzerland. § Professor, Division of Anesthesiology, Geneva University Hospitals, and Faculty of Medicine, University of Geneva.

Received from the Division of Anesthesiology, Department of Anesthesiology, Clinical Pharmacology & Critical Care, Geneva University Hospitals, Geneva, Switzerland. Submitted for publication October 13, 2011. Accepted for publication January 25, 2012. Supported by the Evidence-based Critical Care, Anesthesia and Pain Treatment Institute, Geneva, Switzerland (to Dr. Elia), and institutional funds from the Department of Anesthesiology, Critical Care & Clinical Pharmacology, Geneva University Hospitals. Presented at the Euroanaesthesia Meeting, Amsterdam, The Netherlands, June 11–14, 2011. Additional information (individual Forest plots) is freely available at: http://anesthesiologie.hug-ge.ch/data.htm.

Address correspondence to Dr. Blaudszun: Division of Anesthesiology, Geneva University Hospitals, Rue Gabrielle-Perret-Gentil 4, 1211 Genève 14, Switzerland. gregoire.blaudszun@hcuge.ch. Anesthesiology 2012; 116:1312–22

◆ This article is accompanied by an Editorial View. Please see: Devereaux PJ, Sessler DI: The potential role of α_2 agonists for noncardiac surgery. ANESTHESIOLOGY 2012; 116:1192–4.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text and are available in both the HTML and PDF versions of this article. Links to the digital files are provided in the HTML text of this article on the Journal's Web site (www.anesthesiology.org).

Conclusions: Perioperative systemic α2 agonists decrease postoperative opioid consumption, pain intensity, and nausea. Recovery times are not prolonged. Common adverse effects are bradycardia and arterial hypotension. The impact of α2 agonists on chronic pain or hyperalgesia remains unclear because valid data are lacking.

COMBINATIONS of strong opioids with nonopioid analgesics (for instance, nonsteroidal antiinflammatory drugs, acetaminophen, ketamine) have become popular in anesthesia.[1] Efficacious multimodal analgesia has been advocated as a basis of successful fast-track surgery.[2] These multidrug regimens aim to decrease postoperative pain, intra- and postoperative opioid requirements, and subsequently, opioid-related adverse effects. It has been claimed that opioid-sparing or opioid-protective anesthesia techniques need to be adopted to avoid iatrogenic increase in the intensity of postoperative pain.[3]

α2 Agonists have pharmacologic characteristics (sedation, hypnosis, anxiolysis, sympatholysis, and analgesia) that make them suitable as adjuvants to multimodal analgesia.[4–6] Their antinociceptive effect is attributed to the stimulation of α2-adrenoreceptors located in the central nervous system and spinal cord. Several studies have confirmed that intrathecal or epidural α2 agonists have an effect on short-term pain after surgery and also on neuropathic and cancer pain. It also has been suggested that α2 agonists, given by systemic route, potentiate the analgesic effects of opioids.[3] Systemic clonidine is thought to have opioid-sparing, anxiolytic, and antiemetic properties; however, dosing is likely to be limited by the adverse-effect profile.[7] Other authors have suggested that new α2 agonists such as dexmedetomidine may provide benefit in the treatment of pain compared with clonidine.[8]

It remains unclear to what extent perioperative systemic α2 agonists decrease postoperative opioid consumption and pain intensity and whether there are additional beneficial effects, such as a decrease in the incidence of opioid-related adverse effects, including hyperalgesia. In addition, the fear of typical α2 agonist-related adverse drug reactions, such as bradycardia or arterial hypotension, may prevent anesthesiologists from using these drugs more frequently. Finally, it would be interesting to know whether there is a clinically relevant difference in the analgesic properties between clonidine and the more specific and shorter-acting dexmedetomidine. We set out to address these questions using data from systematically searched randomized controlled trials.

Materials and Methods

We report this systematic review according to the PRISMA recommendations.[9]

Eligibility Criteria

We conducted a comprehensive search for published full reports of randomized, controlled trials testing the effect of systemic (intravenous, intramuscular, subcutaneous, oral, transdermal) α2 agonists administered before, during, or after surgery, compared with placebo or no treatment in adults undergoing noncardiac surgery under general anesthesia. Relevant studies had to report data on postoperative cumulative opioid consumption and/or postoperative pain intensity.

When surgery was performed during sedation or locoregional anesthesia (with or without general anesthesia), the study was not considered. Studies with fewer than 10 patients per group were excluded.

Information Sources

We searched Medline, Embase, and Central using the terms "clonidine," "dexmedetomidine," "α2 agonist," "pain," "opioid," "an(a)esthesia," and combinations of those, and without restriction to year or language of publication. The last search was in March 2011. We checked bibliographies of retrieved articles. Authors were contacted to obtain additional information if necessary.

Study Selection

All articles identified through the literature search were reviewed for inclusion by one author (GB). Queries were solved through discussion with two other authors (CL, MRT).

Risk of Bias in Individual Studies

We applied a modified four-item, seven-point, Oxford scale (assessing the quality of randomization, concealment of allocation, degree of blinding, and description of the flow of patients) to assess the quality of data reporting of individual trials.[10] Because we included only randomized trials, the minimum score was 1. One author (GB) scored all potentially relevant studies. The scores were independently checked by another author (CL). Any disagreement was solved through discussion with a third author (MRT).

Data Extraction Process

One author (GB) extracted relevant information from the original reports, and a second author (CL) independently checked all extracted data. Data extraction was performed on a computerized Excel (Microsoft®, Redmond, WA) sheet that was extended as new outcomes were extracted.

Data Items

Extracted information included number of patients in experimental and control groups, type of surgery, regimens of α2 agonists, pain outcomes, and adverse events. Relevant pain outcomes included postoperative pain intensity and cumulative opioid consumption.

For pain intensity, we extracted 0–10 cm visual analog scale (VAS) data ranging from 0 (no pain) to 10 (worst pain). Data from alternative numerical or verbal pain scales were not considered. For opioid consumption, we extracted any data on the cumulative amount of postoperative opioid us-

age, independent of route or mode of administration. Doses of opioids other than morphine were converted to morphine equivalents using standard conversion factors (*i.e.*, 0.1 for meperidine,[11] 0.75 for piritramide,[12] 1.33 for oxycodone,[13] 5 for hydromorphone,[13] and 100 for fentanyl[11]).

We also extracted data on postoperative recovery times and adverse events. Definitions of recovery times and adverse events were taken as reported in the original trials.

Synthesis of Results

There was a *pre hoc* decision to analyze data on different α2 agonists separately. To minimize any random play of chance, we arbitrarily decided to analyze outcomes only when they were reported in at least five trials or when data from at least 100 patients could be combined.

Continuous data were extracted as means with standard deviations. We computed mean differences at the study level, and when deemed appropriate, we pooled the estimates and computed a weighted mean difference (WMD) with 95% CI.

Dichotomous outcomes were extracted as the presence or absence of an effect. We computed risk ratios with 95% CI at the study level and pooled these estimates whenever possible. If the 95% CI did not include 1, we assumed that the difference between α2 agonist and control was statistically significant at the 5% level.

To estimate the clinical relevance of a beneficial or harmful effect, we computed numbers needed to treat (NNT) or numbers needed to harm with 95% CI using risk ratio point estimates and control event rates (*i.e.*, the average incidence of an event in the control group). Numbers needed to treat/harm were computed only when the risk ratio indicated a statistically significant result.

Formal heterogeneity testing was performed to choose the adequate model for pooling of the estimates. A fixed effect model was used when the data were homogeneous ($P \geq 0.1$); a random effects model was used when the data were heterogeneous. Because statistical tests of heterogeneity have low power and may fail to detect a modest degree of true heterogeneity, the point estimates of all studies were plotted, using forest plots, for a graphical assessment.

Analyzes were conducted using Microsoft® Excel® 11.6.2 (Microsoft) for Mac® (Apple Inc., Cupertino, CA) and Review Manager computer program (RevMan version 5.0.22; Copenhagen, Denmark: The Nordic Cochrane Centre, The Cochrane Collaboration).

Results

Study Selection

We identified 159 trials and subsequently excluded 129 (fig. 1). We contacted 16 authors for supplementary data; 3 answered, and the data from 2 of these could be included in our analyses.[14,15] We eventually analyzed 30 valid trials with data on 1,792 adult patients, of whom 933 received a systemic α2 agonist (table 1).[14–43]

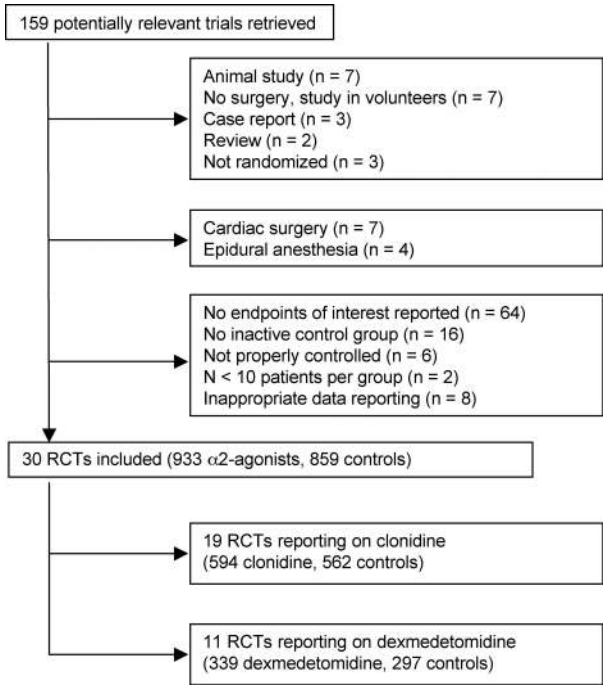

Fig. 1. Flow chart of retrieved, excluded, and analyzed trials. α2 agonists = clonidine, dexmedetomidine; control = placebo or no treatment; RCT = randomized controlled trial.

Study Characteristics

The studies were published between 1990 and 2009 and were performed in 16 countries: Turkey (6 trials); China, Germany, and United States of America (3 each); Belgium, France, and United Kingdom (2 each); Australia, Brazil, Canada, Egypt, Finland, Greece, Iran, Italy, and the Netherlands (1 each). Trial sizes ranged from 24 to 200 patients. The median quality score was 4 (range, 2–7). Surgery was abdominal (14 studies), hysterectomy (5), spine (4), ear–nose–throat (1), orthopedic (1), vascular (1), and not specified or a composite of different surgeries in 4.

Two α2 agonists were tested, clonidine (19 studies) and dexmedetomidine (11 studies). None tested these two drugs in a head-to-head comparison. Routes of administration were intravenous as boluses or continuous infusions (20 studies) or oral (10); in two studies, a transdermal therapeutic system also was used. α2 Agonists were given before (10 studies), during (6), or after surgery (4) or throughout the perioperative period (10). Because of multiple administration regimens, cumulative doses of clonidine or dexmedetomidine could not be estimated; thus, we were unable to test for dose responsiveness.

Synthesis of Results

Postoperative Consumption of Morphine Equivalents. Data on postoperative cumulative consumption of a variety of opioids were reported in 26 trials.[14–16,18–31,33–35,37–41,43]

Data on cumulative consumption of morphine equivalents could be combined from 10 trials that tested clonidine (fig. 2; see Supplemental Digital Content 1,

http://links.lww.com/ALN/A847, figs. 1–3, which are individual Forest plots).[18,20,21,24,26,29,33,37,38,43] At 2 h after surgery, the median of all average cumulative morphine equivalents in control subjects was 12.2 mg (range, 7.0–17.3); clonidine did not significantly decrease this amount.[33,37] At 12 h, the median of the average cumulative morphine-equivalents in controls was 30.1 mg (range, 10.8–36.0), and clonidine showed a significant morphine-sparing effect (WMD −9.8 mg).[18,20,24,26] At 24 h, the median of the average cumulative morphine equivalents in controls was 16.7 mg (range, 11.0–49.9), and clonidine significantly decreased this amount (WMD −4.1 mg).[21,29,38,43]

Data on cumulative consumption of morphine equivalents could be combined from eight trials that tested dexmedetomidine (fig. 2; see Supplemental Digital Content 1, http://links.lww.com/ALN/A847, figs. 4–6, which are individual Forest plots).[14–16,22,23,34,39,40] At 2 h after surgery, the median of all average cumulative morphine equivalents in control subjects was 15.5 mg (range, 10.2–19.5), and dexmedetomidine significantly decreased this amount (WMD −6.3 mg).[16,23,34,40] At 12 h, the median of the average cumulative morphine equivalents in controls was 24.0 mg (range, 13.3–34.8), and dexmedetomidine showed a significant morphine-sparing effect (WMD −6.0 mg).[14,40] At 24 h, the median of all average cumulative morphine equivalents in controls was 45.2 mg (range, 17.5–49.0), and dexmedetomidine significantly decreased this amount (WMD −14.5 mg).[14–16,22,39,40]

Postoperative Pain Intensity. Data on pain scores at different postoperative time points were reported in 14 trials.[15,17,18,21,23,29–33,37–39,41]

Ten trials tested clonidine,[17,18,21,29,31–33,37,38,41] and data on VAS pain scores at 1, 2, 4, 12, 24, or 48 h after the end of surgery could be combined (fig. 3; see Supplemental Digital Content 1, http://links.lww.com/ALN/A847, figs. 7–12, which are individual Forest plots). At 1, 2, and 4 h, clonidine did not significantly decrease pain intensity. At 1 h, the median of the average VAS pain scores in control subjects was 3.6 cm (range, 2.8–5.0),[32,33,37,38,41] at 2 h it was 3.3 cm (range, 1.8–5.0),[21,33,38] and at 4 h, it was 4.6 cm (range, 1.0–4.6).[21,31,33] At 12 and 24 h, clonidine significantly decreased pain intensity. At 12 h, the median of the average pain scores in controls was 4.9 cm (range, 3.7–5.1), WMD −1.5 cm.[17,18,31] At 24 h, the median of the average pain scores in controls was 3.7 cm (range, 2.4–5.3), WMD −0.7 cm.[17,21,29,31] At 48 h, the median of the average pain scores in controls was 3.1 cm (range, 2.8–3.5) and the effect of clonidine was not significant anymore.[21,29,31]

Four trials tested dexmedetomidine,[15,23,30,39] and data on VAS pain scores at 1, 2, 24, or 48 h after the end of surgery could be combined (fig. 3; see Supplemental Digital Content 1, http://links.lww.com/ALN/A847, figs. 13–16, which are individual Forest plots). At 1 h, the median of the average VAS pain scores in control subjects was 5.3 cm (range, 2.5–6.0), and dexmedetomidine significantly decreased this pain intensity (WMD −1.4 cm).[15,23,30,39] At 2 h, the median of the average VAS pain scores in controls was 3.2 cm (range, 2.3–4.1 cm); dexmedetomidine did not significantly decrease this pain intensity.[15,23] At 24 h, the median of the average VAS pain scores in controls was 3.1 cm (range, 1.9–4.0), and dexmedetomidine significantly decreased this pain intensity (WMD −0.6 cm).[15,23,39] At 48 h, the median of the average pain scores in controls was 2.8 (range, 1.6–4.0) and the effect of dexmedetomidine was not significant anymore.[23,39]

Only one trial, testing dexmedetomidine, reported pain outcomes beyond the forty-eighth postoperative hour[39]; patients were followed up until the seventh postoperative day. At day 7, there was no difference in pain scores between the active and the control group. None of the trials reported data on hyperalgesia or chronic pain.

Most studies specified that no concomitant nonsteroidal antiinflammatory drugs were administered. In only one trial,[32] rectal diclofenac was administered systematically in all patients after induction. The limited number of relevant trials did not allow performing sensitivity analyses to test whether the concomitant usage of nonsteroidal antiinflammatory drugs had any impact on the analgesic efficacy of $\alpha 2$ agonists.

Postoperative Nausea and Vomiting. Dichotomous data on postoperative nausea and vomiting (PONV) could be extracted from 15 trials (table 2; see Supplemental Digital Content 1, http://links.lww.com/ALN/A847, figs. 17–22, which are individual Forest plots).[14,15,20,22,24,29,30,34,36–42] Both clonidine and dexmedetomidine decreased the incidence of early PONV (cumulative incidence to 8 h after surgery), NNT 8.9 and 9.3, respectively. In most trials, antiemetics were used only as a rescue medication to treat established PONV symptoms. However, in two trials, both testing dexmedetomidine,[22,39] ondansetron was administered prophylactically to all patients at the end of surgery. The limited number of relevant trials did not allow performing sensitivity analyses to test whether the concomitant usage of "classic" antiemetics had any impact on the antiemetic efficacy of $\alpha 2$ agonists.

Intra- and Postoperative Hemodynamic Effects. Data on intra- and postoperative hemodynamic effects could be extracted from 13 studies (table 3; see Supplemental Digital Content 1, http://links.lww.com/ALN/A847, figs. 23–30, which are individual Forest plots).[18,20,25,26,28,29,32,35,37–39,41,42]

The definition of bradycardia included heart rate less than 40 or less than 45 min^{-1}, need for atropine, or it was not further defined. With clonidine, the increase in the risk of intra- and postoperative bradycardia did not reach statistical significance. With dexmedetomidine, the risk of postoperative bradycardia was increased significantly (number needed to harm, 3.1). There were not enough data on intraoperative bradycardia with dexmedetomidine to warrant meta-analysis.

The definition of arterial hypotension included a decrease in the mean arterial pressure more than 20% of the baseline, or mean arterial pressure less than 60 mmHg, or need for a

Table 1. Included Randomized Controlled Trials

Reference	Comparison (#) = Number of Analyzed Patients [ ] = Regimen Was Not Considered	Timing		
		Premedication	Intraoperatively	Postoperatively
Altindis *et al.*, 2008[14]	1. Dex IV 0.5 μg · kg^{-1} · 10 min^{-1} + PCA Dex 10 μg/Meperidine 5 mg (20) 2. Placebo (20)		x	x
Bakhamees *et al.*, 2007[16]	1. Dex IV 80 μg · kg^{-1} · 10 min^{-1} + 0.4 μg · kg^{-1} · h^{-1} (40) 2. Placebo (40)		x	
Benhamou *et al.*, 1994[17]	1. Clonidine PO 300 μg 60′ PM + 300 μg 12 h post-op (20) 2. Placebo (20)	x	x	x
Bernard *et al.*, 1991[18]	1. Clonidine IV 5 μg · kg^{-1} · 60 min^{-1} + 0.3 μg · kg^{-1} · h^{-1} 11 h (25) 2. Placebo (25)			x
De Deyne 2000[19]	1. Clonidine IV 3 μg/kg 15′ PM (30) 2. Placebo (30)	x		
De Kock *et al.*, 1992[20]	1. Clonidine IV 4 μg · kg^{-1} · 30 min^{-1} at induction + 2 μg · kg^{-1} · h^{-1} (96) 2. No treatment (91)		x	
Dimou *et al.*, 2003[21]	1. Clonidine TTS 0.3 mg/24 h + Clonidine IV 1 μg/kg 10′ PM (18) 2. Placebo (20)	x	x	x
Gunes *et al.*, 2008[22]	1. Dex IV 0.1 μg/kg (32) 2. No treatment (32)			x
Gurbet *et al.*, 2006[23]	1. Dex IV 1 μg · kg^{-1} · 30 min^{-1} PM + 0.5 μg · kg^{-1} · h^{-1} (25) 2. Placebo (25)	x	x	
Jeffs 2002[24]	1. Clonidine IV 4 μg · kg^{-1} · 20 min^{-1} end surgery + PCA Clonidine 20 μg/Morphine 1 mg (30) 2. Placebo IV + PCA Morphine 1 mg (30)		x	x
Lawrence and De Lange, 1997[25]	1. Dex IV 2 μg/kg 15′ PM (25) 2. Placebo (25)	x		
Lin *et al.*, 2009[15]	1. Dex 5 μg/ml (50) 2. No treatment (48)			x
Marinangeli *et al.*, 2002[26]	1. Clonidine IV 2 μg · kg^{-1} · 30 min^{-1} 30′ before end surgery + 0.3 μg · kg^{-1} · h^{-1} 12 h post-op (20) 2. Clonidine IV 3 μg · kg^{-1} · 30 min^{-1} 30′ before end surgery + 0.3 μg · kg^{-1} · h^{-1} 12 h post-op (20) 3. Clonidine IV 5 μg · kg^{-1} · 30 min^{-1} 30′ before end surgery + 0.3 μg · kg^{-1} · h^{-1} 12 h post-op (20) 4. Placebo (20)		x	x
Mohammadi and Seyedi, 2008[27]	1. Clonidine PO 200 μg 60′ PM (40) 2. [Gabapentin PO 300 mg 60′ PM (40)] 3. Placebo (40)	x		
Morris et al., 2005[28]	1. Clonidine PO 3 μg/kg 60′ PM (21) 2. Placebo (18)	x		
Owen *et al.*, 1997[29]	1. Clonidine PO 0.3/0.4 mg + Clonidine TTS 0.2 mg/24 h (14) 2. Placebo (14)	x	x	x
Ozkose *et al.*, 2006[30]	1. Dex IV 1 μg · kg^{-1} · 10 min^{-1} PM + 0.2 μg · kg^{-1} · h^{-1} (20) 2. Placebo (20)	x	x	
Park *et al.*, 1996[31]	1. Clonidine PO 5 μg/kg 90′ PM + 12 h + 24 h after initial dose (20) 2. Placebo (19)	x		x
Pawlik *et al.*, 2005[32]	1. Clonidine PO 2 μg/kg bedtime + 2 h PM (15) 2. Placebo (15)	x		
Rohrbach *et al.*, 1999[33]	1. Clonidine IV 5 μg · kg^{-1} · 30 min^{-1}, 30′ post induction (20) 2. Placebo (20)		x	
Scheinin *et al.*, 1992[34]	1. Dex IV 0.6 μg^{-1} · kg^{-1} · min^{-1} 10′ PM (12) 2. Placebo (12)	x		
Segal *et al.*, 1991[35]	1. Clonidine TTS 7 cm^2 (= 0.2 mg/24 h) + PO 3 μg/kg bedtime + PO 3 μg/kg morning (14) 2. Clonidine TTS 10.5 cm^2 + PO 4.5 μg/kg bedtime + PO 6 μg/kg 60′ PM (14) 3. Placebo (15)	x	x	x
Simoni *et al.*, 2009[36]	1. Clonidine IV 2 μg/kg 5′ before surgery (42) [2. Methadone IV 0.1 mg/kg 5′ before surgery (42)] 3. Placebo (42)		x	
Striebel *et al.*, 1993[37]	1. Clonidine IV 300 μg/2 h post-op (30) 2. Placebo (30)			x
Sung *et al.*, 2000[38]	1. Clonidine PO 150 μg 60 to 90′ PM (43) 2. Alugel hydroxide PO 300 mg (65)	x		
Tufanogullari *et al.*, 2008[39]	1. Dex IV 0.2 μg · kg^{-1} · h^{-1} (20) 2. Dex IV 0.4 μg · kg^{-1} · h^{-1} (20) 3. Dex IV 0.8 μg · kg^{-1} · h^{-1} (20) 4. Placebo (20)		x	
Unlugenc *et al.*, 2005[40]	1. Dex IV 1 μg/kg 10′ PM (30) 2. Placebo (30)	x		
Wright *et al.*, 1990[41]	1. Clonidine PO 0.3 mg 75 to 105′ PM 2. Placebo	x		
Yildiz *et al.*, 2006[42]	1. Dex IV 1 μg · kg^{-1} · 5 min^{-1} (25) 2. Placebo (25)		x	
Yu *et al.*, 2003[43]	1. Clonidine PO 150 μg 60 to 90′ PM (15) 2. Placebo (15)	x		

Randomization: 0 = none or pseudo-randomization; 1 = yes but not specified; 2 = yes and adequate. Concealment: 0 = none; 1 = yes. Follow-up: 0 = none; 1 = reported but intention-to-treat analysis not possible; 2 = reported and intention-to-treat analysis possible.

Dex = dexmedetomidine; intra-op = intraoperative; ITT = intention to treat; IV = intravenous; PCA = patient controlled analgesia; PM = premedication; post-op = postoperative; PO = per os; TTS = transdermal therapeutic system.

Table 1. Continued

Quality Assessment						
		Blinding				
Randomization	Concealment	Patient	Provider	Observer	Follow-up	Surgery
1	0	1	1	1	1	Lower abdominal
1	0	1	0	1	1	Laparoscopic gastric bypass
1	0	1	1	0	0	Major abdominal
1	0	1	1	0	1	Spinal
1	0	1	1	0	0	Abdominal laparoscopy
1	0	1	0	1	2	Major abdominal
2	0	1	1	1	1	Abdominal hysterectomy
1	0	1	0	1	0	Lumbar disc
2	0	1	1	1	1	Abdominal hysterectomy
2	0	1	1	1	1	Lower abdominal and gynecological
1	0	1	1	0	0	Elective minor (general, urological, orthopedic)
2	0	1	1	1	2	Abdominal hysterectomy
1	0	1	1	0	0	Lumbar hemilaminectomy
2	0	1	1	0	0	Abdominal
1	0	1	0	0	0	Lower limb vascular
2	0	1	1	0	1	Abdominal hysterectomy
2	0	1	0	0	0	Lumbar disc
1	0	1	0	0	1	Knee
2	0	1	0	0	1	Ear-nose-throat
1	0	1	0	0	0	Abdominal hysterectomy
1	0	1	1	0	0	Elective
1	0	1	1	0	1	Elective abdominal
2	0	1	1	1	0	Non-gynecological video laparoscopy
1	0	1	0	0	0	Cholecystectomy
1	0	1	0	0	0	Laparoscopic cholecystectomy
2	1	1	1	1	1	Laparoscopic bariatric
2	0	1	1	1	0	Abdominal
1	0	1	1	0	1	Pelvic laparoscopy
1	0	1	0	0	0	Minor elective
1	0	1	1	0	1	Laparoscopic cholecystectomy

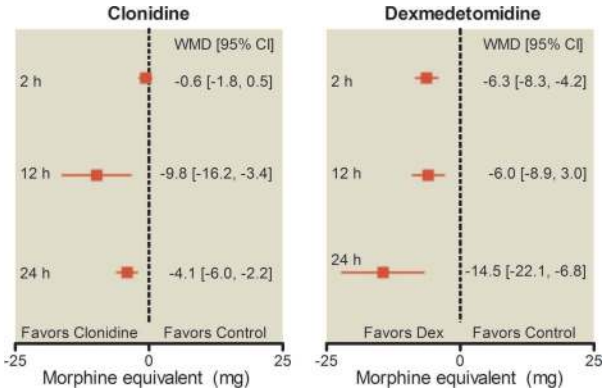

Fig. 2. Postoperative morphine-sparing. Doses of opioids other than morphine were converted to morphine equivalents. See figs. 1–6, Supplemental Digital Content 1, http://links.lww.com/ALN/A847, which are individual Forest plots. Dex = dexmedetomidine; WMD = weighted mean difference.

vasoactive drug, or it was not further defined. With clonidine, the risk of both intra- and postoperative hypotension was increased significantly (number needed to harm, 9.0 and 20, respectively). For dexmedetomidine, there were not enough data to warrant meta-analysis.

The definition of arterial hypertension included an increase in mean arterial pressure more than 20% of the baseline, or the need for a vasoactive drug, or it was not further defined. With clonidine, the risk of postoperative hypertension was decreased significantly (NNT 13). With dexmedetomidine, the risk of intraoperative hypertension was decreased significantly (NNT 2.3). Data on postoperative hypertension with dexmedetomidine were lacking.

Recovery Times. Time to extubation was reported in five trials,[16,20,30,39,40] time to spontaneous eye opening in four,[25,30,36,39] and time to response to verbal command in nine (table 4; see Supplemental Digital Content 1, http://links.lww.com/ALN/A847, figs. 31–34, which are individual Forest plots).[16,19,25,28,30,34,35,39,40]

In dexmedetomidine trials, the median of all average times to extubation in control subjects was 7.0 min (range, 5.7–7.5). Dexmedetomidine significantly shortened that time (WMD −1.6 min). For clonidine, there were not enough data to warrant meta-analysis.

In dexmedetomidine trials, the median of all average times to spontaneous eye opening in control subjects was 6.0 min (range, 3.2–6.9). Dexmedetomidine did not change that time. For clonidine, there were not enough data to warrant meta-analysis.

In dexmedetomidine trials, the median of all average times to response to verbal command in control subjects was 6.0 min (range, 3.9–10.3) and in clonidine trials was 11 min (range, 7.5–13.2). Both clonidine and dexmedetomidine did not change that time.

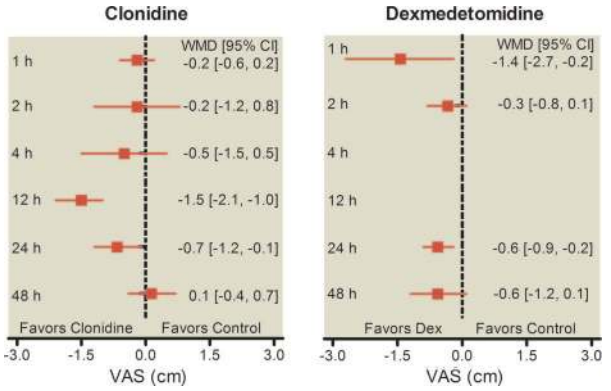

Fig. 3. Postoperative pain intensity. See figs. 7–16, Supplemental Digital Content 1, http://links.lww.com/ALN/A847, which are individual Forest plots. Dex = dexmedetomidine; VAS = 0–10 cm visual analog scale; WMD = weighted mean difference.

Discussion

This meta-analysis was designed to evaluate the impact of perioperative systemic usage of α2 agonists on postoperative opioid consumption and pain intensity. We retrieved data on two α2 agonists, clonidine and dexmedetomidine, and because these molecules have a different selectivity for α2-adrenoceptors,[4] we analyzed them separately. There are two main results.

First, both clonidine and dexmedetomidine reduce morphine consumption after surgery. With dexmedetomidine, a statistically significant decrease in opioid consumption was observed from the second postoperative hour until the twenty-fourth hour; with clonidine, the decrease was from the twelfth until the twenty-fourth postoperative hour. At 24 h, the decrease in cumulative morphine equivalents was approximately 25% with clonidine; it was 30% with dexmedetomidine. This degree of morphine-sparing is stronger than what has been reported with acetaminophen[44,45] but weaker than with ketamine or nonsteroidal antiinflammatory drugs.[10,44] Indirect comparison suggested that morphine-sparing with dexmedetomidine was more pronounced than with clonidine; on average 15 mg morphine were spared in dexmedetomidine trials, compared with only 4 mg with clonidine. However, in trials testing dexmedetomidine, postoperative morphine consumption in controls tended to be higher (median, 45 mg) than in trials testing clonidine (median, 17 mg); this could partly explain the difference.

Second, with both clonidine and dexmedetomidine, pain intensity at 24 h was decreased by approximately 0.7 cm on the 10 cm VAS scale. Again, this degree of analgesic efficacy was stronger than what has been reported with acetaminophen but weaker than with nonsteroidal antiinflammatory drugs.[44] At 48 h, α2 agonists had lost their pain-relieving effect.

Apart from these two beneficial analgesic effects (and although this meta-analysis was not specifically designed to

Table 2. Postoperative Nausea and Vomiting

	Number of Trials	Number of Patients with Event/Total Number of Patients (%)		Risk Ratio [95% CI]	Number Needed to Treat [95% CI]	References
		Active	Control			
Early emetic outcomes						
Nausea						
Clonidine	3	14/103 (13.6)	31/125 (24.8)	0.50 [0.29, 0.88]	8.9 [4.7, 86]	37, 38, 41
Dexmedetomidine	4	49/144 (34.0)	47/105 (44.8)	0.73 [0.53, 0.99]	9.3 [4.4, 65]	15, 34, 39, 42
Vomiting						
Clonidine	3	13/103 (12.6)	8/125 (6.4)	1.81 [0.81, 4.08]	—	37, 38, 41
Dexmedetomidine	3	15/132 (11.4)	21/93 (22.6)	0.59 [0.32, 1.08]	—	15, 39, 42
Late emetic outcomes						
Nausea						
Clonidine	1	n/a	n/a	n/a	n/a	20
Dexmedetomidine	3	34/112 (30.4)	50/110 (45.5)	0.46 [0.13, 1.59]	—	15, 22, 40
Vomiting						
Clonidine	1	n/a	n/a	n/a	n/a	20
Dexmedetomidine	3	17/112 (15.2)	22/110 (20.0)	0.75 [0.44, 1.27]	—	15, 22, 40

Vomiting included retching. Early = cumulative incidence up to 8 h postoperatively; late = cumulative incidence up to 48 h postoperatively. For nonsignificant results, numbers needed to treat are not shown. See figs. 17–22, Supplemental Digital Content 1, http://links.lww.com/ALN/A847, which are individual Forest plots.

CI = confidence interval; n/a = not enough valid data available to warrant meta-analysis (*i.e.,* fewer than 5 trials and/or fewer than 100 patients).

address additional issues), we are able to report on three additional outcomes.

First, and not unexpectedly, α2 agonists were shown to affect hemodynamics. We found evidence that clonidine increased the risk of intra- and postoperative arterial hypotension. For dexmedetomidine, only three trials reported on hemodynamic outcomes; the only evidence we found was an increase in the risk of postoperative bradycardia. The clinical relevance of these hemodynamic effects remains uncertain because none of the trials reported on major adverse outcomes, such as patients needing prolonged hemodynamic support with catecholamines. However, it has been shown that the perioperative use of β blockers, which share similar hemodynamic properties with α2 agonists, increased the risk of stroke and death.[46] Probably as a direct consequence of the hypotensive effect, both drugs significantly decreased the risk of arterial hypertension. Again, it remained unclear what the clinical implications of this potentially cardioprotective effect was. Anesthesiologists may use α2 agonists perioperatively to blunt surgery-related hemodynamic stress responses.

Second, α2 agonists reduced the incidence of early postoperative nausea. Whereas classic antiemetic drugs reduced the absolute risk of PONV compared with placebo by approximately 20–30% (NNT, 3–5),[47] the NNT to prevent nausea with clonidine or dexmedetomidine was approximately nine. This beneficial, albeit weak and short-lived antinausea effect may be explained by direct antiemetic properties of α2 agonists, although the biologic basis remains obscure. Alternatively, consumption of intraoperative anesthetics and opioids, which have been considered risk factors for PONV,[47] may be reduced with the use of α2 agonists.[5] We did not analyze intraoperative anesthetic or opioid consumption because this would have gone beyond the principle aim of our analysis. However, postoperative opioid-sparing with α2 agonists was moderate only, and it has been suggested that even with nonopioid adjuvants that cause a considerably stronger opioid-sparing, a reduction in the incidence of opioid-related adverse effects was unlikely.[48] Finally, the observed antinausea effect of α2 agonists may be explained through a decrease in sympathetic tone; it has been suggested that PONV may be triggered by high catecholamine concentrations.[49] Our analyses did not allow addressing the question whether the α2 agonist-related, PONV-decreasing effect was reinforced when classic antiemetics were administered concomitantly.

Finally, we found no evidence that α2 agonists lengthened recovery times although they are well known for their sedative properties. This may be explained through a concomitant intraoperative anesthetic-sparing.[5]

This meta-analysis has limitations; these are related mainly to the quality of the analyzed trials. Most studies were of small size and thus at risk of overestimating treatment effects and of underreporting relevant adverse effects. In addition, our analyses of secondary endpoints may be subject to selection bias. For instance, we analyzed data on PONV, recovery times, or hemodynamic effects from trials that were systematically searched for a different purpose. Thus, strictly speaking, the data on secondary endpoints were based on a selected group of trials. The retrieved trials presented a large variety of drug regimens and types of surgery. This illustrates that the management of α2 agonists in clinical practice is not based on evidence but merely on institutional or personal habits. In addition, these trials reported on many different nonstandardized endpoints, which precluded the compari-

Table 3. Intra- and Postoperative Hemodynamic Events

	Number of Trials	Number of Patients with Event/Total Number of Patients (%)		Risk Ratio [95% CI]	Number Needed to Treat (NNT) Number Needed to Harm (NNH) [95% CI]	References
		Active	Control			
Intraoperative events						
Bradycardia						
Clonidine	6	16/214 (7.5)	8/228 (3.5)	1.95 [0.95, 3.98]	—	18, 20, 28, 29, 32, 38
Dexmedetomidine	1	n/a	n/a	n/a	n/a	42
Hypotension						
Clonidine	6	31/229 (13.5)	6/243 (2.5)	4.75 [2.17, 10.4]	NNH 9.0 [6.3, 16]	18, 20, 28, 29, 38, 41
Dexmedetomidine	1	n/a	n/a	n/a	n/a	39
Hypertension						
Clonidine	4	15/103 (14.6)	62/122 (50.8)	0.46 [0.16, 1.29]	—	18, 28, 29, 38
Dexmedetomidine	2	9/85 (10.6)	24/45 (53.3)	0.26 [0.13, 0.52]	NNT 2.3 [1.7, 3.7]	39, 42
Postoperative events						
Bradycardia						
Clonidine	4	4/160 (2.5)	3/155 (1.9)	1.33 [0.36, 4.90]	—	20, 26, 29, 37
Dexmedetomidine	2	16/50 (32.0)	0/50 (0.0)	17.0 [2.35, 123]	NNH 3.1 [2.2, 5.2]	25, 42
Hypotension						
Clonidine	5	15/230 (6.5)	3/185 (1.6)	3.37 [1.27, 8.92]	NNH 20 [12, 82]	20, 26, 29, 37, 41
Dexmedetomidine	1	n/a	n/a	n/a	n/a	42
Hypertension						
Clonidine	2	0/111 (0.0)	8/106 (7.5)	0.06 [0.00, 0.94]	NNT 13 [8.0, 40]	20, 32
Dexmedetomidine	0	n/a	n/a	n/a	n/a	—

Definitions of bradycardia, hypotension, or hypertension are provided in the text. For nonsignificant results, numbers needed to treat are not shown. See figs. 23–30, Supplemental Digital Content 1, http://links.lww.com/ALN/A847, which are individual Forest plots.

CI = confidence interval; n/a = not enough valid data available to warrant meta-analysis (*i.e.*, fewer than 5 trials and/or fewer than 100 patients); NNH = number needed to harm; NNT = number needed to treat.

son of trial results and pooling of data from independent studies. For instance, data on postoperative sedation could not be analyzed because almost each trial that reported on sedation was referring to yet another scale. Particularly in dexmedetomidine trials, endpoint reporting seemed sometimes selective, and less favorable results may have been omitted. For instance, of four adverse hemodynamic endpoints (*i.e.*, intra- and postoperative bradycardia or hypotension), all four could be analyzed for clonidine, but only one for dexmedetomidine. Complete data reporting, including data on adverse effects, is important to allow informed decision-making.

Our meta-analysis summarizes the entire scope of the current scientific knowledge on the role of perioperative systemic α2 agonists for postoperative pain control. Consequently, this analysis may serve as a rationale basis for future research. In fact, our systematic review raises several unre-

Table 4. Recovery Times

	Number of trials	Number of patients	WMD (95% CI)	References
Time to extubation (min)				
Clonidine	1	187	n/a	20
Dexmedetomidine	4	260	−1.6 [−2.9, −0.2]	16, 30, 39, 40
Time to spontaneous eye opening (min)				
Clonidine	1	84	n/a	36
Dexmedetomidine	3	170	−0.9 [−3.3, 1.5]	25, 30, 39
Time to response to verbal command (min)				
Clonidine	3	142	1.0 [−0.5, 2.4]	19, 28, 35
Dexmedetomidine	6	334	−0.1 [−1.6, 1.3]	16, 25, 30, 34, 39, 40

Definitions were taken as reported in the original trials. Meta-analyses were performed using a fixed effect model. See figs. 31–34, Supplemental Digital Content 1, http://links.lww.com/ALN/A847, which are individual Forest plots.

CI = confidence interval; n/a = not enough valid data available to warrant meta-analysis (*i.e.*, fewer than 5 trials and/or fewer than 100 patients); WMD = weighted mean difference.

solved issues. For instance, the choice between the two $\alpha 2$ agonists remains difficult. We did not retrieve any randomized head-to-head comparison. Clonidine is still widely used in Europe,[6] but dexmedetomidine is known to be approximately eight times more specific at the receptor.[50] Although the analgesic efficacy of these two drugs seems comparable, their risk-benefit profiles may differ.[4] In addition, for both drugs, the best dose and timing of administration remain largely unknown because they were administered before surgery, throughout the perioperative period, and through multiple routes of administration. For $\alpha 2$ agonists to be used in daily clinical practice, evidence-based regimens that provide a maximum of benefit and a minimum of harm need to be defined. Finally, one aim of multimodal analgesia is to reduce the risk of chronic postoperative pain.[51] Prospective studies that evaluate the impact of drugs on the development of chronic postoperative pain are sparse.[3] Curiously, only one of these trials reported on a follow-up period that went beyond 48 postoperative h,[39] and none studied hyperalgesia. We are yet unable to determine the impact of systemic $\alpha 2$ agonists on chronic postoperative pain or hyperalgesia; this should be elucidated.

In conclusion, in patients undergoing surgery with general anesthesia, there is evidence that perioperative systemic administration of $\alpha 2$ agonists decreases postoperative opioid consumption, pain intensity, and nausea. There is no evidence that $\alpha 2$ agonists delay recovering times. Data on any potential impact of $\alpha 2$ agonists on chronic postoperative pain or hyperalgesia are lacking. For clinical decision-making, the beneficial analgesic effects should be balanced against an increased risk of intra- and postoperative hypotension and bradycardia. Additional studies that clarify the adverse effect profile of clonidine and dexmedetomidine and that define rational regimens are required before systemic $\alpha 2$ agonists can be recommended as regular components of multimodal analgesia.

The authors thank Dilek Karaaslan, M.D. (Department of Anesthesiology and Reanimation, Suleyman Demirel University, Medical School, Isparta, Turkey), Yasemin Gunes, M.D. (Department of Anesthesiology, Cukurova University Faculty of Medicine, Adana, Turkey), and Wei-Zen Sun, M.D. (Department of Anesthesiology, National Taiwan University Hospital, Taipei, Taiwan, Republic of China), who responded to our inquiry. The authors also thank Cigdem Inan, M.D. (Division of Anesthesiology, Geneva University Hospitals, Geneva, Switzerland), for translation of reports published in Turkish.

References

1. Rasmussen ML, Mathiesen O, Dierking G, Christensen BV, Hilsted KL, Larsen TK, Dahl JB: Multimodal analgesia with gabapentin, ketamine and dexamethasone in combination with paracetamol and ketorolac after hip arthroplasty: A preliminary study. Eur J Anaesthesiol 2010; 27:324–30
2. Kehlet H, Wilmore DW: Evidence-based surgical care and the evolution of fast-track surgery. Ann Surg 2008; 248:189–98
3. Grosu I, de Kock M: New concepts in acute pain management: Strategies to prevent chronic postsurgical pain, opioid-induced hyperalgesia, and outcome measures. Anesthesiol Clin 2011; 29:311–27
4. Khan ZP, Ferguson CN, Jones RM: Alpha-2 and imidazoline receptor agonists: Their pharmacology and therapeutic role. Anaesthesia 1999; 54:146–65
5. Kamibayashi T, Maze M: Clinical uses of $\alpha 2$-adrenergic agonists. ANESTHESIOLOGY 2000; 93:1345–9
6. Mantz J, Josserand J, Hamada S: Dexmedetomidine: New insights. Eur J Anaesthesiol 2011; 28:3–6
7. Lui F, Ng KF: Adjuvant analgesics in acute pain. Expert Opin Pharmacother 2011; 12:363–85
8. Smith H, Elliott J: Alpha(2) receptors and agonists in pain management. Curr Opin Anaesthesiol 2001; 14:513–8
9. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group: Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. BMJ 2009; 339:b2535
10. Elia N, Tramèr MR: Ketamine and postoperative pain: A quantitative systematic review of randomised trials. Pain 2005; 113:61–70
11. Stoelting RK, Hilier SC: Opioid agonists and antagonists, Pharmacology and Physiology in Anesthetic Practice, 4th edition. Philadelphia, Lippincott Williams & Wilkins, pp 87–126
12. Kay B: A clinical investigation of piritramide in the treatment of postoperative pain. Br J Anaesth 1971; 43:1167–71
13. Schug SA, Gandham N: Opioids: Clinical use, Wall and Melzack's Textbook of Pain, 5th edition. Edited by MacMahon SB, Koltzenburg M. Philadelphia, Elsevier Churchill Livingstone, pp 443–57
14. Altindis NT, Karaaslan D, Peker TT, Ozmen S, Bulbul M: Comparison of meperidine alone with meperidine plus dexmedetomidine for postoperative patient-controlled analgesia. Neurosciences (Riyadh) 2008; 13:117–21
15. Lin TF, Yeh YC, Lin FS, Wang YP, Lin CJ, Sun WZ, Fan SZ: Effect of combining dexmedetomidine and morphine for intravenous patient-controlled analgesia. Br J Anaesth 2009; 102:117–22
16. Bakhamees HS, El-Halafawy YM, El-Kerdawy HM, Gouda NM, Altemyatt S: Effects of dexmedetomidine in morbidly obese patients undergoing laparoscopic gastric bypass. Middle East J Anesthesiol 2007; 19:537–51
17. Benhamou D, Narchi P, Hamza J, Marx M, Peyrol MT, Sembeil F: Addition of oral clonidine to postoperative patient-controlled analgesia with i.v. morphine. Br J Anaesth 1994; 72:537–40
18. Bernard JM, Hommeril JL, Passuti N, Pinaud M: Postoperative analgesia by intravenous clonidine. ANESTHESIOLOGY 1991; 75: 577–82
19. De Deyne C, Struys M, Heylen R, De Jongh R, Van der Laenen M, Buyse L, Deghislage J, Rolly G: Influence of intravenous clonidine pretreatment on anesthetic requirements during bispectral EEG-guided sevoflurane anesthesia. J Clin Anesth 2000; 12:52–7
20. De Kock MF, Pichon G, Scholtes JL: Intraoperative clonidine enhances postoperative morphine patient-controlled analgesia. Can J Anaesth 1992; 39:537–44
21. Dimou P, Paraskeva A, Papilas K, Fassoulaki A: Transdermal clonidine: Does it affect pain after abdominal hysterectomy? Acta Anaesthesiol Belg 2003; 54:227–32
22. Gunes Y, Ozbek TH, Gunduz HM, Gedik YE, Erman T, Ozcengiz D: Patient-controlled analgesia comparison of morphine to dexmedetomidine plus morphine in patients undergoing laminectomy. Neurosurgery Quarterly 2008; 18:178–81
23. Gurbet A, Basagan-Mogol E, Turker G, Ugun F, Kaya FN, Ozcan B: Intraoperative infusion of dexmedetomidine reduces perioperative analgesic requirements. Can J Anaesth 2006; 53:646–52
24. Jeffs SA, Hall JE, Morris S: Comparison of morphine alone with morphine plus clonidine for postoperative patient-controlled analgesia. Br J Anaesth 2002; 89:424–7
25. Lawrence CJ, De Lange S: Effects of a single pre-operative

dexmedetomidine dose on isoflurane requirements and perioperative haemodynamic stability. Anaesthesia 1997; 52: 736–44

26. Marinangeli F, Ciccozzi A, Donatelli F, Di Pietro A, Iovinelli G, Rawal N, Paladini A, Varrassi G: Clonidine for treatment of postoperative pain: A dose-finding study. Eur J Pain 2002; 6:35–42
27. Mohammadi SS, Seyedi M: Comparing oral gabapentin *versus* clonidine on early postoperative pain, nausea, and vomiting after general anesthesia. Int J Pharmacol 2008; 4:153–6
28. Morris J, Acheson M, Reeves M, Myles PS: Effect of clonidine pre-medication on propofol requirements during lower extremity vascular surgery: A randomized controlled trial. Br J Anaesth 2005; 95:183–8
29. Owen MD, Fibuch EE, McQuillan R, Millington WR: Postoperative analgesia using a low-dose, oral-transdermal clonidine combination: Lack of clinical efficacy. J Clin Anesth 1997; 9:8–14
30. Ozkose Z, Demir FS, Pampal K, Yardim S: Hemodynamic and anesthetic advantages of dexmedetomidine, an alpha 2-agonist, for surgery in prone position. Tohoku J Exp Med 2006; 210:153–60
31. Park J, Forrest J, Kolesar R, Bhola D, Beattie S, Chu C: Oral clonidine reduces postoperative PCA morphine requirements. Can J Anaesth 1996; 43:900–6
32. Pawlik MT, Hansen E, Waldhauser D, Selig C, Kuehnel TS: Clonidine premedication in patients with sleep apnea syndrome: A randomized, double-blind, placebo-controlled study. Anesth Analg 2005; 101:1374–80
33. Rohrbach A, Jage J, Olthoff D: Intraoperative clonidine modulates sympathetic tone in the early postoperative period after remifentanil. A double blind, placebo-controlled study. Acute Pain 1999; 2:129–38
34. Scheinin B, Lindgren L, Randell T, Scheinin H, Scheinin M: Dexmedetomidine attenuates sympathoadrenal responses to tracheal intubation and reduces the need for thiopentone and perioperative fentanyl. Br J Anaesth 1992; 68:126–31
35. Segal IS, Jarvis DJ, Duncan SR, White PF, Maze M: Clinical efficacy of oral-transdermal clonidine combinations during the perioperative period. Anesthesiology 1991; 74:220–5
36. Simoni RF, Cangiani LM, Pereira AM, Abreu MP, Cangiani LH, Zemi G: Efficacy of intraoperative methadone and clonidine in pain control in the immediate postoperative period after the use of remifentanil. Rev Bras Anestesiol 2009; 59:421–30
37. Striebel WH, Koenigs DI, Krämer JA: Intravenous clonidine fails to reduce postoperative meperidine requirements. J Clin Anesth 1993; 5:221–5
38. Sung CS, Lin SH, Chan KH, Chang WK, Chow LH, Lee TY: Effect of oral clonidine premedication on perioperative hemodynamic response and postoperative analgesic requirement for patients undergoing laparoscopic cholecystectomy. Acta Anaesthesiol Sin 2000; 38:23–9
39. Tufanogullari B, White PF, Peixoto MP, Kianpour D, Lacour T, Griffin J, Skrivanek G, Macaluso A, Shah M, Provost DA: Dexmedetomidine infusion during laparoscopic bariatric surgery: The effect on recovery outcome variables. Anesth Analg 2008; 106:1741–8
40. Unlugenc H, Gunduz M, Guler T, Yagmur O, Isik G: The effect of pre-anaesthetic administration of intravenous dexmedetomidine on postoperative pain in patients receiving patient-controlled morphine. Eur J Anaesthesiol 2005; 22: 386–91
41. Wright PM, Carabine UA, McClune S, Orr DA, Moore J: Preanaesthetic medication with clonidine. Br J Anaesth 1990; 65:628–32
42. Yildiz M, Tavlan A, Tuncer S, Reisli R, Yosunkaya A, Otelcioglu S: Effect of dexmedetomidine on haemodynamic responses to laryngoscopy and intubation: Perioperative haemodynamics and anaesthetic requirements. Drugs R D 2006; 7:43–52
43. Yu HP, Hseu SS, Yien HW, Teng YH, Chan KH: Oral clonidine premedication preserves heart rate variability for patients undergoing laparoscopic cholecystectomy. Acta Anaesthesiol Scand 2003; 47:185–90
44. Elia N, Lysakowski C, Tramèr MR: Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. Anesthesiology 2005; 103:1296–304
45. Remy C, Marret E, Bonnet F: Effects of acetaminophen on morphine side-effects and consumption after major surgery: Meta-analysis of randomized controlled trials. Br J Anaesth 2005; 94:505–13
46. POISE Study Group, Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Málaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P: Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): A randomised controlled trial. Lancet 2008; 371:1839–47
47. Gan TJ, Meyer TA, Apfel CC, Chung F, Davis PJ, Habib AS, Hooper VD, Kovac AL, Kranke P, Myles P, Philip BK, Samsa G, Sessler DI, Temo J, Tramèr MR, Vander Kolk C, Watcha M, Society for Ambulatory Anesthesia: Society for Ambulatory Anesthesia guidelines for the management of postoperative nausea and vomiting. Anesth Analg 2007; 105:1615–28
48. Elia N, Tramèr MR: Is opioid sparing clinically relevant? Systematic Reviews in Pain Research: Methodology Refined. Edited by McQuay HJ, Kalso E, Moore RA. Seattle, IASP Press, 2008, pp 119–32
49. Watcha MF, White PF: Postoperative nausea and vomiting. Its etiology, treatment, and prevention. Anesthesiology 1992; 77:162–84
50. Paris A, Tonner PH: Dexmedetomidine in anaesthesia. Curr Opin Anaesthesiol 2005; 18:412–8
51. Katz J, Seltzer Z: Transition from acute to chronic postsurgical pain: Risk factors and protective factors. Expert Rev Neurother 2009; 9:723–44