ELSEVIER

CrossMark

SURGERY FOR OBESITY AND RELATED DISEASES

Surgery for Obesity and Related Diseases 13 (2017) 1434–1448

Review article

Perioperative analgesic profile of dexmedetomidine infusions in morbidly obese undergoing bariatric surgery: a meta-analysis and trial sequential analysis

Preet Mohinder Singh, M.D., D.N.B.[a,*], Rajesh Panwar, M.S., M.Ch.[b], Anuradha Borle, M.D.[a], Jan P. Mulier, M.D., Ph.D.[c], Ashish Sinha, M.D., M.B.A.[d], Basavana Goudra, M.D., F.R.C.A., F.C.A.R.C.S.I.[e]

[a]*Department of Anesthesia, All India Institute of Medical Sciences, New Delhi, India*
[b]*Department of Gastrointestinal Surgery & Liver Transplantation, All India Institute of Medical Sciences, New Delhi, India*
[c]*Department of Anesthesiology, Intensive Care and Reanimation, AZ Sint Jan Brugge-Oostende, Bruges, Belgium*
[d]*Department of Anesthesiology, Temple University, Philadelphia, PA, USA*
[e]*Hospital of the University of Pennsylvania and Perleman School of Medicine, Philadelphia, Pennsylvania*

Received January 5, 2017; revised February 5, 2017; accepted February 25, 2017

Abstract

Background: Opioid-sparing analgesia for bariatric surgery in morbidly obese can potentially prevent catastrophic airway complications. Our meta-analysis attempts to consolidate the evidence on dexmedetomidine evaluating its analgesic and safety profile.

Methods: Trails comparing perioperative dexmedetomidine infusion to conventional analgesic regimens for bariatric surgery were searched. Comparisons were made for 24-hour and post-anesthesia care unit (PACU) morphine consumed, PACU pain scores, postoperative nausea and vomiting pain scores, and heartrate. Meta-regression was performed for length of stay to evaluate various analgesic control subgroups.

Results: Six trials were included in the final analysis. Dexmedetomidine infusion (reported in 5 intraoperative subgroups and 2 postoperative subgroups) decreased 24-hour morphine by 18.13 ± 6.11 mg (random effects: $P < .001$, $I^2 = 95.48\%$). Despite the small number of included studies, the sample size for avoiding a false positive result was adequate as the trial sequential analysis found the present sample size (362) to be well past the required "sample size" (n = 312) for 85% power. Meta-regression for infusion dose on morphine consumption difference found a predictability of 49% (coefficient = 39.93, random-effects, $Tau^2 = 396.08$), and predictability of the model improved to 68% on inclusion of time of initiation of infusion. The dexmedetomidine group had lower PACU morphine consumption (by 6.91 ± 1.19, $I^2 = 34.37\%$), lower pain scores (scale of 0–10 ± 2.27, $I^2 = 88.14\%$), lower postoperative nausea and vomiting incidence (odds ratio = ±0.26, $I^2 = 0\%$), and lower heart rate (73.25 versus. 83.50) (mean difference = ±10.15 $I^2 = 94.04\%$). No adverse events were reported across trials.

Conclusion: Perioperative dexmedetomidine infusion in obese patients undergoing bariatric surgery is a promising and safe alternative. Both intraoperative or postoperative infusions lead to significant opioid sparing in early and extend postoperative recovery phase. Morbidly obese patients

*Correspondence: Preet Mohinder Singh, M.D., D.N.B., Department of Anesthesia, All India Institute of Medical Sciences, New Delhi, India 110029.

E-mail: Preetrajpal@gmail.com

http://dx.doi.org/10.1016/j.soard.2017.02.025

receiving perioperative dexmedetomidine infusions have overall better pain control and lower incidence of postoperative nausea-vomiting. All the aforementioned merits come with a stable hemodynamic profile and without any reported major adverse events. (Surg Obes Relat Dis 2017;13:1434–1448.)

Keywords: Dexmedetomidine in bariatric surgery; Opioid sparing analgesia; Dexmedetomidine in morbidly obese

Optimal analgesia for obese patients undergoing bariatric surgery has always been challenging for the perioperative team. Since the introduction of bariatric surgery, use of opioid sparing agents in potentially opioid-free techniques has attracted substantial research. Evidence-based enhanced recovery after surgery (ERAS) guidelines for bariatric surgery clearly recognize the benefits of eliminating perioperative opioids and strongly advocate the use of opioid sparing regimens [1,2]. On the other hand, it is a well-established fact that inadequate analgesia in the perioperative period significantly increases complication rates [3], more so in obese patients, in whom pain-related shallow breathing predisposes to perioperative pneumonia and atelectasis [4]. Evidence clearly suggests that perioperative opioid use is associated with an increase in the incidence of perioperative complications in obese [5,6]. The postoperative apnea–hypopnea index and sleep-disordered breathing directly correlate with the quantity of perioperative opioid use [7]. Thus any intervention that provides analgesia without further compromising airway tone or increasing obstructive sleep apnea or obstructive sleep apnea (OSA) (unlike opioids) would be a desirable change.

The increased alpha-2 A selectivity and affinity of dexmedetomidine contributes to the observed analgesic effects, surpassing its predecessors [8]. Another property unique to dexmedetomidine that makes it an attractive choice in obese patients is its minimal respiratory depressant effect. Analgesic drugs that possess high sedative potential (opioids) can aggravate or even induce OSA in these patients. Dexmedetomidine, despite its sedative effects, does not compromise airway tone or reflexes. Thus, OSA-related complication rates are not exaggerated [9]. In addition, opioids also significantly add to sedation and thus can be associated with delayed awakening in obese. Interestingly, multiple comparisons between remifentanil (which is the shortest-acting opioid) and dexmedetomidine have found that postoperative sedation levels in obese patients are comparable [10,11]. These trials report a smaller number of airway-related adverse events with the use of dexmedetomidine, thus highlighting better safety potential despite equivalent sedation to remifentanil. Understandably, due to its short duration of action, remifentanil is not a preferred postoperative analgesic and thus any other opioid (longer acting) is more likely to be associated with prolonged postoperative sedation. Although no direct comparisons exist, intuitively dexmedetomidine is likely to be associated with a lesser degree of sedation as an analgesic adjuvant in comparison with longer-acting opioids.

Building on this hypothesis, perioperative (mainly intraoperative and postoperative) infusions of dexmedetomidine have already been evaluated by multiple trials in patients undergoing both bariatric and nonbariatric surgery [12,13]. As the quantity of opioids used for perioperative analgesia correlates directly with the incidence of adverse events and patient sedation, the opioid-sparing effect of dexmedetomidine (without compromising analgesia) can estimate its efficacy in improving perioperative safety in obese patients. Many trials globally recognizing the aforementioned safety-enhancing potential have already investigated this aspect of dexmedetomidine in obese patients. In the present meta-analysis, meta-regression and eventually a trial sequential analysis (TSA), we evaluate and quantify the various dimensions (pain scores and associated effects) of the opioid-sparing potential of dexmedetomidine in morbidly obese patients undergoing bariatric surgery.

Methods

The preferred reporting items for systemic reviews and meta-analyses (PRISMA) approach was followed to perform this meta-analysis [14] (Figure 1). We adhered to the PICOS approach (population, intervention, control, and outcome study design) for identifying relevant trials and defining the final selection criterion (Table 1). Comparative trials evaluating the use of perioperative dexmedetomidine with intention of eliminating or alleviating opioids use in obese patients undergoing bariatric surgery were included. We defined perioperative opioid consumption in terms of "morphine equivalents" for consistency during comparisons [15]. The effect of dexmedetomidine infusion used during the perioperative period on 24-hour postoperative morphine consumption was set as the primary endpoint to be evaluated across trials. For secondary/exploratory objectives, we planned to evaluate other parameters with consistent documentation across included trials. The salient features of trials included in the final analysis that met the above criteria are shown in Table 2.

Literature search strategy

Two independent reviewers (P.M.S. and R.P) searched the online literature available on MEDLINE, Science Citation Index Expanded, Embase, Scopus, Cochrane Central Register of

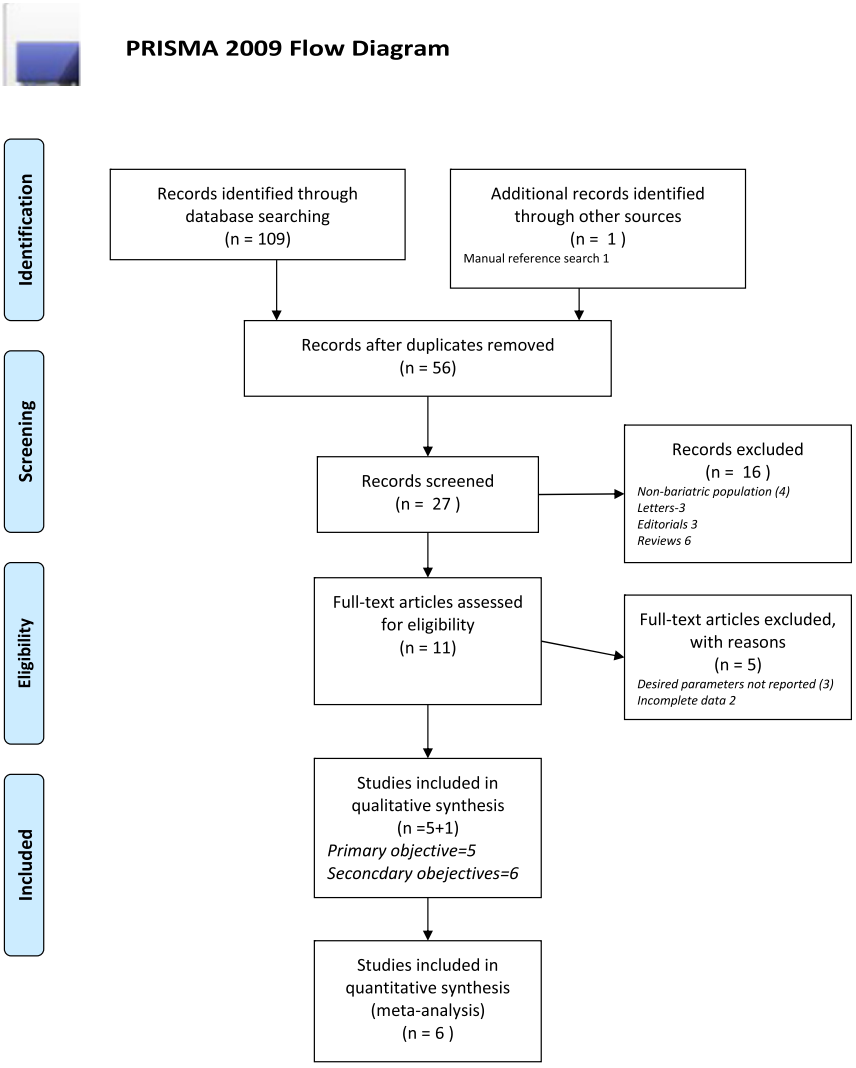


Fig. 1. PRISMA flow diagram illustrating flow chart outlining retrieved, excluded, and included studies. PRISMA = Preferred Reporting Items for Systemic Reviews and Meta-analyses.

Controlled Trials, clinical trials registry, and meta-register of controlled for published manuscripts until December 2, 2016. The following MeSH terms were searched in the aforementioned databases: "dexmedetomidine bariatric surgery," "bariatric surgery analgesia," "opioid sparing bariatric surgery," "morphine sparing dexmedetomidine perioperative," "dexmedetomidine in obese," and "opioid free bariatric surgery." We excluded the following terms from the search string: "nonbariatric surgery," "ambulatory bariatric surgery," and "nonobesity procedures." We included only comparative studies in which at least one intervention group received an infusion of dexmedetomidine (intraoperative or postoperative phase). We intended to evaluate the "dexmedetomidine infusion dose response curve" using a regression model, so we used the mean infusion rates documented in the included trials. Our search extended to research articles published either as full manuscripts or meeting abstracts in peer-reviewed journals. We also manually searched the references of comparable meta-analysis for relevant trials. Our search intended to include pertinent trials published in both English and non-English languages. Once the abstract was analyzed by the searching reviewer and found appropriate, the full text of the article was studied. The decision to include a study in the final analysis was based on the independent assessment of the 2 reviewers. Any disagreements between the 2 were harmonized by consensus and if needed via arbitration by a neutral third researcher. Based on the recommendations by the Cochrane Collaboration, another independent researcher assessed the included trials for quality of evidence and possible methodological bias [16].

Data extraction

The data obtained from relevant studies were abstracted into a structured standardized format. Reported variables were entered extracted into Microsoft Excel 2016 (Windows Edition, Microsoft). The following data were

Table 1
PICOS data extraction framework

PICOS Framework	
Population	Morbidly obese patients undergoing bariatric surgery
Interventions	Use of perioperative dexmedetomidine infusion (both) ● Intraoperative ● Postoperative
Controls	Bariatric patients receiving conventional medications including opioids or analgesic adjuvants other than dexmedetomidine
Outcomes	**Primary** ● 24-hr morphine consumption **Exploratory objectives** ● PACU morphine consumption ● PACU pain scores ● PONV incidence ● Hemodynamic profile comparison
Study Design	Comparative trials (dexmedetomidine Versus Control)-Both Randomized/nonrandomized trials

PACU = postanesthesia care unit; PICOS framework = population, intervention, control, and outcome study design; PONV = postoperative nausea vomiting.

extracted from each of the included trials: year and country of publication, study design, patient demographic profile, type of laparoscopic bariatric surgery (sleeve gastrectomy, Roux-en-Y bypass, biliopancreatic diversion if separately described), pain scores at various time points, analgesic regimens planned/used, intraoperative opioid use, 24-hour postoperative opioid used, control group analgesics, dexmedetomidine dose used, time of initiation, dose and duration of infusion, comparative hemodynamics in both groups, postoperative nausea and vomiting (PONV) rates, length of postoperative hospital stay, and any particular complication reported. We attempted to extract details of adverse events related, frequency data of individual complications; however, reporting was very inconsistent and thus a valid pooled analysis was not feasible.

If in any trial the data were found to be incomplete, attempts were made to contact the corresponding author via email for the relevant data. If data of interest were expressed in terms of median and interquartile range, authors were contacted for the mean and standard deviation (SD) values. However, if no response was obtained, we estimated the mean and standard deviation using the validated Hozo's formula [17,18]. In a few of the trials, if variance associated with means was not available, authors were contacted for the same. However, if no response was received, we imputed these variances as per Cochrane collaboration recommendations using mean from available variances from other included studies. Analysis could be performed for variables wherever the values for 3 or more of the following subgroups were reported across the studies:

1. First postoperative day opioid consumption: This included a comparison of the total amount of "morphine equivalents consumed by patients during the first 24 hours after surgery.
2. Postanesthesia care unit (PACU) opioid consumption: This was defined as the comparative dose of opioids in morphine equivalents consumed within the first 6 hours after surgery.
3. Pain scores: Postoperative PACU pain scores were available in >3 studies and could be compared. All studies reported the pain scores on a numeric pain scale of 0 to 10, where 0 means no pain and 10 is the worst possible pain.
4. PONV incidence rates: Incidence rates for nausea/vomiting during the first 24 hours after surgery were reported in >3 trials and were compared in the pooled analysis.
5. PACU heart rate: Consistent documentation of mean heart rate during the patient's stay in the PACU was available in most trials, and a pooled comparison was thus made. Attempts were made to compare the blood pressures as well; however, the reporting was not consistent, and a valid mathematical pooling was not possible.

Statistical analysis

Pooled data was analyzed using the Comprehensive Meta Analysis (Version 3, Biostat Inc.). Meta-analysis was first performed using the fixed effect modeling. If the heterogeneity was $>40\%$, random effects modeling was ultimately used. Heterogeneity between the included trials was quantified using the I^2 statistic. Values of $I^2 < 40\%$ were considered nonsignificant, 40%–60% were considered to represent moderate heterogeneity, and values $>60\%$ were reported as high heterogeneity. Pooled mean difference was used for analyzing continuous variables. For the frequency-based variables, we used the Mantel–Haenszel pooled odds ratio to quantify the associations.

TSA was used to grade the strength of the meta-analysis and to evaluate the possibility of false positive results for the primary outcome. Meta-regression for continuous variable (dexmedetomidine infusion dose) and nominal variable (time of dexmedetomidine infusion initiation) was performed using random effects modeling. This allowed us to quantify the contribution of both the above factors to the variations seen across the trials. The R^2 statistic was used to report the explained variation in the 24-hour morphine consumption based on the aforementioned 2 identified (and consistently reported) factors. A pooled result was considered statistically significant if it was associated with a $P < .05$. Potential publication bias in the included trials was quantified using the Egger's regression test and further evaluated using a funnel plot.

TSA

TSA was performed because our meta-analysis had only 6 trials meeting the inclusion criteria. Consistent with the small number of included studies, a possibility of false-positive demonstrable benefit (decreased morphine consumption with dexmedetomidine) existed. TSA is a useful

Table 2
Details of the included trials

Study Name	Country	Study type	Groups	Dexmedetomidine dose/ Time	Compared endpoints	Control	Adverse Events	Comments
1 Halaweh et al. 2016 [10]	Boston, USA	Randomized controlled trial	Two ● Dexmedetomidine infusion ● Morphine infusion	**Dose** ***Bolus***: no details ***Infusion:*** .3 μgm/kg/hr Duration- 24-hr Postoperative infusion only	● Postoperative opioid use ● Paracetamol dose ● PACU morphine ● PACU pain scores	Postoperative morphine infusion 3 mg/hr for 24 hours	● PONV ● Desaturation rates ● Reintubation rates	● Desaturation and intubation rates were comparable (no values given) ● Before initiation of infusion-Baseline pain scores were higher in dexmedetomidine groups (no reasons documented) ● Paracetamol requirement was similar
2 Bakhamees et al. 2007 [11]	Cairo, Egypt	Randomized controlled trial	Two (patients undergoing Roux-en-Y gastric bypass on TIVA) ● Dexmedetomidine infusion ● Placebo (saline) infusion: with rescue opioids PCA	Dose- ***Bolus***: Slow 0.8 μgm/kg ***Infusion:*** .40.μgm/kg/hr. ***Duration***: intraoperative (no exact duration reported)	● Postoperative Opioid use ● Intraoperative fentanyl consumption ● PONV ● Hemodynamic profile ● PACU pain scores ● Time to extubation	TIVA: Propofol + Fentanyl along with placebo (saline) infusion PCA morphine consumption reported	● Respiratory parameter adequacy was better in Dexmedetomidine group ● Control group had delayed extubation and spontaneous respiration	● Overall recovery profile (respiratory) was better with dexmedetomidine ● Intraoperative fentanyl requirements were lower with dexmedetomidine ● Both intraoperative and postoperative hemodynamics better with dexmedetomidine
3 Dholakia et al. 2007 [12]	Madison, WI, USA	Retrospective Cohort Nonrandomized	Two (most patients for gastric bypass- other procedures also included) ● Dexmedetomidine infusion ● Conventional analgesics + opioids PCA	Dose ***Bolus***: Slow 1 μgm/kg ***Infusion***: Mean dose .50.μgm/kg/hr (range .2-0.7) ***Duration:*** No exact reported ***Initiated:*** Toward the end of surgery continued into the early postoperative phase	● Postoperative opioid use ● Length of stay ● PACU pain scores ● Number of patients discharged on day 1 ● Antiemetic requirements	Conventional opioid based treatment-Morphine PCA comparison Adjuvant MgSO4 (for analgesia used)	● No adverse effects compared ● None reported	● Day 1 discharge criteria met in more patients with dexmedetomidine ● Lower per day requirements of MgSO4 with dexmedetomidine ● Mean length of stay was comparable
4 Feld et al. 2006[13]	Chicago, IL, USA	Randomized controlled trial	Two (gastric bypass) Desflurane-based general anesthesia ● Dexmedetomidine infusion ● Fentanyl infusion	Dose- ***Bolus***: Slow 0.5 μgm/kg ***Infusion***: .40.μgm/kg/hr ***Duration***: intraoperative (no exact duration reported)	● Primary endpoint (24-hr morphine consumed) not measured ● Postoperative pain scores ● PACU opioid consumption ● Hemodynamics	Fentanyl Infusion Dose Bolus- .5 μgm/kg ***Infusion***: .40.μgm/kg/hr (Fentanyl equivalents converted into morphine equivalents)	● None specific reported/ compared ● One patient in fentanyl group required prolonged ventilation	● Time to extubation was shorter with dexmedetomidine ● Desflurane required to maintain anesthetic depth lower with dexmedetomidine

5	Tufanogullari et al. 2008 [14]	Texas, USA	Randomized controlled trial	Four (Gastric banding and bypass) Dose determining study ● Dexmedetomidine infusion (0.20.μgm/kg/hr). ● Dexmedetomidine infusion (0.40.μgm/kg/hr) ● Dexmedetomidine infusion (0.80.μgm/kg/hr) ● Placebo (Saline) Data given separately for each group	Dose Bolus: None in any group ● Group −0.2 ***Infusion***: .20.μgm/kg/hr. ● Group .4 ***Infusion***: .40.μgm/kg/hr. ● Group .8 ***Infusion***: .80.μgm/kg/hr. ***Duration***: intraoperative (no exact duration reported) Timing for all groups Intraoperative: Variable for all groups	● Opioid consumption: early and late ● Rescue analgesics ● PACU stay ● Time to wake up ● PONV ● Time for extubation ● Hemodynamics ● Time to ambulation and oral diet ● Patient satisfaction scores	Placebo- Saline infusion PCA opioid consumption during 48-hour period	● Nausea scores were higher in control group ● Dexmedetomidine groups were comparable for most of the parameters ● Anesthesia duration was prolonged in the control group	● Most benefits did not increase with increasing dose of dexmedetomidine ● Early discharge was seen in patients in dexmedetomidine group ● No bradycardia episodes were reported in any of the dose groups. ● Patient satisfaction was higher on recurrent delayed and early assessment
6	Salama et al. 2016 [15]	Cairo, Egypt	Randomized controlled trial	Two (sleeve gastrectomy) ● Dexmedetomidine infusion ● Placebo	Dose ***Bolus***: Slow 0.5 μgm/kg ***Infusion***: .40.μgm/kg/hr. ***Duration***: intraoperative (no exact duration reported) ***Timing***: Intraoperative infusion	● Opioid consumption ● Intraoperative opioid consumption ● Pain scores ● Sedation levels ● Hemodynamics	The dexmedetomidine group was also given additional pregabalin Control group: Placebo (saline) infusion	● No specific side effects compared ● Higher nausea scores in the control group	● Pregabalin was a confounding factor in the study ● Sedation scores were higher in dexmedetomidine group

PCA = patient controlled analgesia; PONV = postoperative nausea vomiting; TIVA = total intravenous anesthesia.

tool in such situations that allows to quantify the required sample size to avoid false-positive reporting. Thus, we could calculate the required sample size (reported as "information size") to achieve a power of 85% or more for our meta-analysis. This approach allowed us to support our conclusions without the possibility of false-positive results despite the number of included studies being small.

Results

The initial search helped us to identify 190 articles published within the aforementioned databases. We used Endnote (Thompson Reuters) to combine the search results of the independent researcher. Desired primary and or secondary outcomes of interest were reported in 6 of the identified trials. A study by Tufanogullari et al. compared 3 different infusion doses of dexmedetomidine (.2, .4, and .8 μgm/kg/min) against a placebo-based control group [19]. The comparative data for each dose group was given independently; thus, we could make 3 different comparisons for this study in the pooled analysis. Filho et al. studied the use of dexmedetomidine in the obese; however, they used a continuous background infusion of alfentanil and did not document any of the parameters we analyzed [13]. Thus, this study had to be eventually excluded from the analysis.

For the primary endpoint (24-hour morphine consumption), complete values were available from 5 studies [19–23]. Feld et al. only reported the morphine equivalents consumed in the PACU [24]. Five of these included trials were prospective randomized controlled trials with adequate controls. One trial by Dholakia et al. compared a retrospective control group with a prospective dexmedetomidine group. All of the 6 trials included 6 evaluated patients undergoing bariatric procedures. However, details on the nature of the procedures (sleeve gastrectomy, Roux-en-y gastric bypass or biliopancreatic diversion, etc.) were not consistently reported. Thus, despite the plan to compare the outcomes based on the type of surgery, an analysis was not possible. Adverse events (both anesthetic and surgical) were not consistently documented across the trials. Thus, a mathematical pooling and eventual conclusions on these were not possible. We were able qto analyze the following parameters to derive statistical conclusions.

Perioperative opioid consumption

We could divide opioid consumption into total 24-hour cumulative amount and the consumption in the PACU. Figure 1

Twenty-four-hour morphine consumption

Data for this comparison were available in 7 subgroups that included 179 patients in the control and 183 patients in the dexmedetomidine infusion group. Patients with dexmedetomidine infusion had significantly lower morphine requirements in the first 24 hours after surgery. Overall, dexmedetomidine had a morphine-sparing effect that amounted to 18.13 mg (95% CI: 6.15–30.10 mg). The mean morphine consumption in the control group was 54.38 mg, and this reduction translates into nearly 33.38% of the total opioid consumption. The heterogeneity for this comparison was 96.18%. To explore the heterogeneity, we performed a subgroup analysis dividing the perioperative infusion into "intraoperative" and "postoperative" groups. Intraoperative infusion group (5 subgroups) was also individually statistically significant ($P < .001$) with $I^2 = 95.48\%$. The postoperative subgroup also had a trend toward lower morphine requirements in the dexmedetomidine arm; however, the pooled P value failed marginally to achieve the preset statistically significant value ($P = .06$; Fig. 2).

TSA

We further performed a TSA using Trial Sequential Analysis software 0.9 (Copenhagen Trial Unit, Denmark). This analysis was performed for the mean difference in morphine consumption between the 2 groups. We performed TSA using dual significance testing methods: the conventional boundary (with alpha error of 5% as limit) and the alpha spending boundary (Upper O'Brien Fleming with type 1 error of 5%). For determining the information size variable, the power was set at 85%. Information size was calculated to be 312 by the alpha spending boundary method. The number of patients in our pooled analysis was well past the required size (n = 362).

The cumulative Z score limit was found to be higher than the limits by either of the previously mentioned methods of analysis (Fig. 3). Thus the possibility of a false-positive result despite a small meta-analysis is very unlikely. Also, the graph shows that the cumulative Z score extended beyond the area of futility, thus demonstrating the superiority of dexmedetomidine compared with the control groups (Fig. 3).

Meta-regression for factors determining morphine consumption

For morphine consumption difference, we performed a meta-regression for 2 available variables. These were set as the moderator variables in the regression modeling, and results were derived as follows.

Dose of dexmedetomidine infusion. Dexmedetomidine reduced opioid use in all the trials included. Taking the dose variation of dexmedetomidine infusion alone, the regression model could explain 49% of variations in the observed decrease in morphine requirements ($R^2 = .49$, $Tau^2 = 396.08$, $dF = 6$, $P = .39$) (Supplementary Fig. 1). The regression coefficient for difference in means (morphine

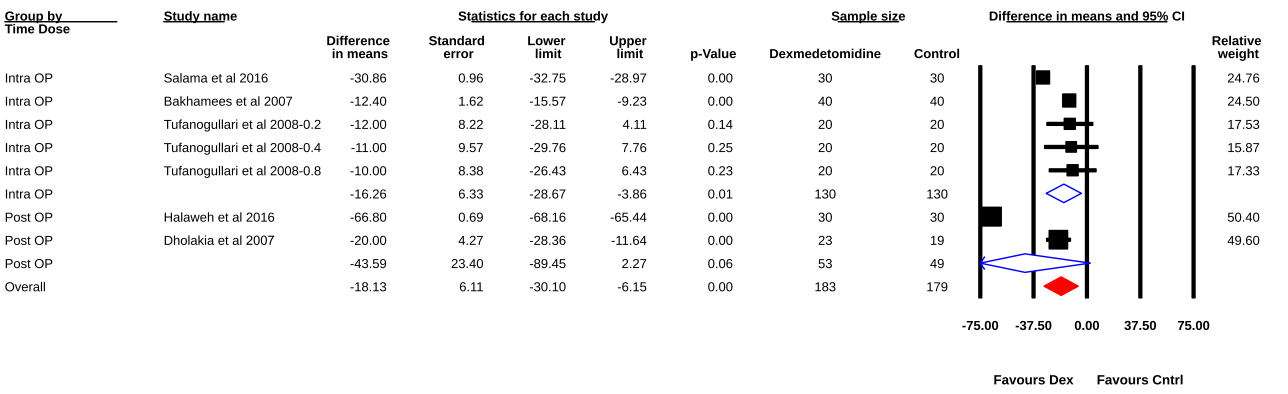


Fig. 2. Forest plot showing pooled mean difference for postoperative 24-hour morphine consumption (Dexmedetomidine group – Control group). Hollow blue diamonds represent net effect of individual subgrouping (intraoperative and postoperative). Solid diamond at the bottom of comparison denotes the final net effect. *This parameter was statistically significant (as $P < .05$).

consumption in dexmedetomidine–morphine consumption in control group) and the infusion dose of dexmedetomidine was 39.93. As the morphine consumption was lower in the dexmedetomidine group, the initial value of morphine consumption difference was negative (Supplementary Fig. 1). Increments in the dexmedetomidine dose found narrowing of this difference, thus highlighting the possibility that increasing the dexmedetomidine dose does not necessarily increase analgesic potential.

Timing of dexmedetomidine dose. Adding the timing of dexmedetomidine administration (intraoperative or postoperative) to the predictability of the aforementioned regression model increased to 68%. The magnitude of difference in means was higher with postoperative infusion (Supplementary

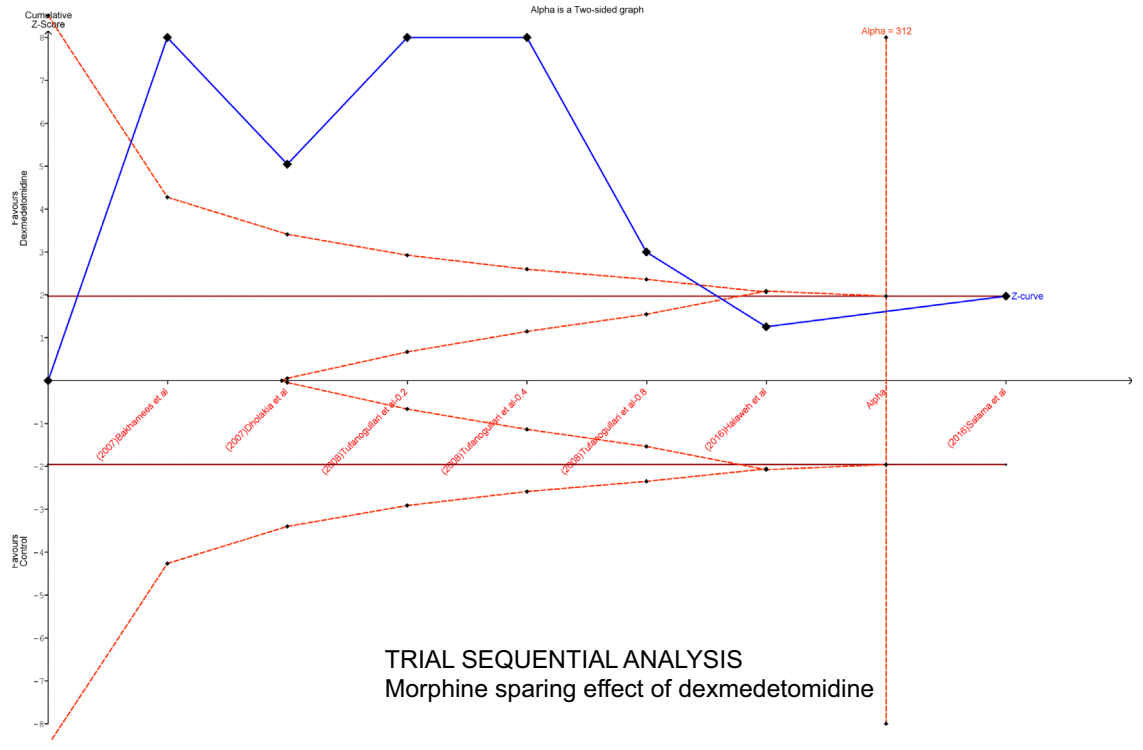


Fig. 3. Trial sequential analysis (TSA) for length of stay. The upper half of the graph above the zero axis falls into the area of advantage with dexmedetomidine infusion. Solid lines at +1.96 and −1.96 on the y-axis represent the conventional model boundaries for TSA with an α of 5%. The information size (IS) for conventional boundary model = 312 (shown on x-axis). Dotted line (green line) at −1.75 represents the alpha-spending boundary (Upper O'Brien Fleming with α of 5% and β of 15%). The wedge between the lines at 1.96 shows the area of futility. Because the cumulative Z-scores are clearly beyond the area of futility, a false positive result with present meta-analysis is ruled out.

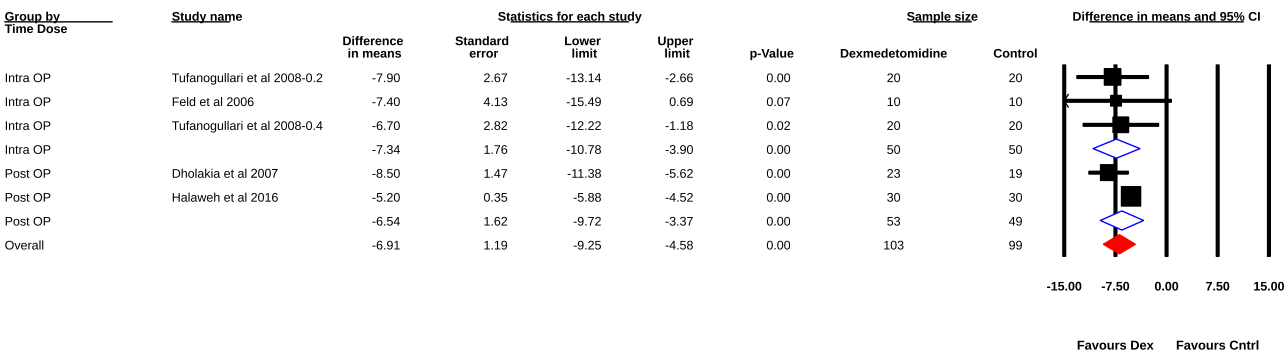


Fig. 4. Forest plot showing pooled mean difference for postanesthesia care unit (PACU) morphine consumption (Dexmedetomidine group – Control group). Hollow blue diamonds represent the net effect of individual subgrouping (intraoperative and postoperative). Solid diamond at the bottom of comparison denotes the final net effect. *This parameter was statistically significant (as $P < .05$).

Fig. 2). The regression coefficient for postoperative use was −28.23 ($Tau^2 = 295.82$, $I^2 = 97.75$, df = 5, $P = .05$).

PACU morphine consumption

Five subgroups reported the comparative opioid consumption during the PACU stay. Data were available for 103 and 99 patients in the dexmedetomidine and control groups, respectively. Use of dexmedetomidine lowered the opioid requirement by 6.91 (95% CI: 4.58–9.25) mg. We reported the values from fixed-effects modeling for this variable as the pooled results had heterogeneity of 34.37%. The included studies were further divided based on the time of dexmedetomidine use. Both intraoperative and postoperative use groups also revealed a statistically significant reduction in opioid requirements (Fig. 4).

To evaluate the analgesic efficacy of dexmedetomidine, we also compared the numeric pain scores during the patients stay in the PACU. Unfortunately, none of the trials reported these values at 24 hours, and thus a mathematical comparison was not possible.

Pain scores in the PACU

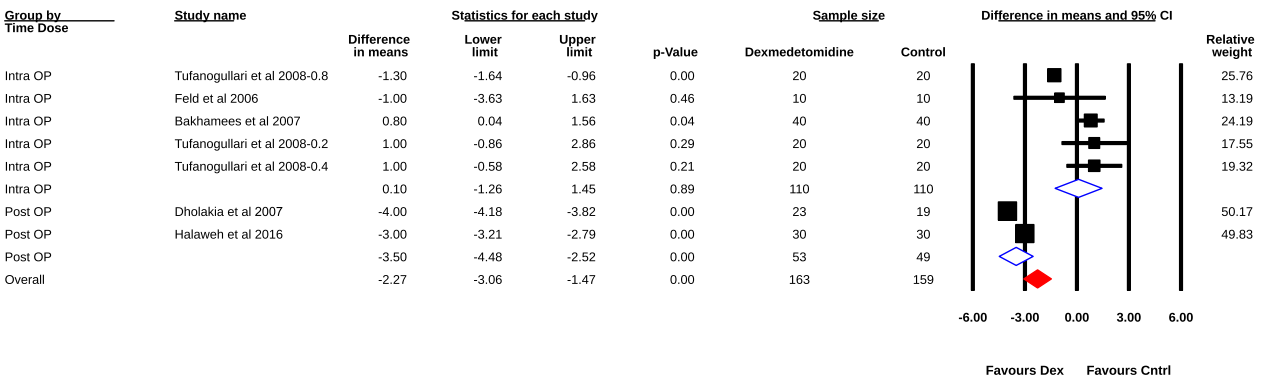
Data were available for 163 and 159 patients in dexmedetomidine and control groups, respectively, in the 7 included subgroups. Overall use of dexmedetomidine infusion revealed a decrease in pain scores of 2.27 (95% CI: 1.47–3.06) in comparison with the controls ($P < .01$). On a 10-point pain scale, this is a reduction of nearly 25%. The heterogeneity for this comparison was 88.14%. For exploration of high heterogeneity, we used a sensitivity analysis using the single study removal method. The study by Halaweh et al. contributed maximally to heterogeneity. On its removal, the heterogeneity only dropped to marginally to 95.84%. We further subdivided our results based on the time of dexmedetomidine use. Postoperative use was associated with a statistically significant drop in pain scores whereas the intraoperative administration of dexmedetomidine infusion failed to reveal a statistically significant improvement in pain scores (Fig. 5).

PONV

Five subgroups involving 130 patients each in the dexmedetomidine and control groups reported PONV values. Significant reduction in PONV was seen with the use of dexmedetomidine in comparison with the control group with the odds ratio for vomiting being .26 (95% CI: .15–.47). The heterogeneity for this comparison was 0% ($P < .01$; Fig. 6). The incidence of vomiting in dexmedetomidine was 23.08% (95% CI: 16.67–31.03) and that in control group was 48.46% (95% CI: 40.04–56.97). The number needed to treat for dexmedetomidine to prevent a single episode of PONV was 3.94. Attempts were made to subgroup the results based on the timing of dexmedetomidine use; however, due to the small number of studies reporting this variable none of the subgroup attained a statistically significant value.

Heart rate comparison

Attempts were made to compare the reported adverse events and effect on hemodynamics with the use of dexmedetomidine. Only heart rate values were consistently reported during the PACU stay. Patients receiving dexmedetomidine have a lower heart rate by 10.15 (95% CI: .15–20.16) beats/min. The heterogeneity for this comparison was 94.04% ($P = .05$, random effects; Fig. 7). The mean heart rate was 83.50 and 73.25 in the control and dexmedetomidine group, respectively, and none of the groups qualified as clinical bradycardia.



Pooled mean difference in Neumeric pain scores in the PACU (Dexmedetomidine - Control)

Fig. 5. Forest plot showing pooled mean difference for postanesthesia care unit pain scores (Dexmedetomidine group – Control group). Hollow blue diamonds represent the net effect of individual subgrouping (intraoperative and postoperative). Solid diamond at the bottom of comparison denotes the final net effect. *This parameter was statistically significant (as $P < .05$).

Evaluation of publication bias

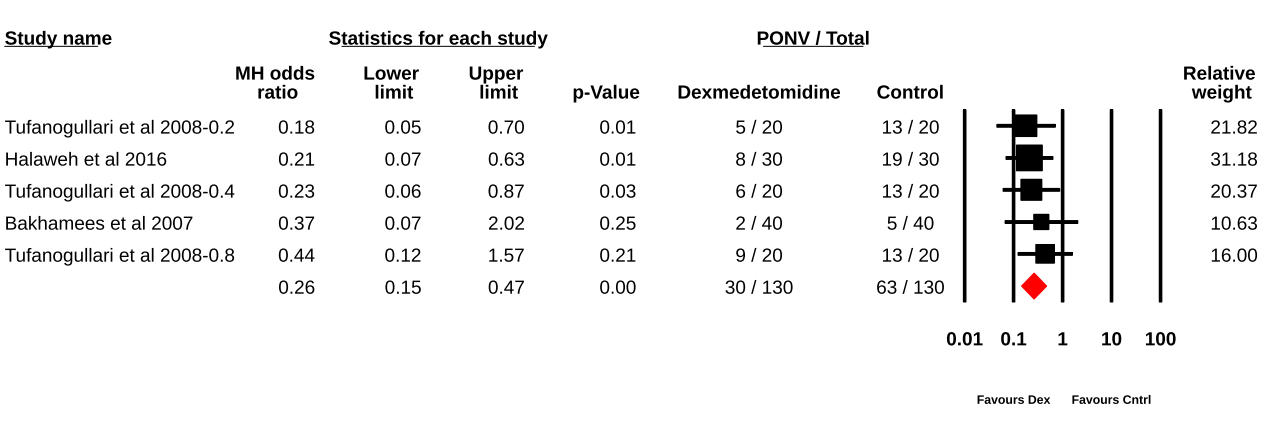
Eggers regression test was used to evaluate the publication bias for 24-hour morphine consumption test reported an X-intercept at 12.02 with 2-tailed *P* value being .006. Thus, the possibility of a publication bias cannot be ruled out. The funnel plot constructed found marginal skew in the distribution of studies around the standard difference of means for morphine consumption (Supplementary Fig. 3).

Study quality assessment

Quality assessment for bias in the included studies was carried out as per other published meta-analysis and the guidelines issued by the Cochrane Collaboration. These results are shown in Supplementary Fig. 4. We used Revman Version 5 (Cochrane Collaboration) for this evaluation and image generation.

Discussion

The present meta-analysis reports on the potential of perioperative dexmedetomidine infusion in lowering perioperative opioid requirements in morbidly obese patients undergoing bariatric surgery. Clinically significant reduction in analgesic need was seen irrespective of the time of initiation of dexmedetomidine infusion. Overall, patients who received dexmedetomidine required nearly one third less opioids in comparison with the controls. Direct results extend beyond evident reduction of opioid consumption.



MH Odds ratio for PONV in first 24 hrs (Dexmedetomidine Vs Control)

Fig. 6. Forest plot showing pooled Mantel–Haenszel odds ratio for vomiting incidence in dexmedetomidine group versus control group. Solid diamond at the bottom of comparison denotes the final net effect. The number needed to treat for the aforementioned comparison is 3.94. *This parameter was statistically significant (as $P < .05$).

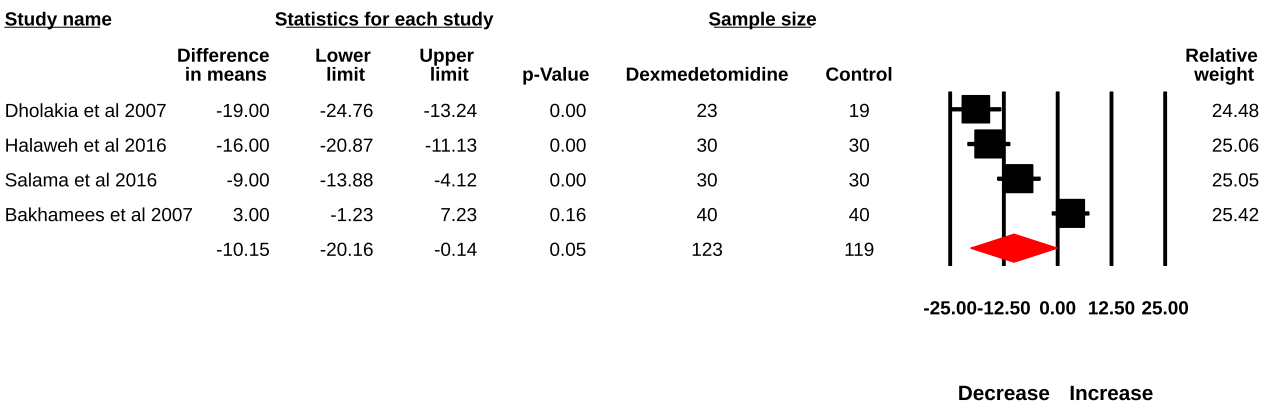


Fig. 7. Forest plot showing pooled mean difference for postanesthesia care unit (PACU) mean heart rate. (Dexmedetomidine group – Control group). Solid diamond at the bottom of comparison denotes the final net effect. *This parameter was statistically significant (as $P < .05$).

Interestingly, pain scores in the PACU also revealed a 25% reduction as well, despite consuming smaller amounts of opioids. Although dexmedetomidine does have sedation potential as well, sedation associated with dexmedetomidine preserves the respiratory drive and airway tone (unlike opioids) [25]. Thus, clinically, this not only is likely to enhance the clinical safety but also is likely to be associated with better patient satisfaction due to a demonstrably favorable analgesic profile.

Early discharge from hospital is another aspect that derives indirect benefit from better pain relief and a favorable recovery profile. This was reported by one of the included trials by Dholkia et al. where 61% patients in the dexmedetomidine group and only 26% patients in the control group met discharge criteria on postoperative day 1 [22]. Dexmedetomidine sedation is associated with conscious sedation where patients often respond to verbal instructions [26–28]. Pain-free patients with better comprehension are more likely to ambulate early as well. Keeping this aspect in mind, the recent ERAS guidelines that target early ambulation have also recommended opioid-sparing analgesia that may be contributory to this outcome [2]. However, with no direct evidence presently available, no recommendations from our side can be made on this aspect.

The meta-regression based on the dose of infusion found that increasing the dose of dexmedetomidine does not necessarily increase the analgesic advantage linearly. In fact, the regression curve (Supplementary Fig. 1) shows that increments in infusion dose decrease the difference in morphine consumption between the compared groups. The upper and lower limits of the ideal dose, however, could not be defined because too few trials are available presently. Most of the trials used a dexmedetomidine infusion dose of .4 μgm/kg/min. Even with the regression curve increasing beyond this dose, it is unlikely to add to the analgesic advantage.

Regression based on the nominal variable of timing of the dose clearly revealed that the morphine-sparing effect was higher in the infusions used in the postoperative phase in comparison with the intraoperative infusions alone (43.59 mg versus 16.26 mg, respectively). Included studies reported marked variation in the total duration of dexmedetomidine infusion used. For the postoperative infusion subgroup, barring the study by Halaweh et al. (which used a 24-hour infusion), no other study mentioned the exact duration of infusion used. Inclusion of total duration of infusion could have allowed us to calculate the total dose of dexmedetomidine used, and eventually quantification of its effect on opioid-sparing potential would also have been possible. Included studies, however, mention the use of postoperative infusions during PACU stay, which was variable in different studies. It would have been interesting to see the opioid-sparing effects on continuation of intraoperative infusion into the postoperative phase. This also was not done by any of the presently available studies, and thus no inferences other than isolated postoperative infusions being better could be drawn.

We attempted to pool the results for intraoperative opioid consumption for studies using dexmedetomidine infusion during the surgery. Although a clear reduction in intraoperative analgesic need was seen, only 2 studies reported these variables. A meta-analysis of this variable was thus inappropriate in the absence of at least 3 subgroups. Immediate PACU opioid consumption was clearly (both clinically and statistically) reduced with the use of dexmedetomidine, irrespective of the time of initiation of dexmedetomidine. In concordance with the terminal half-life being 2–3 hours [29], the analgesic benefits of intraoperative

infusions extended into the PACU period as well (Fig. 4). Analogous to this, the total 24-hour opioid use was also lower with only intraoperative infusions attributing to significant drop in opioid needs in the PACU.

Both perioperative pain and higher opioid consumption are directly related to the increased incidence of PONV. Retching and emesis in patients immediately after bariatric surgery can adversely affect patient satisfaction with the surgical experience. Thus, alleviating PONV incidence in bariatric surgery is an important aspect of perioperative care. Use of dexmedetomidine also proved to be advantageous in preventing postoperative emesis in bariatric surgery. Dexmedetomidine infusion was associated with 76% reduction in PONV in comparison with controls. One must realize this is a very clinically significant reduction without any additional antiemetic drug being used. Needless to say, newer or additional drugs would come at additional costs and with side effects [30].

The potential disadvantages of the use of dexmedetomidine as per the available literature is occasional bradycardia [8,31]. This is more common with boluses than with slow infusions. Keeping this in mind, many of the included trials also monitored patients for potential bradycardia in the postoperative period. We evaluated the available data in the included trials for associated heart rate changes (bradycardia). Only mean heart rates in PACU were consistently reported in the trials and thus a meta-analysis was feasible. Pooled mean heart rates were lower with the use of dexmedetomidine (by nearly 10 beats/min). However, the mean heart rate was 73 beats/min, and it would be inappropriate to call this bradycardia. In addition to the direct effects of dexmedetomidine, better pain control and lower incidence of PONV could have also been contributory. After bolus administration, transient hypertension is possible, followed by hypotension. We cannot draw any conclusion on blood pressure changes because of insufficient data. Yet another disadvantage that may be associated with the use of dexmedetomidine is that it has to be used as an infusion. This may make ambulation difficult (both due to mechanical hindrance and associated sedation).

Limitations

Our analysis has many limitations due to the nature of reporting by the included trials. We do answer many clinically relevant questions on dexmedetomidine, yet we also raise unanswered questions as well that need further research. Most studies reported using a slow bolus before initiating the dexmedetomidine infusion; however, the doses used were contrasting and could not be pooled for interpretations. As already stated, the infusion durations were not consistently reported and total dose response curve could not be analyzed. For infusion dose, a regression curve could not determine the upper and lower limit of the potentially beneficial infusion rate. This was due to a small number of studies evaluating various dose regimens in the included patients. With attempts to divide results based on timing of infusion (intraoperative or postoperative), not all variables reached the desired statistical significance, highlighting the need for more studies to reach stronger conclusions.

The regression test for possible publication bias reported a statistically significant value. Thus, a possibility of positive reporting always exists. However, most (5 of 6) included trials are randomized controlled trials and add to the strength of analysis. We also performed a TSA that clearly found that the number of patients for calculated pooled 24-hour morphine consumption was clearly higher than the information size required for a power of 85%. In addition, TSA also found that the cumulative Z scores were beyond the area futility wedge (Fig. 3). This translates into the fact that for the present meta-analysis a false-positive result is unlikely.

Another limitation is that the studies found significant heterogeneity in total morphine consumed. Some of this heterogeneity may be explained by the fact that different studies included different bariatric procedures. In addition, one of the major reasons for increased heterogeneity in the result is variations within the control groups used by different studies. Another challenge we faced to summarize the evidence was inability to stratify the results according to type of procedures; this, however, could not be done because documentation in the included trials was incomplete. Also, despite planning to analyze variables like adverse events (desaturations, OSA incidence) and hemodynamics (blood pressures), an analysis was not possible due to poor documentation across the trials. No trial reported any major adverse effects with the use of dexmedetomidine infusion, and thus an analysis was not possible.

Conclusion

Perioperative dexmedetomidine infusion in obese patients undergoing bariatric surgery is an attractive and safe option. Both intraoperative or postoperative infusions lead to significant opioid sparing in the early and extended postoperative recovery phase. Morbidly obese patients receiving perioperative dexmedetomidine infusions have overall better pain control and lower incidence of PONV. All the aforementioned merits come with a better hemodynamic profile (heart rate) and without any demonstrable significant adverse events.

Disclosures

The authors have no commercial associations that might be a conflict of interest in relation to this article.

Appendix

Supplementary data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.soard.2017.02.025.

References

[1] Singh PM, Panwar R, Borle A, et al. Efficiency and safety effects of applying ERAS protocols to bariatric surgery: a systematic review with meta-analysis and trial sequential analysis of evidence. Obes Surg 2017;27(2):489–501.

[2] Thorell A, MacCormick AD, Awad S, et al. Guidelines for Perioperative Care in Bariatric Surgery: Enhanced Recovery After Surgery (ERAS) Society Recommendations. World J Surg 2016;40 (9):2065–83.

[3] Alvarez A, Singh PM, Sinha AC. Postoperative analgesia in morbid obesity. Obes Surg 2014;24(4):652–9.

[4] Singh PM, Borle A, Shah D, et al. Optimizing prophylactic CPAP in patients without obstructive sleep apnoea for high-risk abdominal surgeries: a meta-regression analysis. Lung 2016;194(2):201–17.

[5] Chung F, Liao P, Elsaid H, Shapiro CM, Kang W. Factors associated with postoperative exacerbation of sleep-disordered breathing. Anesthesiology 2014;120(2):299–311.

[6] Lam KK, Kunder S, Wong J, Doufas AG, Chung F. Obstructive sleep apnea, pain, and opioids: is the riddle solved? Curr Opin Anaesthesiol 2016;29(1):134–40

[7] Turan A, You J, Egan C, et al. Chronic intermittent hypoxia is independently associated with reduced postoperative opioid consumption in bariatric patients suffering from sleep-disordered breathing. PLoS One 2015;10(5):e0127809.

[8] Kaur M, Singh PM. Current role of dexmedetomidine in clinical anesthesia and intensive care. Anesth Essays Res 2011;5(2):128–33.

[9] Ankichetty S, Wong J, Chung F. A systematic review of the effects of sedatives and anesthetics in patients with obstructive sleep apnea. J Anaesthesiol Clin Pharmacol 2011;27(4):447–58.

[10] Sudré ECM, Salvador M do C, Bruno GE, et al. Remifentanil versus dexmedetomidine as coadjutants of standardized anesthetic technique in morbidly obese patients [in Portuguese]. Revista Brasileira de Anestesiologia 2004;54(2):178–89.

[11] Altiparmak B, Çeleb N. Dexmedetomidine versus remifentanil sedation for obese patients undergoing cataract surgery. Int J Clin Exp Med 2016;9:14728–33.

[12] Cortínez LI, Anderson BJ, Holford NHG, et al. Dexmedetomidine pharmacokinetics in the obese. Eur J Clin Pharmacol 2015;71 (12):1501–8.

[13] Piccinini Filho L, Mathias da ST, Malheiros CA, Gregori WM de, Guaratini ÁA, Vieira JE. Dexmedetomidine in morbid obese patients undergoing gastroplasty: cardiovascular stability and consumption of intravenous anesthetics. A retrospective study [in Portuguese]. Revista Brasileira de Anestesiologia 2006;56(2):109–18.

[14] Moher D, Shamseer L, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 2015;4:1.

[15] Singh PM, Borle A, Trikha A, Michos L, Sinha A, Goudra B. Role of periarticular liposomal bupivacaine infiltration in patients undergoing total knee arthroplasty-a meta-analysis of comparative trials. J Arthroplasty 2016;32(2):675–88.

[16] Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011;343:d5928.

[17] Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol 2005;5:13.

[18] Singh PM, Arora S, Borle A, Varma P, Trikha A, Goudra BG. Evaluation of etomidate for seizure duration in electroconvulsive therapy: a systematic review and meta-analysis. J ECT 2015;31 (4):213–25.

[19] Tufanogullari B, White PF, Peixoto MP, et al. Dexmedetomidine infusion during laparoscopic bariatric surgery: the effect on recovery outcome variables. Anesth Analg 2008;106(6):1741–8.

[20] Abu-Halaweh S, Obeidat F, Absalom AR, et al. Dexmedetomidine versus morphine infusion following laparoscopic bariatric surgery: effect on supplemental narcotic requirement during the first 24 h. Surg Endosc 2016;30(8):3368–74.

[21] 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 Anaesthesiol 2007;19(3):537–51.

[22] Dholakia C, Beverstein G, Garren M, Nemergut C, Boncyk J, Gould JC. The impact of perioperative dexmedetomidine infusion on postoperative narcotic use and duration of stay after laparoscopic bariatric surgery. J Gastrointest Surg 2007;11(11):1556–9.

[23] Salama AK, Abdallah NM. Multimodal analgesia with pregabalin and dexmedetomidine in morbidly obese patients undergoing laparoscopic sleeve gastrectomy: a prospective randomized double blind placebo controlled study. Egyptian Journal of Anaesthesia 2016;32 (3):293–8.

[24] Feld JM, Hoffman WE, Stechert MM, Hoffman IW, Ananda RC. Fentanyl or dexmedetomidine combined with desflurane for bariatric surgery. J Clin Anesth 2006;18(1):24–8.

[25] Tobias JD, Leder M. Procedural sedation: A review of sedative agents, monitoring, and management of complications. Saudi J Anaesth 2011;5(4):395–410.

[26] Manne G, Upadhyay M, Swadia V. Effects of low dose dexmedetomidine infusion on haemodynamic stress response, sedation and post-operative analgesia requirement in patients undergoing laparoscopic cholecystectomy. Indian J Anaesth 2014;58(6):726c31.

[27] Ard JL, Bekker AY, Doyle WK. Dexmedetomidine in awake craniotomy: a technical note. Surg Neurol 2005;63(2):114–7.

[28] Kallapur BG, Bhosale R. Use of dexmedetomidine infusion in anaesthesia for awake craniotomy. Indian J Anaesth 2012;56 (4):413–5.

[29] Venn RM, Karol MD, Grounds RM. Pharmacokinetics of dexmedetomidine infusions for sedation of postoperative patients requiring intensive care†. Br J Anaesth 2002;88(5):669–75.

[30] Singh PM, Borle A, Rewari V, et al. Aprepitant for postoperative nausea and vomiting: a systematic review and meta-analysis. Postgrad Med J 2016;92(1084):87–98.

[31] Mohammed A, Maheshwari A, Manns S. Outcomes of obese patients on dexmedetomidine in the critical care. Chest 2016;150 (4S):346A.