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Original Research Article

Sevoflurane-Sparing Effect of Opioid-Free Dexmedetomidine Infusion under Entropy Guidance: Randomized Controlled Trial

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Abstract

Background: Dexmedetomidine, a selective α_2-agonist, may reduce anesthetic/opioid needs while stabilizing hemodynamics. We assessed its anesthetic-sparing effect under entropy guidance.

Methods: In a prospective, randomized trial, 120 adults (ASA I–II) undergoing elective surgery were allocated 1:1 to dexmedetomidine (DEX) or control. DEX received 1 µg/kg over 10 min then 0.2–0.8 µg/kg/h; controls received saline. Sevoflurane was titrated to maintain entropy 40–60. Primary outcome was mean end-tidal sevoflurane (ETsevo) during maintenance; secondary outcomes included entropy metrics, hemodynamics, rescue drugs, early recovery, and adverse events.

Results: Baseline characteristics were similar. At matched depth, DEX required less sevoflurane (ETsevo 1.18 ± 0.25% vs 1.50 ± 0.30%; Δ −0.32%, P<0.001), confirmed by lower time-weighted ETsevo (1.16 ± 0.23 vs 1.47 ± 0.28; P<0.001). Time within entropy target was comparable (90.3 ± 6.8% vs 88.9 ± 7.2%; P=0.29). DEX showed lower heart rate (69 ± 9 vs 76 ± 10 min^{-1}; P<0.001) and MAP (82 ± 8 vs 86 ± 9 mmHg; P=0.004), fewer >20% hypertensive/tachycardic episodes (0.6 ± 0.9 vs 1.3 ± 1.1 per patient; P<0.001), and reduced opioid rescue (15.0% vs 48.3%; P<0.001; lower dose when needed, P=0.02). Emergence and PACU transfer times were similar (all P>0.05). Bradycardia was more frequent with DEX (18.3% vs 6.7%; P=0.05); hypotension trended higher (20.0% vs 10.0%; P=0.14). No serious respiratory events or unplanned ICU admissions occurred.

Conclusions: Under entropy-guided anesthesia, dexmedetomidine infusion without intraoperative opioids reduces sevoflurane requirements and improves intraoperative stability without delaying early recovery; expected bradycardia/hypotension were manageable.

Keywords: Dexmedetomidine; General Anesthesia; Entropy; Anesthetic-Sparing; Hemodynamic Stability.

Introduction

Gynecological surgeries for benign etiologies, such as hysterectomy, myomectomy, and ovarian cystectomy, are among the most common surgical procedures performed in women1. Patients undergoing benign gynecological surgeries usually share common features, including relatively younger age, fewer comorbidities, and a higher risk of postoperative nausea and vomiting (PONV) [1].

Owing to these characteristics, this population might benefit greatly from enhanced recovery after surgery (ERAS) protocols, including multimodal analgesia and robust PONV prevention [2]. Dexmedetomidine, a selective alpha-2 adrenergic agonist, has been increasingly utilized in perioperative environments [3]. Specifically, dexmedetomidine has been used in anesthesia programs for multiple surgeries to facilitate postoperative recovery owing to its analgesic mechanism, which is different from that of opioids, and its antiemetic properties [3,4]. Furthermore, dexmedetomidine has been reported to attenuate perioperative stress and inflammation in surgical patients [5] and may improve chronic pain after surgery [6]. However, the benefits of dexmedetomidine are influenced by its diverse administration routes and dosages, and the hemodynamic suppression and sedative effect of dexmedetomidine should also be taken into consideration [7,8].

Notably, the only systematic review on dexmedetomidine in gynecological surgeries was published in 2021, and it concluded that dexmedetomidine increased intraoperative hemodynamic stability in patients undergoing hysterectomy [9]. However, this aforementioned study might be biased as it combined laparotomy and laparoscopic hysterectomies, intravenous and neuraxial dexmedetomidine administrations, and

active medication and placebo [9]. Dexmedetomidine is a selective α2-adrenoceptor agonist that has evoked considerable interest due to peculiar pharmacological profile as a sedative-hypnotic and analgesic agent [10]. It has been used extensively in different clinical areas; in ICU, in operations, as well as in the general and spinal anaesthesia [11]. In contrast to conventional sedatives, dexmedetomidine is an attractive choice both for short-term and for long-term sedation analgesia [12]. It offers a perfect way of handling such patients who need sedation as it does not cause important changes in respiratory indices or severe hemodynamic changes [13]. Clinical trials conducted by Inagaki et al., 2022 have shown that for sedation purposes and post-operative analgesia, dexmedetomidine is effective along with reduction in use of other intra-operational anaesthetic agents [10-14]. It helps decrease hemodynamic demand and postoperative pain as well as anaesthetic and opioid requirements while ensuring satisfactory respiratory status [15]. In ICU sedation, when used instead of other sedative agents, dexmedetomidine shortens length of ICU stay, decreases incidence of delirium, and reduces complications related to sedation16.

Objectives

Primary Objective

- To determine whether a continuous dexmedetomidine infusion, used without opioids, lowers the sevoflurane requirement needed to maintain target anesthetic depth when depth is monitored continuously with entropy.

Secondary Objectives

- To verify that depth of anesthesia remains within the predefined entropy range in both groups.
- To compare intraoperative hemodynamic stability (heart rate, blood pressure, vasoactive use) between groups.
- To assess immediate safety events related to dexmedetomidine (bradycardia, hypotension) and their management.

Material and Methods

This prospective, randomized, parallel-group study was conducted in a tertiary-care center. Adults (18–65 years), ASA I–II, scheduled for elective surgery under general anesthesia with tracheal intubation and expected duration ≥60 minutes were enrolled.

Exclusions included significant cardiovascular disease, hepatic/renal dysfunction, neurologic/ psychiatric illness, chronic opioid/sedative use, pregnancy/lactation, BMI >35 kg/m², anticipated difficult airway, or inability to obtain reliable entropy monitoring. Participants were allocated 1:1 to dexmedetomidine or control using a computer-generated, concealed sequence. An anesthesiologist uninvolved in assessments prepared indistinguishable infusions; patients and the outcomes recorder were blinded, and vaporizer settings were shielded.

All patients received standardized anesthesia: routine monitoring (ECG, NIBP, SpO_2, $ETCO_2$), inspired and end-tidal sevoflurane measurement, and entropy (Response/State). Induction used an IV hypnotic with non-depolarizing neuromuscular blockade; maintenance was with sevoflurane in oxygen/air (or O_2/N_2O) and controlled ventilation to $ETCO_2$ 32–38 mmHg. Depth of anesthesia was targeted at entropy 40–60 throughout. The dexmedetomidine group received a 1 µg/kg loading dose over 10 minutes before induction followed by 0.2–0.8 µg/kg/h; the control group received volume-matched saline. Sevoflurane was titrated in 0.2–0.3% steps to maintain entropy 40–60 (typical ET upper limit ≈2.5%). Hemodynamic excursions were treated by a prespecified algorithm: increase sevoflurane, then fentanyl 1 µg/kg for persistent hypertension/tachycardia; beta-blocker if needed. Hypotension prompted sevoflurane reduction, fluids, and vasopressors (e.g., ephedrine/phenylephrine); bradycardia was managed by reducing infusion and atropine as required. All interventions were recorded. The primary outcome was sevoflurane requirement during maintenance, expressed as mean end-tidal sevoflurane (and time-weighted exposure/MAC-fraction when available). Secondary outcomes included entropy values and time in target, heart rate and mean arterial pressure trajectories, vasoactive and opioid rescue use, immediate recovery times (eye opening, extubation, PACU transfer), and adverse events (bradycardia, hypotension, desaturation, arrhythmias, unplanned ICU admission).

Variables were recorded at baseline, induction, 1 and 5 minutes post-intubation, 5–60 minutes after incision, then every 15 minutes to closure, and at extubation and OR exit. Sample size was calculated a priori for a between-group difference in mean end-tidal sevoflurane (α=0.05, power=0.80) with 10% over-recruitment for attrition. Analyses followed intention-to-treat; continuous data used t-tests or Mann–Whitney U, repeated measures used linear mixed-effects models, and categorical data used chi-square or Fisher's exact tests. Two-sided $P<0.05$ was considered significant.

Results

The present study enrolled a total of 120 patients divided into dexmedetomidine (n=60) and control (n=60).

Table 1: Baseline characteristics

Variable	Dexmedetomidine (n=60)	Control (n=60)	P value
Age, years (mean ± SD)	45.6 ± 12.1	46.2 ± 11.7	0.78
Female, n (%)	28 (46.7)	27 (45.0)	0.85
Weight, kg (mean ± SD)	66.9 ± 9.8	67.5 ± 10.2	0.75
ASA class I / II, n	36 / 24	35 / 25	0.84
Duration of anesthesia, min (mean ± SD)	104 ± 28	108 ± 31	0.47
Baseline HR, min^{-1} (mean ± SD)	79 ± 10	80 ± 11	0.63
Baseline MAP, mmHg (mean ± SD)	93 ± 8	94 ± 9	0.51

At baseline, the Dexmedetomidine and Control groups (each n=60) were comparable across all variables: age 45.6 ± 12.1 vs 46.2 ± 11.7 years (P=0.78); females 28 (46.7%) vs 27 (45.0%) (P=0.85); weight 66.9 ± 9.8 vs 67.5 ± 10.2 kg (P=0.75); ASA class I/II 36/24 vs 35/25 (P=0.84); duration of anesthesia 104 ± 28 vs 108 ± 31 min (P=0.47); baseline HR 79 ± 10 vs 80 ± 11 min^{-1} (P=0.63); and baseline MAP 93 ± 8 vs 94 ± 9 mmHg (P=0.51).

None of the differences were statistically significant, indicating successful randomization and allowing valid between-group comparisons.

Table 2: Primary outcome and depth maintenance

Outcome	Dexmedetomidine (n=60)	Control (n=60)	P value
Mean ET sevoflurane, %	1.18 ± 0.25	1.50 ± 0.30	<0.001
Time-weighted ET sevo, %·min/min	1.16 ± 0.23	1.47 ± 0.28	<0.001
Time in entropy target (SE/RE 40–60), %	90.3 ± 6.8	88.9 ± 7.2	0.29
SE at 30 min, mean ± SD	48.6 ± 5.2	49.3 ± 5.5	0.46
RE at 30 min, mean ± SD	50.7 ± 5.6	51.5 ± 5.9	0.46

At matched hypnotic depth, dexmedetomidine markedly reduced sevoflurane needs.

The mean end-tidal sevoflurane was 1.18 ± 0.25% with dexmedetomidine versus 1.50 ± 0.30% in control ($P < 0.001$), a relative reduction of ~21%. The time-weighted ET sevo showed the same pattern (1.16 ± 0.23 vs 1.47 ± 0.28, $P < 0.001$). Depth of anesthesia was equivalent between groups: time in entropy target (SE/RE 40–60) was 90.3 ± 6.8% vs 88.9 ± 7.2% (P=0.29), with similar SE at 30 min (48.6 ± 5.2 vs 49.3 ± 5.5, P = 0.46) and RE at 30 min (50.7 ± 5.6 vs 51.5 ± 5.9, P = 0.46).

Dexmedetomidine confers a clear anesthetic-sparing effect without compromising hypnotic depth.

Table 3: Intraoperative hemodynamics and rescue medication

Variable	Dexmedetomidine (n=60)	Control (n=60)	P value
Mean intraop HR, min^{-1}	69 ± 9	76 ± 10	<0.001
Mean intraop MAP, mmHg	82 ± 8	86 ± 9	0.004
Episodes HR or MAP >20% above baseline, n/patient	0.6 ± 0.9	1.3 ± 1.1	<0.001
Fentanyl rescue, any n (%)	9 (15.0)	29 (48.3)	<0.001
Fentanyl total dose in those rescued, μg (median [IQR])	50 [50–75]	75 [50–100]	0.02
Beta-blocker use (metoprolol/labetalol), n (%)	6 (10.0)	15 (25.0)	0.03
Vasopressor use (ephedrine/phenylephrine), n (%)	14 (23.3)	9 (15.0)	0.24

Compared with control, dexmedetomidine produced a steadier, more sympatholytic profile.

Mean intraoperative heart rate was lower (69 ± 9 vs 76 ± 10 min^{-1}; P<0.001) and mean MAP was modestly lower (82 ± 8 vs 86 ± 9 mmHg; P=0.004). Hypertensive/tachycardic surges were fewer with dexmedetomidine (0.6 ± 0.9 vs 1.3 ± 1.1 episodes per patient; P<0.001). Opioid rescue was substantially reduced (15.0% [9/60] vs 48.3% [29/60]; P<0.001), and among those needing rescue the fentanyl dose was lower (50 [50–75] vs 75 [50–100] μg; P=0.02). Need for beta-blockers was also less frequent (10.0% vs 25.0%; P=0.03). Vasopressor use trended higher with dexmedetomidine (23.3% vs 15.0%), but the difference was not significant (P=0.24). Dexmedetomidine improved hemodynamic stability and reduced opioid and beta-blocker requirements, with a non-significant increase in vasopressor support consistent with expected α_2-agonist physiology.

Table 4: Immediate recovery and adverse events

Outcome	Dexmedetomidine (n=60)	Control (n=60)	P value
Time to eye opening, min (mean ± SD)	8.6 ± 3.5	9.1 ± 3.7	0.48
Extubation time, min (mean ± SD)	10.9 ± 4.2	11.3 ± 4.5	0.63
PACU transfer time, min (mean ± SD)	16.8 ± 5.9	17.5 ± 6.1	0.55
Bradycardia (HR <50), n (%)	11 (18.3)	4 (6.7)	0.05
Hypotension (MAP <65 or >20%↓), n (%)	12 (20.0)	6 (10.0)	0.14
Desaturation (SpO_2 <92%), n (%)	1 (1.7)	2 (3.3)	1.00
Atropine administered, n (%)	8 (13.3)	3 (5.0)	0.12
Ephedrine/phenylephrine given, n (%)	14 (23.3)	9 (15.0)	0.24
Unplanned ICU admission, n (%)	0 (0)	0 (0)	-

Immediate recovery profiles were similar between groups: time to eye opening (8.6 ± 3.5 vs 9.1 ± 3.7 min; P=0.48), extubation (10.9 ± 4.2 vs 11.3 ± 4.5 min; P=0.63), and transfer to PACU (16.8 ± 5.9 vs 17.5 ± 6.1 min; P=0.55) did not differ significantly. As expected with an α_2-agonist, bradycardia occurred more often with dexmedetomidine (18.3% vs 6.7%; P=0.05), while hypotension trended higher but was not statistically significant (20.0% vs 10.0%; P=0.14). Desaturation was rare and comparable (1.7% vs 3.3%; P=1.00). Atropine use showed a non-significant increase with dexmedetomidine (13.3% vs 5.0%; P=0.12), and vasopressor administration was numerically higher but not different (23.3% vs 15.0%; P=0.24). No unplanned ICU admissions occurred in either arm. Overall dexmedetomidine did not delay recovery and showed predictable, manageable hemodynamic adverse effects without serious sequelae.

Discussion

In this randomized, entropy-guided study, dexmedetomidine given as a continuous infusion without intraoperative opioids produced a clear anesthetic-sparing effect lowering end-tidal sevoflurane at matched hypnotic depth while improving intraoperative hemodynamic stability, reducing opioid rescue, and preserving early recovery times; as expected for an α_2-agonist, bradycardia (and to a lesser extent hypotension) occurred more often but was readily managed with protocolized therapy.

Anesthetic requirement (primary outcome): In the present study, mean ET-sevoflurane during maintenance was 1.18 ± 0.25% with dexmedetomidine vs 1.50 ± 0.30% in control (≈21% relative reduction), with time in entropy 40–60 comparable (90.3% vs 88.9%).

This closely mirrors the entropy-guided RCT by Patel CR et al., (2013) [17], which also demonstrated an anesthetic-sparing effect of dexmedetomidine at matched depth (entropy 40–60), reporting an average sevoflurane reduction of about 21.5% versus fentanyl-based anesthesia. In Gupta K et al., (2016) [18], dexmedetomidine similarly reduced the volatile requirement (lower dialed isoflurane concentration to maintain hemodynamic targets) during modified.

Depth of anesthesia: Our groups spent similar time within the entropy target (90.3% vs 88.9%) and had overlapping SE/RE values at fixed time points, indicating equivalent hypnotic depth despite lower ET-sevo in the dexmedetomidine arm. Patel CR et al., (2013) [17] designed their trial around this same principle—depth by entropy remained equivalent while anesthetic requirement fell supporting that the sparing effect is not due to lighter anesthesia (Gupta K et al., 2016) [18].

Hemodynamics and sympathetic surges: Dexmedetomidine yielded lower intraoperative HR (69 ± 9 vs 76 ± 10 min^{-1}; P<0.001) and modestly lower MAP (82 ± 8 vs 86 ± 9 mmHg; P=0.004), with fewer >20% excursions (0.6 ± 0.9 vs 1.3 ± 1.1 per patient; P<0.001). Gupta K et al., (2016) [18] reported a similar sympatholytic profile - lower HR/controlled hypotension and improved surgical field visibility alongside reduced volatile needs. Obara S (2018) [19] also emphasizes predictable dose-dependent hemodynamic effects that can be leveraged intraoperatively.

Opioid-sparing and rescue drugs: Fewer patients in our dexmedetomidine arm required fentanyl rescue (15.0% vs 48.3%; P<0.001), and doses were smaller among those rescued (median 50 µg vs 75 µg; P=0.02). Gupta K et al., (2016) [18] likewise showed reduced fentanyl requirements with dexmedetomidine. At a broader level, the gynecologic-surgery meta-analysis by Hung TY et al., (2023) [20] found lower 24-h opioid consumption (mean difference −4.85 mg morphine equivalents) with IV dexmedetomidine versus controls.

Recovery endpoints: Emergence and early recovery were similar in our study (eye-opening, extubation, PACU transfer; all P>0.05). Gupta K et al., (2016) [18] reported preserved recovery times despite better surgical fields and lower volatile/opioid use, in line with our findings.

Adverse events: As expected for an α2-agonist, bradycardia was more frequent with dexmedetomidine in our cohort (18.3% vs 6.7%;

P=0.05), and hypotension trended higher (20.0% vs 10.0%; P=0.14), both manageable with protocolised atropine/vasopressors and without serious sequelae. The 2023 meta-analysis by Hung TY et al., (2023) [20] quantified these risks (bradycardia RR 3.21, hypotension RR 2.17) while noting no serious adverse events across included RCTs. The Obara S (2018) [19] editorial similarly frames these as predictable, dose-related effects that are acceptable with vigilant monitoring.

Conclusion

In this randomized, entropy-guided study, dexmedetomidine administered as a continuous infusion without intraoperative opioids significantly reduced sevoflurane requirements at matched anesthetic depth, improved intraoperative hemodynamic stability, and lowered opioid rescue needs, while preserving emergence and early recovery times. The safety profile reflected predictable α_2-agonist effects, with more frequent bradycardia and a non-significant trend toward hypotension, both readily managed using predefined protocols and without serious sequelae. Taken together, these findings support dexmedetomidine as a useful adjuvant to balanced general anesthesia when depth is objectively monitored, provided dosing is titrated and hemodynamics are vigilantly supervised. This approach can reduce volatile and opioid exposure without compromising recovery, offering a practical pathway to safer, more stable intraoperative care.

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