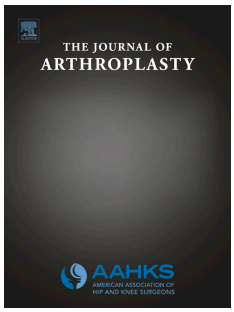
Accepted Manuscript



Intranasal low-dose dexmedetomidine reduces postoperative opioid requirement in patients undergoing hip arthroplasty under general anesthesia

Dr Panu Uusalo, M.D., Dr Henrik Jätinvuori, M.D., Mrs. Eliisa Löyttyniemi, M.Sc, Dr. Jussi Kosola, M.D., PhD, Teijo I. Saari, M.D., PhD, Prof.

PII: S0883-5403(18)31238-5

DOI: https://doi.org/10.1016/j.arth.2018.12.036

Reference: YARTH 56973

To appear in: *The Journal of Arthroplasty*

Received Date: 12 November 2018

Revised Date: 12 December 2018

Accepted Date: 28 December 2018

Please cite this article as: Uusalo P, Jätinvuori H, Löyttyniemi E, Kosola J, Saari TI, Intranasal low-dose dexmedetomidine reduces postoperative opioid requirement in patients undergoing hip arthroplasty under general anesthesia, *The Journal of Arthroplasty* (2019), doi: https://doi.org/10.1016/j.arth.2018.12.036.

Intranasal low-dose dexmedetomidine reduces postoperative opioid requirement in patients undergoing hip arthroplasty under general anesthesia

Dr. Panu Uusalo, M.D.[1, 2]*

Dr. Henrik Jätinvuori, M.D. [1,2]

Mrs. Eliisa Löyttyniemi, M.Sc [3]

Dr. Jussi Kosola M.D., PhD [4]

Prof. Teijo I. Saari M.D., PhD [1,2]

[1]Department of Anaesthesiology and Intensive Care, University of Turku, P.O. Box 51 Kiinamyllynkatu 4-8, FI-20521 Turku, Finland

[2]Division of Perioperative Services, Intensive Care and Pain Medicine, Turku University Hospital, P.O. Box 51 Kiinamyllynkatu 4-8, FI-20521 Turku, Finland

[3]Department of Biostatistics, University of Turku, Kiinamyllynkatu 10 FI-20520 Turku, Finland

[4]Department of Orthopedics and Traumatology, Helsinki University Hospital, Finland, Topeliuksenkatu 5, P.O. Box 266 FI-00290 Helsinki, Finland

*__Corresponding author:__ Dr. Panu Uusalo, Department of Anaesthesiology and Intensive Care, University of Turku, P.O. Box 51 (Kiinamyllynkatu 4-8), FI-20521 Turku, Finland, e-mail: pijuus@utu.fi, tel: +358 2 313 0000, Orcid-ID 0000-0001-5120-8854

Intranasal low-dose dexmedetomidine reduces postoperative opioid requirement in patients undergoing hip arthroplasty under general anesthesia

Abstract

Background: Patients undergoing total hip arthroplasty (THA) need substantial amount of opioids for postoperative pain management, which necessitates opioid sparing modalities. Dexmedetomidine is a novel alpha-2-adrenoceptor-activating drug for procedural sedation. In addition to its sedative effect, dexmedetomidine has analgesic and antiemetic effects. We evaluated retrospectively the effect of intraoperatively administered intranasal low-dose dexmedetomidine on postoperative opioid requirement in patients undergoing THA.

Methods: We included 120 patients with ASA status 1-2, age between 35 and 80 years and scheduled for unilateral primary THA under general anesthesia with total intravenous anesthesia. Half of the patients received 50 µg of intranasal dexmedetomidine after anesthesia induction, while the rest were treated conventionally. Postoperative opioid requirements were calculated as morphine equivalent doses for both groups. The impact of intranasal dexmedetomidine on postoperative hemodynamics and length of stay was evaluated.

Results: The cumulative postoperative opioid requirement was significantly reduced in the dexmedetomidine group compared to the control group (26.3 mg, 95% CI 15.6 to 36.4, $P < 0.001$). The cumulative dose was significantly different between the groups already at 12, 24 and 36 h postoperatively ($p = 0.01$; $p = 0.001$; $p < 0.001$). Dexmedetomidine group had lower mean arterial pressure in post anesthesia care unit compared to control group ($p = 0.01$). There was no difference in post anesthesia care unit stay or postoperative length of stay between the two groups. ($p = 0.47$; $p = 0.10$, respectively)

Conclusion: Compared to the control group, intraoperative use of intranasal low-dose dexmedetomidine decreases opioid consumption and sympathetic response during acute postoperative period in patients undergoing THA.

Keywords: Anesthesia, Pain, Opioid crisis, Hip Arthroplasty

Background

Total hip arthroplasty (THA) causes severe pain and perioperative pain therapy during THA is challenging to manage. (1) It has been shown that efficient pain management of THA facilitates early mobilization, improves postoperative outcome, and reduces the length of hospital stay (LOS) (2). While THA is one of the most common orthopedic procedures, significant amount of the patients – 7 % - 23 % - still exhibit long-term postoperative pain (3) or highly disabling postoperative chronic pain syndrome, which both might be attenuated with proper early postoperative pain management (4-5).

Opioids remain a primary modality for postoperative acute pain management (6-7), and most patients undergoing THA need substantial amount of opioids for postoperative analgesia. (8) Surgery is one of the main causes for chronic pain and postoperative opioid use predisposes patients to a significant risk for opioid dependence or abuse. Opioid overdoses appear to occur more frequently in medical opioid users than in young nonmedical users. (7, 9) Thus there is a strong emphasis for opioid sparing pain therapies. (10)

Dexmedetomidine is a novel alpha-2-adrenoceptor-activating sedative drug, which also has analgesic and antiemetic effects. It has been used widely as an anesthesia adjunct and several studies have shown the opioid sparing effect of intraoperatively administered dexmedetomidine, even at low doses. (11-13) Compared to traditional anesthetic agents, dexmedetomidine has minimal effects on respiration. A recent meta-analysis showed that perioperative dexmedetomidine also reduces postoperative delirium, which is common in elderly population. (14) Previous studies in patients undergoing THA further show that perioperative administration of intravenous dexmedetomidine reduces postoperative pain scores and has cardioprotective properties. (15-16)

We evaluated retrospectively the effect of intraoperative intranasal (IN) low-dose (50 µg) dexmedetomidine on postoperative opioid requirement in patients undergoing THA under general anesthesia. The purpose of our study was to illustrate whether the above-mentioned dose is sufficient to reduce post-operative opioid consumption. There is no previous study of the effect of IN dexmedetomidine to the need for post-operative analgesics in patients undergoing THA. Our hypothesis was that the use of IN dexmedetomidine reduces postoperative opioid consumption in patients undergoing THA under general anesthesia even at low doses (0.5-1,0 µg/kg).

Methods

Ethics

The study protocol was approved by the Hospital District of Southwest Finland. Informed consent was not sought for this retrospective register-based study.

Patient population

We collected and included in the study retrospectively 120 consecutive patients with ASA status 1-2, age between 35 and 80 years, weight between 50 and 100 kg and scheduled for primary unilateral hip arthroplasty under total intravenous anesthesia in Turku University Hospital, Salo Unit, South-West Finland between March 2017 and February 2018.

We excluded patients with prescribed preoperative opioids, patients receiving other adjuvant analgesics such as ketamine, gabapentinoids, clonidine or tricyclic antidepressants pre-, intra- or postoperatively, or patients with clinically significant abnormalities in preoperative medical examination (eg. liver or kidney failure), ECG or laboratory values. Furthermore patients with unexpected perioperative bleeding over 1000 ml and patients undergoing spinal or inhalational anesthesia.

Eligible patients were identified and patient data were retrieved from the anesthesia reports and patient database of the hospital. Sixty consecutive patients who met the inclusion criteria and did not receive any dexmedetomidine were identified between March and June 2017 (control group; CTRL). Sixty consecutive patients who met the inclusion criteria and received intraoperatively 50 µg of IN dexmedetomidine were identified between October 2017 and February 2018 (dexmedetomidine group; DEX). All patients received the intervention during this period. In July and August 2017 operation room was closed due vacations. During September and October 2017 the use of dexmedetomidine and intranasal device was implemented in the perioperative care of patients undergoing THA..

Surgical technique

The THA procedure were done per routine via posterolateral or anterolateral (modified Hardinge) approach. Two surgeons took care of the majority of the cases, and altogether four surgeons were involved. All patients received an intra- and periarticular LIA-block with 145 ml of 0,125 % levobupivacaine and 5 ml of epinephrine 0.01 %. Blood loss was measured intraoperatively by taking account the amount of the blood in suction bottles and the weighed swabs.

Anesthetic management

All patients received preoperatively 1000 mg of paracetamol orally. General anesthesia was maintained with propofol and remifentanil target controlled infusions (TCI). Propofol TCI was administered with Schnider effect-site model and remifentanil with Minto effect-site model. We monitored the depth of anesthesia with entropy (GE B850 Monitor Entropy Module, Helsinki, Finland) and our aim was to keep the target state entropy (SE) between 35 and 45. Mean arterial pressure (MAP) target was between 65 and 75 mmHg depending on the patients age and disease history. In DEX group 50 µg of IN dexmedetomidine was administered to all patients within 30 min of anesthesia induction.

All patients received intraoperatively 4 mg of ondansetron and 4 mg of betamethasone for prophylaxis of postoperative nausea and vomiting (PONV). If patients received further antiemetics postoperatively, it was considered as PONV. In the end of surgery intravenous 30 mg of ketorolac was given to the patients who did not have any contraindications for the use of non-steroidal anti-inflammatory drugs. Anesthesia was managed by two senior anesthesia consultants.

Pain management

In postoperative anesthesia care unit (PACU), pain was treated with intravenous fentanyl and intravenous oxycodone. After stopping administration of remifentanil in the end of surgery patients received 100 ug of intravenous fentanyl. In PACU patients received 0,03-0,05 mg/kg of intravenous oxycodone if there was moderate or intense pain (Visual Analog Scale; VAS > 3). The dose is repeated after 15 minutes until VAS score is 3 or under. In the ward patients received daily 3000 mg of paracetamol for postoperative pain. Stronger pain (VAS > 3) was managed with 0,05-0,1 mg/kg of oral oxycodone and from the first postoperative day onwards patients without contraindications for non-steroidal anti-inflammatory drugs (NSAID) received oral naproxen/esomeprazol 500/20 mg twice a day.

Pharmacodynamic measurements

Heart rate and mean arterial blood pressure were recorded preoperatively, at the time of incision, one hour after the anesthesia induction, at the end of surgery and in the postoperative anesthesia care unit (PACU) one hour after surgery. Entropy (SE) and effect site TCI target concentrations were collected at the time of incision, one hour after the anesthesia induction, and at the time of wound closure.

PACU time and time to discharge

PACU time and time to the discharge were defined as the period of time between the end of surgery and the time of discharge of the patient from PACU and from the orthopedic inpatient ward. Clock times were obtained from the hospital's patient information system.

Statistics

The primary outcome variable was the amount of opioids administered to the patients (morphine equivalent dose; MED) within 2, 12, 24, 36 and 48 h after the end of surgery. (17) A 15 % reduction in opioid consumption was considered clinically significant. Secondary outcomes were the MAP and HR values recorded during the perioperative period. The sample size was based on previous experience in similar retrospective studies. (18-19) The Shapiro-Wilks test ($P > 0.05$) was used to assess normality assumptions. Student´s t-test was used to compare the groups with normally distributed data, and Wilcoxon's rank sum test was used to test non-normally distributed data. Nominal data were tested using chi-square analysis. $P < 0.05$ (two-tailed) was considered statistically significant. A subgroup analysis was performed with Kruskal-Wallis test and Wilcoxon all pair between patients receiving and not receiving NSAID therapy. The results are expressed as mean values with standard deviations (SD), and as medians with interquartile ranges (IQR) when the normality assumption was not met. The analyses were performed with JMP Pro 13.0 and SAS®System programs, version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Sixty consecutive patients were included in both study groups (DEX and CTRL) (Supplemental Figure 1). Demographic data and patient characteristics are shown in Table 1. There were no statistically significant differences in the patient characteristics between the two groups. The median (IQR) IN dexmedetomidine dose was 0.66 (0.58-0.72) µg/kg.

Significantly lower opioid amount was needed postoperatively in the DEX group compared to the CTRL group. The cumulative postoperative opioid requirement was (mean and SD) 152 (29) mg in the DEX group and 178 (40) mg in the CTRL group (difference 26.3 mg, 95% CI 15.6 to 36.4, $P < 0.001$). Differences in the postoperative opioid requirements were statistically significant already at 12, 24 and 36 h after the end of surgery ($p = 0.01$; $p = 0.001$; $p < 0.001$). In more detailed analysis, the greatest increase in the cumulative dose difference occurred between 36 and 48 hours (Table 2 and Figure 1).

The heart rate of the DEX group was lower compared to the CTRL group in PACU ($P = 0.008$) (Figure 2). There was higher intraoperative mean arterial pressure in the DEX group compared to the CTRL group, but patients in the DEX group received significantly more ephedrine intraoperatively ($p = 0.01$). The mean arterial pressure of the DEX group was lower compared the CTRL group in PACU ($P < 0.001$). The difference in intraoperative MAP did not have an effect on intraoperative bleeding and there was no statistically significant difference in the intraoperative blood loss (Table 3).

More patients received NSAID therapy in CTRL group ($n = 43$) compared to the DEX group ($n = 40$). In a subgroup analysis of patients receiving NSAID therapy there was higher opioid requirement 0-48 h postoperatively in the CTRL group compared to the DEX group ($p = 0.02$). Similarly in subgroup analysis of patients that were not receiving NSAID therapy there was higher opioid requirement 0-48 h postoperatively in the CTRL group compared to the DEX group ($p < 0.001$). (Supplementary Table 1)

There was no statistically significant differences in PACU stay, LOS or incidence of PONV between two groups. Median (IQR) PACU stay was 89 (75-102) min in DEX group and 87 (70-101) min in CTR group (p = 0.47). Median (IQR) LOS was 49 (48-52) h in DEX group and 51 (48-71) h in CTRL group hours (p = 0.07). Eight patients had postoperative nausea and vomiting in CTRL group compared to seven patients in DEX group (p = 0.78).

Intraoperative target concentrations of propofol and remifentanil were similar in both groups, and the intraoperative entropy (SE) levels were not affected by dexmedetomidine dosing (Figure 3, Figure 4 and Supplementary Table 2).

In the DEX and CTR groups 23 and 29 patients underwent anterolateral approach, whereas 37 and 31 patients underwent posterolateral approach, respectively (p=0.27). There was no association on postoperative 0-48 h opioid consumption between anterolateral and posterolateral surgical approaches: (median 150 vs 153 mg in the DEX group, respectively; p=0.72, and 178 vs 178 mg in the CTR group, respectively; p=0.99).

Adverse events

There were no adverse events recorded.

Discussion

Our results demonstrate that intraoperative use of intranasal low-dose dexmedetomidine reduces opioid requirement in patients undergoing THA. The cumulative dose was significantly different between the groups already at 12, 24 and 36 h postoperatively. Previously, adjunct use of intravenous dexmedetomidine has shown to reduce postoperative pain in other orthopedics procedures (20-21), but IN dexmedetomidine has been not been previously studied in this patient population. According to earlier studies on the effect of other adjuvants on postoperative opioid consumption in patients undergoing THA, the clinically important morphine-sparing effect has been considered to be 10-15 mg over intravenous morphine 48 h postoperatively (Kardash 2008 Anesth Analg), suggesting that our findings are clinically meaningful.

The rationale for the use of extravascular dexmedetomidine instead of intravenous administration route is to overcome the adverse hemodynamic effects after intravenous dosing. (24-25) IN administration is feasible during anesthesia and allows bolus administration of the drug. Perioperatively administered IN dexmedetomidine as an adjunct has been mostly studied in pediatric population and there are only few studies on adult patients in this regard. In these previous studies, used dose of IN dexmedetomidine was higher (i.e. 1,5-2,0 µg/kg) than in our study. (26-28)

Dexmedetomidine has a biphasic effect on blood pressure, since it decreases heart rate and cardiac output by centrally mediated sympatholysis, but in the same time increases vascular resistance by peripherally mediated vasoconstriction (29). Previous studies show that sympatholysis is less evident and clinically insignificant after extravascular dosing of dexmedetomidine compared to intravenous dosing. (24-25) We observed lower postoperative HR and MAP in DEX-group, but intraoperative MAP was higher in DEX group compared to CTRL group. Since 1,5 µg/kg of IN dexmedetomidine caused transient

elevation in MAP of healthy volunteers, but dosages of 1 µg/kg did not, (11, 24) it is most likely that higher intraoperative MAP of DEX group was related to higher amount of intraoperatively administered ephedrine. Difference in intraoperative MAP did not have an effect on intraoperative bleeding between the groups. Patients in DEX group had lower HR and MAP in PACU, but compared to the CTR group there was no difference in PACU time, hemodynamic parameters remained clinically acceptable and no treatments were needed. Together with analgesic effect sympatolythic properties of dexmedetomidine may be beneficial for patients with ischaemic heart disease. (15)

Use of dexmedetomidine has been studied in critically ill patients and there is evidence that dexmedetomidine decreases postoperative opioid consumption and delirium in sick and elderly patient population. In the same time use of higher dexmedetomidine dosages have been well tolerated in elderly and sick population. (14-16) We wanted to use healthy ASA 1-2 patients with weight of 50 to 100 kg in order to avoid bias related to comorbidity and in order to maintain dose of intranasal dexmedetomidine between 0,5 and 1,0 ug/kg.

THA can be managed with general anesthesia, regional anesthesia or combination of both. There has been comparative studies on different anesthesia methods for THA. Harsten et al (2015) compared 120 patients who underwent hip arthroplasty under regional or general anesthesia. In acute postoperative setting patients treated with regional anesthesia had lower pain scores at the beginning, but higher six hours after surgery compared with patients who receive general anesthesia. Patients were satisfied with their anesthetic treatment in both groups, but those with regional anesthesia were more likely to choose for general anesthesia if operated again. (30) A large multi-center study Greimel et al (2017) showed that THA with regional anesthesia alone or combined with general anesthesia has beneficial effect on the postoperative pain scores, analgesic use, functional parameters, and patient satisfaction compared to the general anesthesia alone, but the differences between the groups were relatively small. (2) Spinal anesthesia may be preferable choice for elderly

people as general anesthesia carries a risk for postoperative cognitive dysfunction (29), but many contraindications preclude regional anesthesia in these patients (32). All our patients received total intravenous anesthesia (TIVA), which has been associated with excellent recovery in daycare surgery. (33) However the use of remifentanil in TIVA may carry a risk for hyperalgesia (34), which favours multimodal management of anesthesia and analgesia in patients undergoing THA under TIVA (35). Since intraoperative use of intravenous dexmedetomidine has been studied in other patient populations undergoing general and spinal anesthesia, it could be postulated that the effects seen in our study might be similar with other anesthetic protocols with intranasal use of dexmedetomidine.

Intra- and periarticular injection of local anesthetics has become common practice in patients undergoing THA. All patients in our study received a high volume LIA with levobupivacaine and epinephrine. Intraoperative infiltration of high-volume levobupivacaine (LIA) has been shown to reduce postoperative opioid consumption compared to placebo in patients undergoing THA (36), but there is still debate whether LIA alone reduces postoperative opioid consumption (37). Probably adding ketorolac to LIA improves its effect. (38) There is also evidence that adding dexmedetomidine to surgical local infiltration anesthesia increases the analgesic effect of local anesthetic. (39-40) However there is no studies of joint arthroplasties on this regard.

All patients received paracetamol for premedication and most of the patients in both groups received intraoperatively ketorolac for postoperative pain. Use of ketorolac has been shown to reduce postoperative pain compared to placebo in patients undergoing THA (41). However NSAIDs may be held in the perioperative period due to concern for increased bleeding or decreased urinary output. We found a statistically significant difference in the postoperative opioid consumption between both groups when NSAID use was taken into account. However, there was only 17 and 20 patients in CTRL and DEX groups,

respectively, who did not receive NSAIDs, which makes statistical comparison of postoperative opioid consumption between these subgroups weak.

Use of glucocorticoids as an adjunct to general anesthesia in patients undergoing THA has been studied. A meta-analysis demonstrated that intravenous glucocorticoids can alleviate pain, the incidence of PONV and decrease the morphine consumption. (42) A recent study revealed that use of dexamethasone in arthroplasty procedures intraoperatively followed by another bolus 24 h after surgery reduced postoperative pain scores and morphine consumption whereas patient satisfaction was 6 weeks postoperatively higher compared to placebo group. (43) All patients in our study received betamethasone, suggesting that dexmedetomidine caused the difference in postoperative opioid consumption between the two groups despite the concomitant administration of betamethasone.

Dexmedetomidine has an anesthetic sparing effect, which may also be reflected in entropy. (20, 24) We used relatively low dose of IN dexmedetomidine in our study, and it did not have statistically significant effect on intraoperative TCI target or entropy levels. However, the use of intraoperative vasoactive medication was higher in DEX group, which might suggest that intraoperative administration of propofol and remifentanil could have been slightly lower after administration of dexmedetomidine.

One of the postoperative major concerns after THA is urinary bladder retention, which can be caused by spinal anesthesia as well as opioids. (44) Thus multimodal anesthesia regimens may reduce the incidence of urinary bladder retention in arthroplasty procedures (45). Postoperative urinary bladder retention was not measured in this study, but it would be interesting to evaluate whether use of dexmedetomidine as adjunct in anesthesia of THA has effect on postoperative urinary bladder function in patients undergoing THA.

Our study has obvious limitations. Retrospective design of this study could have affected the results, even when only consecutive patients were collected in order to avoid any selection bias. Dexmedetomidine dose used in our study was relatively small, which may have limited effects especially on secondary outcomes. Patients receiving IN dexmedetomidine were in a supine position, which could have affected drug absorption. However, in a recent pharmacokinetic study in anesthetized pediatric patients undergoing heart surgery and receiving 1 to 2 µg/kg dose of intranasal dexmedetomidine in supine position were shown to have a relative bioavailaibility of 84 %.

Despite intranasal administration route of dexmedetomidine is off-label, its use is increasing as premedication and intraoperative adjunct. Reducing postoperative opioid consumption is a common interest of all caretakers and understanding multimodal analgesia and opioid sparing techniques will help physicians to improve postoperative pain management.

Conclusion

In conclusion, IN dexmedetomidine administered as low doses as 0,5-1,0 µg/kg decreases postoperative opioid consumption in patients undergoing THA. Our results encourage to further study the dose-response of IN dexmedetomidine on postoperative analgesia in patients undergoing THA under general anesthesia.

Ethics

This was a retrospective register-based study that did not according to Finnish law require Ethics Committee approval.

Funding

This work was supported by governmental research grant number 13821 from the Hospital District of South-West Finland, Finland.

Disclosures

This was a non-commercial, investigator-initiated study, and it has not received any funding from the industry. T. Saari and P. Uusalo have received honoraria for speaking at symposia organized by Orion Pharma. The other authors declare that they have no conflicts of interest.

Acknowledgements

The late professor Riku Aantaa is greatly acknowledged for giving many insights and inspiring the authors for dexmedetomidine studies. Dr. Matti Helkiö is acknowledged for his gratuitous assistance to initiate this study in Salo Secondary Hospital, South-West Finland.

References

1. Gerbershagen, HJ, Pogatzki-Zahn, E, Aduckathil, S et al. Procedure-specific risk factor analysis for the development of severe postoperative pain. Anesthesiology 2014;120:1237-1245.

2. Greimel, F, Maderbacher, G, Zeman, F et al. No Clinical Difference Comparing General, Regional, and Combination Anesthesia in Hip Arthroplasty: A Multicenter Cohort-Study Regarding Perioperative Pain Management and Patient Satisfaction. J Arthroplasty 2017;32:3429-3433.

3. Beswick, AD, Wylde, V, Gooberman-Hill, R et al. What proportion of patients report long-term pain after total hip or knee replacement for osteoarthritis? A systematic review of prospective studies in unselected patients. BMJ Open 2012;2:e000435.

4. Golladay GJ, Balch KR, Dalury DF et al. Oral Multimodal Analgesia for Total Joint Arthroplasty. J Arthroplasty 2017;32:69-73.

5. Goesling J, Moser SE, Zaidi B, Hassett AL, Hilliard P, Hallstrom B, Clauw DJ, Brummett CM. Trends and predictors of opioid use after total knee and total hip arthroplasty. Pain. 2016;157:1259-65.

6. Wunsch H, Wijeysundera DN, Passarella MA, Neuman MD. Opioids Prescribed After Low-Risk Surgical Procedures in the United States, 2004-2012. JAMA. 2016 Apr 19;315(15):1654-7.

7. Hah JM, Bateman BT, Ratliff J, Curtin C, Sun E. Chronic Opioid Use After Surgery: Implications for Perioperative Management in the Face of the Opioid Epidemic. Anesth Analg. 2017 Nov;125(5):1733-1740.

8. Gaffney, CJ, Pelt, CE, Gililland, JM et al. Perioperative Pain Management in Hip and Knee Arthroplasty. Orthop Clin North Am 2017;48:407-419.

9. Higgins, C, Smith, BH, Matthews, K. Incidence of iatrogenic opioid dependence or abuse in patients with pain who were exposed to opioid analgesic therapy: a systematic review and meta-analysis. Br J Anaesth 2018;120:1335-1344.

10. Kumar, K, Kirksey, MA, Duong, S et al. A Review of Opioid-Sparing Modalities in Perioperative Pain Management: Methods to Decrease Opioid Use Postoperatively. Anesth Analg 2017;125:1749-1760.

11. Yuen, VM, Irwin, MG, Hui, TW et al. A double-blind, crossover assessment of the sedative and analgesic effects of intranasal dexmedetomidine. Anesth Analg 2007;105:374-380.

12. Peng, K, Liu, HY, Wu, SR et al. Effects of Combining Dexmedetomidine and Opioids for Postoperative Intravenous Patient-controlled Analgesia: A Systematic Review and Meta-analysis. Clin J Pain 2015;31:1097-1104.

13. Schnabel, A, Meyer-Frießem, CH, Reichl, SU et al. Is intraoperative dexmedetomidine a new option for postoperative pain treatment? A meta-analysis of randomized controlled trials. Pain 2013;154:1140-1149.

14. Duan, X, Coburn, M, Rossaint, R et al. Efficacy of perioperative dexmedetomidine on postoperative delirium: systematic review and meta-analysis with trial sequential analysis of randomised controlled trials. Br J Anaesth 2018;121:384-397.

15. Xu, L, Hu, Z, Shen, J et al. Does dexmedetomidine have a cardiac protective effect during non-cardiac surgery? A randomised controlled trial. Clin Exp Pharmacol Physiol 2014;41:879-883.

16. Wu, ZL, Zhou, ZF, Xu, LX et al. Effect of dexmedetomidine on patient-controlled intravenous analgesia with fentanyl in elderly patients after total hip replacement. Nan Fang Yi Ke Da Xue Xue Bao 2011;31:701-704.

17. McPherson ML. Introduction to opioid conversion calculations. In: Demystifying Opioid Conversion Calculations: A Guide for Effective Dosing. Bethesda, MD: American Society of Health-System Pharmacists; 2010:1-15.

18. Ökmen, K, Ökmen, BM. The efficacy of serratus anterior plane block in analgesia for thoracotomy: a retrospective study. J Anesth 2017;31:579-585.

19. Su, S, Ren, C, Zhang, H et al. The Opioid-Sparing Effect of Perioperative Dexmedetomidine Plus Sufentanil Infusion during Neurosurgery: A Retrospective Study. Front Pharmacol 2016;7:407.17.

20. Kim, HJ, Shin, WJ, Park, S et al. The sedative effects of the intranasal administration of dexmedetomidine in children undergoing surgeries compared to other sedation methods: A systematic review and meta-analysis. J Clin Anesth 2017;38:33-39.

21. Shin, HJ, Do, SH, Lee, JS et al. Comparison of Intraoperative Sedation With Dexmedetomidine Versus Propofol on Acute Postoperative Pain in Total Knee Arthroplasty Under Spinal Anesthesia: A Randomized Trial. Anesth Analg 2018 [Epub ahead of print].

22. Kardash KJ, Sarrazin F, Tessler MJ et al. Single-dose dexamethasone reduces dynamic pain after total hip arthroplasty. Anesth Analg. 2008;106:1253-1257.

23. Martinez V, Cymerman A, Ben Ammar S et al. The analgesic efficiency of combined pregabalin and ketamine for total hip arthroplasty: a randomised, double-blind, controlled study. Anaesthesia. 2014;69:46-52.

24. Iirola, T, Vilo, S, Manner, T et al. Bioavailability of dexmedetomidine after intranasal administration. Eur J Clin Pharmacol 2011;67:825-831.

25. Uusalo, P, Al-Ramahi, D, Tilli, I et al. Subcutaneously administered dexmedetomidine is efficiently absorbed and is associated with attenuated cardiovascular effects in healthy volunteers. Eur J Clin Pharmacol 2018; ;74(8):1047-1054.

26. Nooh, N, Sheta, SA, Abdullah, WA et al. Intranasal atomized dexmedetomidine for sedation during third molar extraction. Int J Oral Maxillofac Surg 2013;42:857-862.

27. Lu, C, Zhang, LM, Zhang, Y et al. Intranasal Dexmedetomidine as a Sedative Premedication for Patients Undergoing Suspension Laryngoscopy: A Randomized Double-Blind Study. PLoS One 2016;11:e0154192.

28. Qiao, H, Chen, J, Li, W et al. Intranasal atomised dexmedetomidine optimises surgical field visualisation with decreased blood loss during endoscopic sinus surgery: a randomized study. Rhinology 2016;54:38-44.

29. Ebert TJ, Hall JE, Barney JA et al. Anesthesiology. The effects of increasing plasma concentrations of dexmedetomidine in humans. 2000;93(2):382-94.

30. Harsten, A, Kehlet, H, Ljung, P et al. Total intravenous general anaesthesia vs. spinal anaesthesia for total hip arthroplasty: a randomised, controlled trial. Acta Anaesthesiol Scand 2015;59:298-309.

31. Schulte, PJ, Roberts, RO, Knopman, DS et al. Association between exposure to anaesthesia and surgery and long-term cognitive trajectories in older adults: report from the Mayo Clinic Study of Aging. Br J Anaesth 2018;121:398-405.

32. Markel, DC, Doerr, T, Lincoln, D et al. Observational study on intrathecal and peridural changes after routine spinal and epidural anesthesia in patients undergoing total joint arthroplasty. J Arthroplasty 2007;22:844-848.

33. Bruderer, U, Fisler, A, Steurer, MP et al. Post-discharge nausea and vomiting after total intravenous anaesthesia and standardised PONV prophylaxis for ambulatory surgery. Acta Anaesthesiol Scand 2017;61:758-766.

34. de Hoogd, S, Ahlers, SJ, van Dongen, EP et al. Is Intraoperative Remifentanil Associated With Acute or Chronic Postoperative Pain After Prolonged Surgery? An Update of the Literature. Clin J Pain 2016;32:726-735.

35. Stevenson, KL, Neuwirth, AL, Sheth, N. Perioperative pain management following total joint arthroplasty: A review and update to an institutional pain protocol. J Clin Orthop Trauma 2018;9:40-45.

456 36. Murphy, TP, Byrne, DP, Curtin, P et al. Can a periarticular levobupivacaine injection
457 reduce postoperative opiate consumption during primary hip arthroplasty. Clin Orthop Relat
458 Res 2012;470:1151-1157.

459 37. Dobie, I, Bennett, D, Spence, DJetal. Periarticular local anesthesia does not improve
460 pain or mobility after THA. Clin Orthop Relat Res 2012;470:1958-1965.

461 38. Niemeläinen, M, Kalliovalkama, J, Aho, AJ et al. Single periarticular local infiltration
462 analgesia reduces opiate consumption until 48 hours after total knee arthroplasty. A
463 randomized placebo-controlled trial involving 56 patients. Acta Orthop 2014;85:614-619.

464 39. Yu JM, Sun H, Wu C, Dong CS, Lu Y, Zhang Y. The Analgesic Effect of Ropivacaine
465 Combined With Dexmedetomidine for Incision Infiltration After Laparoscopic
466 Cholecystectomy. Surg Laparosc Endosc Percutan Tech. 2016;26(6):449-454.

467 40. Mitra S, Purohit S, Sharma M. Postoperative Analgesia After Wound Infiltration With
468 Tramadol and Dexmedetomidine as an Adjuvant to Ropivacaine for Lumbar Discectomies: A
469 Randomized-controlled Clinical Trial. J Neurosurg Anesthesiol. 2017;29(4):433-438.

470 41. Zhou, TJ, Tang, J, White, PF. Propacetamol versus ketorolac for treatment of acute
471 postoperative pain after total hip or knee replacement. Anesth Analg 2001;92:1569-1575.

472 42. Fan, ZR, Ma, J, Ma, XL et al. The efficacy of dexamethasone on pain and recovery after
473 total hip arthroplasty: A systematic review and meta-analysis of randomized controlled trials.
474 Medicine (Baltimore) 2018;97:e0100.

475 43. Dissanayake, R, Du, HN, Robertson, IK et al. Does Dexamethasone Reduce Hospital
476 Readiness for Discharge, Pain, Nausea, and Early Patient Satisfaction in Hip and Knee
477 Arthroplasty? A Randomized, Controlled Trial. J Arthroplasty 2018;33:3429-3436.

478 44. Balderi, T, Carli, F. Urinary retention after total hip and knee arthroplasty. Minerva
479 Anestesiol 2010;76:120-130.

480 45. Kehlet, H, Aasvang, EK. Regional or general anesthesia for fast-track hip and knee
481 replacement - what is the evidence. F1000 Res 2015;4.

482

483

484

Figure legends

Figure 1. Cumulative postoperative opioid requirement of dexmedetomidine (DEX) and control (CTRL) groups in morphine equivalent doses (MED) within 2, 12, 24, 36 and 48 h of surgery.

Figure 2. Perioperative hemodynamics in dexmedetomidine (DEX) and control (CTRL) groups preoperatively, at incision, 1 h after anesthesia induction, at the end of surgery and before admission from post anesthesia care unit (PACU). Heart rate are shown as beats per minute and mean arterial pressure (MAP) are shown as mmHg.

Figure 3. Intraoperative target controlled infusion (TCI) target levels in dexmedetomidine (DEX) and control (CTRL) groups at incision, 1 h after anesthesia induction and during wound closure. Remifentanil target levels are shown as ng/ml and Propofol target levels are shown as µg/kg.

Figure 4. Intraoperative Entropy levels in dexmedetomidine (DEX) and control (CTRL) groups at incision, 1 h after anesthesia induction and during wound closure.

Supplemental Figure 1. Flow diagram of the study

TABLE 1. Patient charasteristics. Data are shown as mean ± standard deviation.

	CTRL (n=60)	DEX (n=60)	p-value
Age (yr)	67 (10)	67 (8)	0.62
Weight (kg)	79.5 (12.0)	76.4 (12.3)	0.18
BMI (kg/m2)	27.9 (3.8)	26.9 (3.5)	0.13
Duration of surgery (min)	67 (16)	70 (16)	0.15

CTRL = control group, DEX = dexmedetomidine group, BMI = body mass index

TABLE 2. Postoperative opioid requirement during five different time intervals.
Data are shown as mean ± standard deviation

	CTRL (n=60)	DEX (n=60)	p-value
Opioid requirement 0-2 h (MED)	81 (22)	71 (16)	0.07
Opioid requirement 0-12 h (MED)	118 (30)	105 (21)	0.01
Opioid requirement 0-24 h (MED)	143 (33)	126 (25)	0.001
Opioid requirement 0-36 h (MED)	151 (35)	133 (27)	< 0.001
Opioid requirement 0-48 h (MED)	178 (40)	152 (29)	< 0.001

CTRL = control group, DEX = dexmedetomidine group, MED = morphine equivalent dose

TABLE 3. Perioperative heart rate, mean arterial pressure and estimated intraoperative blood loss. Data are shown as median and inter-quartile range.

Parameter	Timepoint	CTRL (n=60)	DEX (n=60)	p-value
Heart rate (bpm)	Pre-op	68 (64-76)	73 (67-83)	0.16
	Incision	62 (56-66)	62 (55-67)	0.81
	1 h of induction	65 (62-75)	66 (56-72)	0.12
	Wound closure	70 (65-80)	68 (62-75)	0.27
	PACU	75 (68-83)	70 (62-80)	0.008
Mean arterial pressure (mmHg)	Pre-op	111 (104-118)	113 (106-121)	0.28
	Incision	66 (61-73)	72 (67-77)	< 0.001
	1 h of induction	75 (67-80)	85 (77-90)	< 0.001
	Wound closure	74 (62-83)	80 (72-86)	0.003
	PACU	94 (85-101)	80 (76-93)	< 0.001
Estimated blood loss (ml)		300 (200-400)	300 (200-400)	0.86

CTRL = control group, DEX = dexmedetomidine group, bpm = beats per minute, Pre-op = preoperative, PACU = post anesthesia care unit