

Efficacy and Safety of Intranasal Dexmedetomidine Combined with Esketamine for Premedication in Children Undergoing Laser Treatment for Burn Scars: A Randomised Self-Controlled Crossover Trial

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Abstract

Background

Children undergoing repeated laser treatment for burn scars require effective premedication to support sedation and cooperation. We compared intranasal dexmedetomidine plus esketamine with esketamine alone.

Methods

In this single-centre, randomised, two-period crossover trial, 24 children aged 2–6 years received both regimens, with 12 per sequence and 63–76 days between sessions. The combination comprised intranasal dexmedetomidine (25 µg at 10.7–19.3 kg or 50 µg at 19.4–28.0 kg) plus intranasal esketamine 0.5 mg/kg; the comparator was esketamine 0.5 mg/kg alone. Both preceded general anaesthesia. Primary outcomes were Ramsay Sedation Scale (RSS) scores, time to RSS ≥ 3 , separation-anxiety, mask-acceptance and Pediatric Anesthesia Emergence Delirium (PAED) scores. Physiological variables and total propofol were secondary outcomes. Mixed-effects models accounted for treatment period, sequence and within-child correlation; Holm adjustment covered nine primary-outcome comparisons.

Results

All children completed both periods. RSS scores were higher with the combination, with the most consistent differences at 30 min and before induction (both Holm-adjusted $P < 0.001$). Two children had RSS 6 at both assessments. Separation-anxiety and mask-acceptance scores were lower (Holm-adjusted $P = 0.004$ and $P < 0.001$). PAED scores were lower by 1.33 points (95% confidence interval [CI] 0.47–2.19; Holm-adjusted $P = 0.016$); no score was ≥ 10 . Time to RSS ≥ 3 was shorter by 3.83 min (95% CI 1.85–5.81; Holm-adjusted $P = 0.003$). Secondary analyses estimated 6.15 mg lower weight-adjusted propofol use (95% CI 2.40–9.91) and lower mean arterial pressure, heart rate and respiratory rate. Scheduled oxygen saturation was 95%–99%; no child required assisted ventilation or treatment for hypotension or bradycardia.

Conclusions

Adding intranasal dexmedetomidine to esketamine improved pre-induction sedation and perioperative behavioural scores. Secondary findings suggest lower propofol requirements. The combination warrants further evaluation as needle-free premedication for burn-scar laser treatment, with appropriate monitoring.

Trial registration:

Chinese Clinical Trial Registry, ChiCTR2500106780. Registered on 30 July 2025.

Background

Hypertrophic scars after deep burns can cause pruritus, contracture, functional impairment and reduced quality of life [1, 2]. Children returning for serial burn-scar treatment may also face perioperative challenges arising from previous painful experiences and altered sensory processing. Persistent peripheral and central sensitisation have been described after burn injury [3], and follow-up studies have identified altered pain and sensory sensitivity in children who sustained burns in infancy [4]. Pain memories can influence subsequent pain expectations and experiences [5]. Together with the relationship between inadequately controlled burn pain and anticipatory distress [6], these observations provide a rationale for assessing anxiety and cooperation before anaesthetic induction, alongside sedation depth.

Ultrapulsed fractional carbon dioxide laser (UFCL) treatment is used to improve paediatric hypertrophic burn scars [7]. Its therapeutic use does not remove the need for appropriate procedural analgesia: a randomised study of 169 children undergoing UFCL documented pain after anaesthetic emergence and lower pain scores with multimodal analgesic regimens [8]. For children requiring repeated sessions, perioperative management therefore involves both preparing the child for induction and providing adequate anaesthesia and analgesia for laser treatment. Effective premedication addresses the first of these needs and complements the subsequent anaesthetic protocol.

Dexmedetomidine produces sedation and anxiolysis through central α_2 -adrenoceptor activity, with sympatholytic effects and relatively limited respiratory depression [9]. Esketamine, the S-enantiomer of ketamine, provides analgesic and sedative effects through N-methyl-D-aspartate (NMDA) receptor antagonism [10]. Their differing pharmacological actions provide a rationale for combination premedication. Paediatric trials and pooled evidence involving dexmedetomidine with racemic ketamine support this approach [11, 12], although evidence involving racemic ketamine and evidence involving esketamine should be distinguished when comparing regimens.

Intranasal administration allows premedication to begin without first establishing intravenous access. In infants and toddlers, atomised intranasal dexmedetomidine had an estimated bioavailability of 83.8%, with plasma concentrations associated with sedative activity reached within approximately 10–20 min and peak concentrations at approximately 46–47 min after 1–2 $\mu\text{g}/\text{kg}$ [13]. Adult population pharmacokinetic data estimated absolute bioavailability of 54% and 51% after esketamine nasal-spray doses of 56 and 84 mg, respectively [14]. These studies support systemic absorption through the intranasal route; the adult nasal-spray estimates should not, however, be assumed to describe paediatric esketamine drops. The route offers a practical means of initiating sedation before venous cannulation.

Paediatric clinical studies have evaluated intranasal dexmedetomidine and esketamine separately in dental and emergency procedural settings [15, 16]. Combination regimens have been studied for anaesthetic induction [17], transthoracic echocardiography [18] and tonsillectomy or adenoidectomy [19]. Behavioural findings vary: a strabismus-surgery trial found comparable parental separation and mask acceptance scores across esketamine and combination regimens [20], whereas dental and facemask-acceptance trials found benefits for selected outcomes [21, 22]. Postoperative pain has also been evaluated [23]. A recent meta-analysis reported faster sedation onset and improved mask acceptance with the combination compared with dexmedetomidine alone [24]. Thus, existing evidence supports further evaluation while indicating that effects depend on the comparator, dose and clinical setting. The choice of comparator is important: trials against dexmedetomidine alone estimate the effect of adding esketamine, whereas the present comparison examines the effect of adding dexmedetomidine to an esketamine regimen.

Most of these studies concern a single treatment episode. Repeated UFCL provides an opportunity to compare premedication regimens within the same child in a recurring burn-scar care setting. This randomised crossover study evaluated whether adding intranasal dexmedetomidine to intranasal esketamine improved pre-induction sedation and perioperative behavioural responses during two scheduled UFCL sessions. Cardiorespiratory observations and total intraoperative propofol use were also assessed.

Methods

Study design and participants

This prospective, single-centre, randomised, two-period, two-sequence crossover trial evaluated intranasal premedication in children undergoing UFCL for hypertrophic burn scars. The study was conducted at Wuhan Third Hospital, in accordance with the Declaration of Helsinki. Reporting was structured with reference to the CONSORT extension for randomised crossover trials [25].

The study was approved by Medical Ethics Committee of Wuhan Third Hospital (approval number KY2024-031-01). Written informed consent was obtained from parents or legal guardians before enrolment. The trial was prospectively registered with the Chinese Clinical Trial Registry (ChiCTR2500106780) on 30 July 2025.

The analysed treatment sessions took place from 6 August 2025 to 20 May 2026. Eligibility criteria were age 2–6 years, American Society of Anesthesiologists (ASA) physical status I or II, body weight 10.7–28.0 kg, and a requirement for laser treatment of hypertrophic burn scars. Exclusion criteria were clinically significant cardiovascular disease, respiratory disease requiring active intervention, allergy or contraindication to a study drug, nasal abnormalities affecting administration, an anticipated difficult airway, or anticipated inability to complete two treatment sessions. All randomised children were included in the analysis.

Sample-size planning was performed using PASS version 15.0, informed by previously reported paediatric behavioural outcomes [19], with a two-sided significance level of 0.05 and 90% power. The target enrolment was 20 children after allowing for 20% attrition. A total of 24 children were enrolled.

Randomisation and treatment periods

A computer-generated randomisation sequence assigned each child to one of two treatment sequences: intranasal dexmedetomidine plus esketamine followed by intranasal esketamine alone (R→C), or the reverse sequence (C→R). Twelve children were assigned to each sequence. Each child received both regimens, with randomisation specifying their order of administration.

Treatment periods were defined within each child using the actual treatment dates: period 1 was the earlier session and period 2 the later session. The anatomical site, treated area and laser parameters were the same for both sessions within each child. Sessions were planned approximately 2–3 months apart; observed intervals were 63–76 days. This spacing was intended to minimise direct pharmacological carryover. Models accounted for treatment period and sequence, and sensitivity analyses considered the actual inter-session interval and linear calendar time.

Premedication and anaesthetic management

For regimen R, intranasal dexmedetomidine spray was administered at 25 µg for children weighing 10.7–19.3 kg and 50 µg for those weighing 19.4–28.0 kg, together with intranasal esketamine drops at 0.5 mg/kg. These weight bands reflected the available fixed-dose dexmedetomidine spray formulation. For regimen C, children received intranasal esketamine alone at 0.5 mg/kg. Study medications were administered within approximately 2 min. Electrocardiography, non-invasive blood pressure, peripheral oxygen saturation (SpO₂) and respiratory rate monitoring began before administration.

Forty minutes after premedication, children were transferred to the operating room. Anaesthesia was induced with 8% sevoflurane in 100% oxygen at 8 L/min. After loss of the eyelash reflex and adequate jaw relaxation, sevoflurane was reduced to 2% and oxygen flow to 2 L/min. Intravenous access was then established, followed by propofol 2 mg/kg and fentanyl 1 µg/kg. Anaesthesia was maintained with sevoflurane; additional propofol 1 mg/kg was administered for movement or inadequate anaesthetic depth.

Caregivers and clinicians administering premedication could not be fully blinded because the preparations differed. Outcome assessors were blinded to allocation. Independent investigators who were not involved in study-drug administration or anaesthetic management assessed parental separation, mask acceptance and emergence-related behaviour.

Haemodynamic and respiratory monitoring continued throughout care. A reduction in mean arterial pressure (MAP) of > 30% from baseline triggered treatment with intravenous ephedrine; a reduction in

heart rate (HR) of > 30% triggered atropine. The protocol used SpO₂ <94% as its oxygen-desaturation criterion, with assisted ventilation when necessary.

Outcome assessment

Primary outcomes. The primary outcomes were Ramsay Sedation Scale (RSS) scores and time to first RSS ≥ 3 , Parental Separation Anxiety Scale (PSAS) scores, Mask Acceptance Scale (MAS) scores, and Pediatric Anesthesia Emergence Delirium (PAED) scores.

Sedation. RSS was assessed before medication (T0), at 15 min (T1), 20 min (T2), 25 min (T3) and 30 min (T4), and immediately before anaesthetic induction (T5). T5 was an event-defined assessment rather than an assumed elapsed time. The six study scoring categories ranged from agitation (1) to deep sleep without a response to calling (6); complete descriptions are provided in Table S6a. Time from medication administration to the first RSS ≥ 3 was recorded separately and was available for all 48 sessions.

Parental separation. The PSAS assessed the child's behaviour when separating from the parent before T5. Scores ranged from 1 (easy separation) to 4 (crying and dependent on the parent). Scores of 1–2 indicated successful separation (Table S6b).

Mask acceptance. The MAS was assessed during inhalational mask induction. Scores ranged from 1 (no fear, cooperative and easy acceptance) to 4 (severe fear of the mask with crying). Scores of 1–2 indicated satisfactory mask acceptance (Table S6b). Lower PSAS and MAS scores indicated better behaviour.

Emergence behaviour. PAED scoring was performed after emergence. The five study items assessed eye contact with the caregiver, purposeful actions, awareness of surroundings, restlessness and distressed crying. Each item was scored from 0 to 4. Items 1–3 were reverse-scored, whereas items 4–5 were scored in the opposite direction. The total ranged from 0 to 20; a score ≥ 10 was the study criterion for emergence delirium. Full item descriptions and response anchors are provided in Table S6c.

Secondary outcomes. MAP, SpO₂, HR and respiratory rate (RR) were recorded at T0–T5, together with total intraoperative propofol dose. Total propofol included induction and any additional administration and was recorded in mg; dose per kg was examined in a supplementary analysis. Same-session T0 values were used for baseline adjustment of repeated physiological outcomes.

Statistical analysis

All 24 children contributed both periods, giving 48 treatment sessions. Continuous data are presented as mean $\pm$ standard deviation (SD), ordinal scores as median [first quartile, third quartile], and categorical data as counts. Study-entry characteristics are described by randomised sequence without baseline significance testing. No outcome values were imputed. The mixed-effects model specifications and

sensitivity analyses were determined after data collection to account for the crossover design and repeated measurements.

Continuous session-level outcomes were analysed using linear mixed-effects models with treatment, period and sequence as fixed effects and a participant-specific random intercept. The total-propofol model additionally adjusted for body weight at that session. Repeated physiological outcomes at T1–T5 were modelled with treatment, categorical assessment time, treatment-by-time interaction, period, sequence and the corresponding same-session T0 measurement as fixed effects. Participant and session-within-participant random intercepts represented between-session and within-session correlation. Gaussian models used restricted maximum likelihood and Satterthwaite-type degrees of freedom [26].

RSS, PSAS and MAS were analysed as ordinal outcomes using cumulative-logit mixed-effects models [27]. PSAS and MAS models included treatment, period, sequence and a participant random intercept. The RSS model also included categorical time, treatment-by-time interaction, baseline RSS and a session-within-participant random intercept. Odds ratios (ORs) compare the odds of a higher score category under R versus C: $OR > 1$ indicates deeper RSS-defined sedation, whereas $OR < 1$ indicates more favourable PSAS or MAS scores.

Holm adjustment was applied to nine primary-outcome comparisons: the five post-dose RSS contrasts, time to first $RSS \geq 3$, PSAS, MAS and PAED [28]. T0 was used for adjustment, not as an additional treatment contrast. The significance threshold was an adjusted two-sided $P < 0.05$. Except where a separate Holm adjustment is specified, P values for other analyses were not adjusted for multiple comparisons. Confidence intervals (CIs) were pointwise and not adjusted for multiplicity. Secondary-outcome and sensitivity analyses provided supporting evidence rather than additional confirmatory tests.

Sensitivity analyses added inter-session interval deviation or linear calendar time separately. Separate-assessment Gaussian RSS models and paired Wilcoxon signed-rank tests were also examined. No preliminary carryover test was used to exclude period-2 observations. Computation used Python 3.13.5, NumPy 2.3.5 and SciPy 1.17.0 [29]; Gaussian estimates were cross-checked using statsmodels 0.14.6. Additional file 1 provides the computational details and supplementary results.

Results

Participants and treatment periods

All 24 children (11 boys and 13 girls) completed both treatment periods, with no dropout or post-randomisation exclusion (Fig. 1). Twelve children received R→C and 12 received C→R. The analysis therefore comprised 24 participants and 48 sessions. Mean age was 4.17 ± 1.34 years. The mean inter-session interval was 68.21 ± 3.36 days (median 68; range 63–76). Characteristics at the first treatment session are shown in Table 1.

Table 1
Participant characteristics at the first treatment session by randomised sequence

Characteristic	R→C (n = 12)	C→R (n = 12)	Overall (n = 24)
Participants, n	12	12	24
Boys, n	7	4	11
Girls, n	5	8	13
Age, years	4.58 ± 1.24	3.75 ± 1.36	4.17 ± 1.34
Height, cm	106.08 ± 9.33	101.92 ± 10.47	104.00 ± 9.93
Body weight, kg	17.71 ± 3.11	15.71 ± 3.05	16.71 ± 3.18
Inter-session interval, days	69.67 ± 3.34	66.75 ± 2.80	68.21 ± 3.36
Interval range, days	65–76	63–72	63–76
Values are mean ± SD unless stated otherwise. R, intranasal dexmedetomidine plus esketamine; C, intranasal esketamine alone. Columns describe the randomised sequences, not separate treatment groups. All 24 children completed both periods. No baseline significance tests were performed.			

Sedation outcomes

Observed RSS trajectories are shown in Fig. 2, with ordinal-model contrasts in Table 2. The treatment-by-time interaction was significant (likelihood-ratio $\chi^2 = 44.60$; 4 degrees of freedom; $P < 0.001$). Holm-adjusted P values for R versus C were 0.039 at T1, 0.039 at T2, 0.016 at T3 and < 0.001 at T4 and T5. At T4, median RSS was 4.5 [4, 5] with R and 4 [3, 4] with C; at T5, the corresponding scores were 5 [4, 5] and 3 [3, 4]. Two children (8.3%) had RSS 6 at both T4 and T5 under R; none had RSS 6 under C. These were the same two children at both assessments. Complete category counts are reported in Additional file 1, Table S5.

Table 2
Ramsay sedation scores and cumulative-logit mixed-model treatment contrasts

Assessment	R (n = 24)	C (n = 24)	Adjusted OR (95% CI)	P	Holm P
T0: baseline	2 [1, 2]	2 [1, 2]	Baseline covariate	—	—
T1: 15 min	2 [2, 3]	2 [2, 2]	5.37 (1.12 to 25.8)	0.036	0.039
T2: 20 min	3 [3, 3]	3 [2, 3]	6.64 (1.35 to 32.6)	0.020	0.039
T3: 25 min	4 [3, 4]	3 [3, 4]	9.31 (1.99 to 43.6)	0.005	0.016
T4: 30 min	4.5 [4, 5]	4 [3, 4]	111.3 (17.5 to 705.8)	< 0.001	< 0.001
T5: pre-induction	5 [4, 5]	3 [3, 4]	2970 (333.1 to 26480)	< 0.001	< 0.001
Values are median [first quartile, third quartile]. OR, cumulative odds ratio for a higher RSS category under R versus C; CI, confidence interval. The model includes treatment, period, sequence, categorical time, treatment-by-time interaction and session-baseline RSS, with participant and nested session random intercepts. Holm adjustment covers nine primary-outcome comparisons: five post-dose RSS contrasts, time to RSS ≥ 3, PSAS, MAS and PAED. P: not adjusted for multiple comparisons; Holm P: Holm-adjusted P value. CIs are pointwise and not adjusted for multiplicity. Large late-assessment ORs have wide CIs and do not represent multiples of clinical benefit. See Additional file 1, Table S4 for sensitivity analyses.					

Late-assessment ordinal ORs were large, with wide CIs, reflecting marked separation of score categories. Separate-assessment Gaussian analyses supported the direction of these differences. In the paired-rank sensitivity analysis, T4 and T5 remained significant after Holm adjustment across the five post-dose comparisons, whereas T1–T3 did not (Additional file 1, Table S4). The late pre-induction differences were therefore the most consistent across analysis approaches.

Recorded time to RSS ≥ 3 was 15.25 ± 3.86 min with R and 19.08 ± 3.62 min with C. The period- and sequence-adjusted mean difference was -3.83 min (95% CI -5.81 to -1.85 ; $P < 0.001$; Holm-adjusted $P = 0.003$; Table 3).

Table 3
Perioperative outcomes and adjusted treatment contrasts

Outcome	R (n = 24)	C (n = 24)	Adjusted effect (95% CI)	P	Holm P
Recorded time to RSS $\geq$ 3, min	15.25 $\pm$ 3.86	19.08 $\pm$ 3.62	MD - 3.83 (- 5.81 to - 1.85)	< 0.001	0.003
PSAS score	2 [1, 2]	3 [2, 3]	OR 0.023 (0.003 to 0.21)	< 0.001	0.004
MAS score	1 [1, 2]	3 [2, 3]	OR 0.016 (0.002 to 0.13)	< 0.001	< 0.001
PAED score	5.46 $\pm$ 1.50	6.79 $\pm$ 1.72	MD - 1.33 (- 2.19 to - 0.47)	0.004	0.016
Total propofol, mg	35.31 $\pm$ 6.37	41.56 $\pm$ 10.01	MD - 6.15 (- 9.91 to - 2.40)	0.003	—
Total propofol, mg/kg	2.10 $\pm$ 0.28	2.47 $\pm$ 0.53	MD - 0.371 (- 0.600 to - 0.143)	0.003	—
Continuous values are mean $\pm$ SD; PSAS and MAS are median [first quartile, third quartile]. MD, adjusted mean difference (R - C); OR, cumulative odds ratio for a higher score (R versus C). RSS onset, PSAS, MAS and PAED are primary outcomes; total propofol is secondary. PSAS and MAS scores of 1–2 indicate successful separation and satisfactory mask acceptance, respectively. Models adjust for period and sequence; the total-propofol (mg) model also adjusts for session body weight. Holm P values cover nine primary-outcome comparisons, including RSS T1–T5 in Table 2. P: not adjusted for multiple comparisons; Holm P: Holm-adjusted P value. CIs are pointwise and not adjusted for multiplicity. Propofol includes induction and additional doses. PAED ranges from 0 to 20; no score was $\geq$ 10. Full scoring instructions are in Tables S6a–S6c.					

Perioperative behavioural outcomes

PSAS and MAS scores were lower with R (Table 3). Median PSAS was 2 [1, 2] versus 3 [2, 3], with an adjusted OR for a higher score of 0.023 (95% CI 0.003–0.21; Holm-adjusted P = 0.004). Median MAS was 1 [1, 2] versus 3 [2, 3], with an adjusted OR of 0.016 (95% CI 0.002–0.13; Holm-adjusted P < 0.001).

Mean PAED scores were 5.46 $\pm$ 1.50 with R and 6.79 $\pm$ 1.72 with C. The adjusted difference was - 1.33 points (95% CI - 2.19 to - 0.47; Holm-adjusted P = 0.016). No child had a PAED score $\geq$ 10 under either regimen.

Secondary haemodynamic and respiratory outcomes

MAP and HR were lower with R at all five post-dose assessments in baseline-, period- and sequence-adjusted models (Figs. 3 and 4; Additional file 1, Table S1). At T4, the adjusted MAP difference was - 10.12 mmHg (95% CI - 12.12 to - 8.11) and the HR difference was - 17.21 beats/min (95% CI - 18.63 to - 15.80), both with P < 0.001. The lowest mean MAP under R was 72.33 $\pm$ 5.84 mmHg at T4. No scheduled MAP or HR measurement met the protocol threshold of a > 30% decline from that session's baseline.

RR was also lower with R at each post-dose assessment; the adjusted T4 difference was -2.38 breaths/min (95% CI -2.98 to -1.77). Scheduled SpO₂ values ranged from 95% to 99%, with small between-regimen differences across time points (Additional file 1, Table S1). No child required assisted ventilation or pharmacological treatment for hypotension or bradycardia under either regimen.

Secondary total propofol consumption

Total propofol use was 35.31 ± 6.37 mg with R and 41.56 ± 10.01 mg with C. The raw paired mean difference was -6.25 mg. Adjustment for period, sequence and session body weight gave a mean difference of -6.15 mg (95% CI -9.91 to -2.40 ; $P = 0.003$). The weight-normalised difference was -0.371 mg/kg (95% CI -0.600 to -0.143 ; $P = 0.003$; Table 3). These estimates refer to the total intraoperative propofol dose, including induction and additional administration.

Period, sequence and sensitivity analyses

Period and sequence estimates are reported in Additional file 1, Table S2. Behavioural estimates were imprecise. Physiological models estimated MAP sequence and HR period differences. Adding inter-session interval deviation or linear calendar time preserved the direction of the principal treatment contrasts (Additional file 1, Table S3). The interval-adjusted latency difference was -3.29 min (95% CI -5.38 to -1.20), and the interval- and weight-adjusted propofol difference was -5.99 mg (95% CI -10.04 to -1.94).

Discussion

In this randomised self-controlled crossover study, adding intranasal dexmedetomidine to esketamine improved pre-induction sedation and perioperative behavioural scores in children undergoing UFCL for burn scars. The most consistent sedation differences occurred at 30 min and immediately before induction. The combination also shortened recorded sedation latency and reduced total propofol use. By comparing both regimens within each child, the study controlled for stable individual characteristics, while adjustment for treatment period and sequence accounted for the structure of the two treatment sessions.

Sedation efficacy and intranasal pharmacology

The sedation findings are consistent with the complementary central α_2 -adrenergic and NMDA-receptor actions of dexmedetomidine and esketamine [9, 10]. Paediatric induction studies have likewise reported improved sedation or cooperation with dexmedetomidine-containing combinations [11, 17]. In the present study, the recorded time to RSS ≥ 3 was approximately 3.83 min shorter with the combination. The more pronounced differences close to induction suggest that its principal practical benefit may be the quality of pre-induction sedation rather than simply an earlier onset.

The timing is also compatible with the gradual absorption of intranasal dexmedetomidine. The paediatric pharmacokinetic study by Miller and colleagues found peak concentrations approximately 46–47 min

after atomised administration [13]. This provides a plausible explanation for the increasing separation of sedation scores towards induction, although drug concentrations were not measured here. The observed RSS distributions and agreement across analyses at T4 and T5 are more clinically informative than the very large ordinal odds ratios. The two children with RSS 6 at both final assessments also emphasise that deeper sedation should be considered alongside cooperation and cardiorespiratory monitoring, rather than treated as an unlimited benefit.

Perioperative behavioural effects

Parental separation and mask acceptance are relevant to children returning to a setting associated with previous painful treatment. Pain-memory and paediatric burn research supports addressing distress before induction [5, 6]. Lower PSAS and MAS scores with the combination indicate improved behaviour at these transitions. This accords with the tonsillectomy/adenoidectomy trial [19] and selected dental and facemask findings [21, 22]. Not all trials agree: the strabismus study found comparable PSAS and MAS scores across regimens [20], and the facemask-focused trial found an MAS benefit without a PSAS difference [22]. Variation in doses, comparators and procedures may explain these differences and supports context-specific interpretation.

PAED scores were also lower with the combination. Trials and pooled evidence support effects of dexmedetomidine-containing regimens on emergence-related behaviour in other paediatric settings [19, 30]. In this cohort, however, neither regimen produced a PAED score ≥ 10 ; the 1.33-point difference therefore describes less severe behavioural disturbance, not a demonstrated reduction in delirium incidence. PAED findings also require consideration of the assessment context [31]. Taken together, the separation, mask-acceptance and emergence scores suggest that the regimen's effects extended across several immediate perioperative transitions rather than being confined to a single sedation assessment.

Cardiorespiratory observations

Lower MAP and HR with the combination are compatible with dexmedetomidine's sympatholytic action [9]. No scheduled measurement met the protocol threshold of a $> 30\%$ decline from the corresponding baseline. RR was also lower, while scheduled SpO₂ values remained between 95% and 99%. No child required assisted ventilation or pharmacological treatment for hypotension or bradycardia. These observations support tolerability under the monitored conditions of this study. They should be interpreted together with the sedation-depth findings: achieving better cooperation does not remove the need for continuous clinical assessment and readiness to support ventilation when necessary.

Multimodal anaesthesia and propofol use

The weight-adjusted reduction of approximately 6.15 mg in total propofol use was close to the raw paired difference of 6.25 mg. Its direction was also preserved after adjustment for inter-session interval or calendar time. This suggests a lower intravenous anaesthetic requirement within the study's sevoflurane-based multimodal protocol. The endpoint included induction and additional propofol, rather than additional boluses alone. Clinical interpretation should therefore remain linked to the complete

anaesthetic pathway. Measuring volatile anaesthetic exposure and recovery times alongside propofol use would help determine whether this reduction translates into additional benefits for short-stay laser care.

Contribution to repeated burn-scar care and clinical implications

Paediatric intranasal dexmedetomidine–esketamine trials have generally evaluated premedication or sedation during an individual procedural episode [18, 19]. Burn-specific combination evidence includes dexmedetomidine with racemic ketamine during dressing changes [32, 33], a different procedure, drug formulation and administration context. The present trial contributes within-child comparative evidence from two scheduled scar-laser sessions. Keeping the treated site, area and laser parameters constant within each child further focused the comparison on the premedication regimen, while period-adjusted analyses accommodated common changes between sessions.

Its immediate clinical relevance lies in combining needle-free administration with improved separation and mask acceptance. In the study protocol, intranasal medication preceded inhalational induction and intravenous cannulation, allowing preparation to begin before an injection was required. This sequence addresses a practical part of repeated burn-scar care without implying that nasal medication alone provides sufficient anaesthesia for laser treatment. Whether a better perioperative experience at one session improves cooperation at later visits is a worthwhile next question, supported conceptually by pain-memory research [5]; it requires follow-up across additional sessions rather than extrapolation from the present two-period comparison.

For a recurring procedure, a premedication regimen should be judged not only by how quickly a sedation threshold is reached, but also by the child's behaviour during separation from the caregiver and acceptance of the anaesthetic mask. The paired improvement in these outcomes provides a more clinically interpretable signal than sedation scores alone and identifies the part of the treatment pathway most likely to benefit.

Limitations

The single-centre sample of 24 children limits precision, generalisability and detection of uncommon adverse events. Sparse ordinal categories contributed to wide confidence intervals, particularly at late RSS assessments. Model-selection uncertainty should also be considered when interpreting the findings. Independent blinded assessment reduced detection bias, but incomplete blinding of caregivers and administering clinicians could still influence perioperative care. Scar characteristics were not systematically quantified at both sessions. Because paediatric scars evolve over time [34], period, interval and calendar-time adjustments cannot fully account for individual changes in scar state or previous treatment experience.

The comparison estimates the incremental effect of adding dexmedetomidine to esketamine. Without a dexmedetomidine-only arm, it cannot establish superiority over dexmedetomidine alone or demonstrate

pharmacological synergy. Fixed-dose dexmedetomidine weight bands also preclude identifying an optimal dose ratio. Outcomes were limited to the immediate perioperative period. Larger trials with clearly specified endpoints should assess dose selection, recovery and adverse events, with additional-session follow-up to examine subsequent cooperation.

Conclusions

In children undergoing UFCL for burn scars, intranasal dexmedetomidine added to esketamine improved pre-induction sedation and perioperative behavioural scores and reduced total propofol use. Sedation differences at 30 min and immediately before induction were the most consistent across analyses. No child required assisted ventilation or treatment for hypotension or bradycardia. The findings support further evaluation of this needle-free premedication strategy in repeated burn-scar care, with appropriate cardiorespiratory monitoring and additional assessment of dose selection and recovery.

Abbreviations

ASA

American Society of Anesthesiologists

CI

confidence interval

HR

heart rate

MAP

mean arterial pressure

MAS

Mask Acceptance Scale

NMDA

N-methyl-D-aspartate

OR

odds ratio

PAED

Pediatric Anesthesia Emergence Delirium

PSAS

Parental Separation Anxiety Scale

RR

respiratory rate

RSS

Ramsay Sedation Scale

SD

standard deviation

SpO₂

peripheral oxygen saturation
UFCL
ultrapulsed fractional carbon dioxide laser.

Declarations

Ethics approval and consent to participate

The study was approved by Medical Ethics Committee of Wuhan Third Hospital (approval number KY2024-031-01). Written informed consent was obtained from the parents or legal guardians of all participants before enrolment.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

GH conceived the study. All authors contributed to the study design. JC and PL collected the data. SD analysed and interpreted the data. S drafted the manuscript. GH and SD revised the manuscript. All authors read and approved the final manuscript.

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Figures

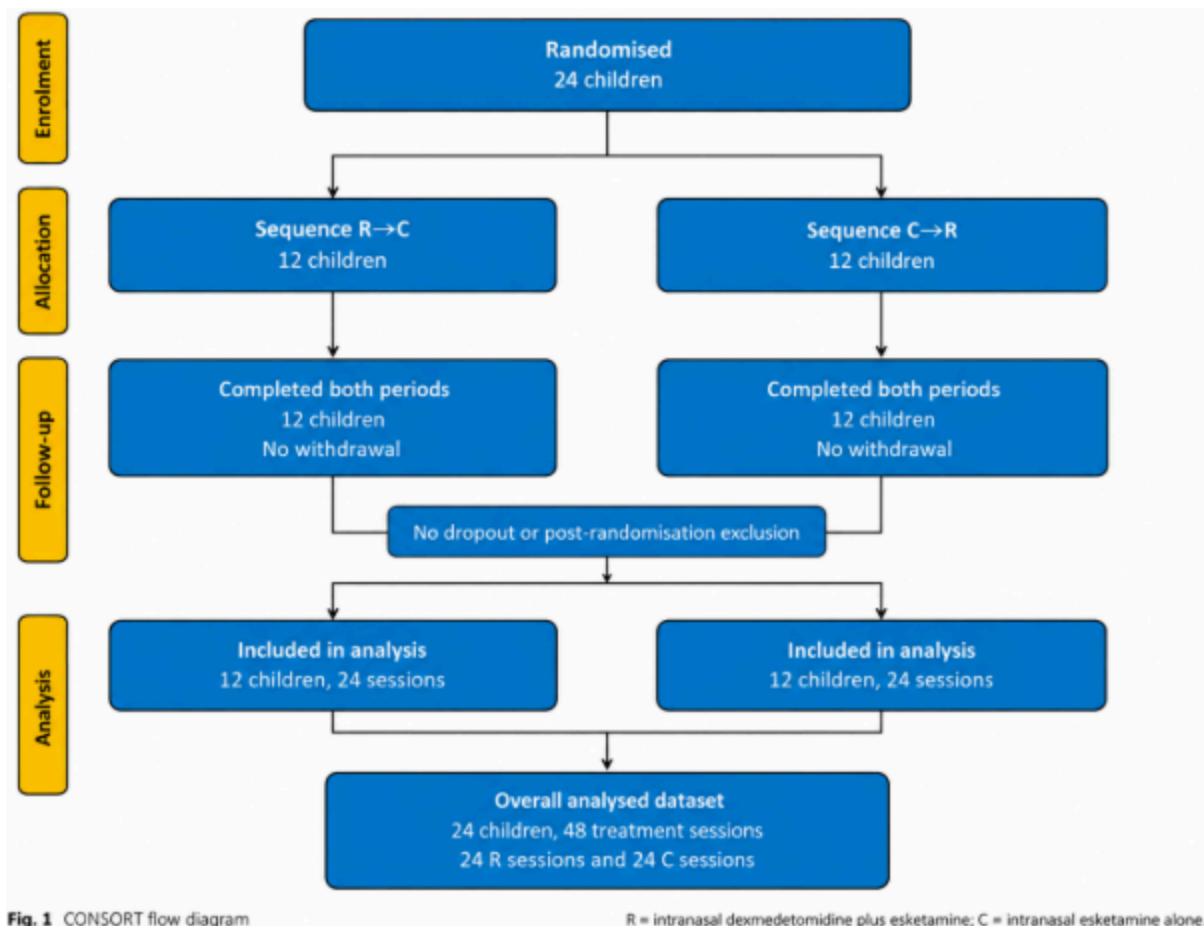


Figure 1

Participant flow through the two-period crossover trial

Twenty-four children were randomised to the R→C or C→R sequence (12 per sequence). Each child received both regimens in the assigned order, with 63–76 days between sessions. All children completed both periods and were included in the analysis, yielding 24 participants and 48 treatment sessions (24 per regimen). There were no dropouts or post-randomisation exclusions. R, intranasal dexmedetomidine plus esketamine; C, intranasal esketamine alone.

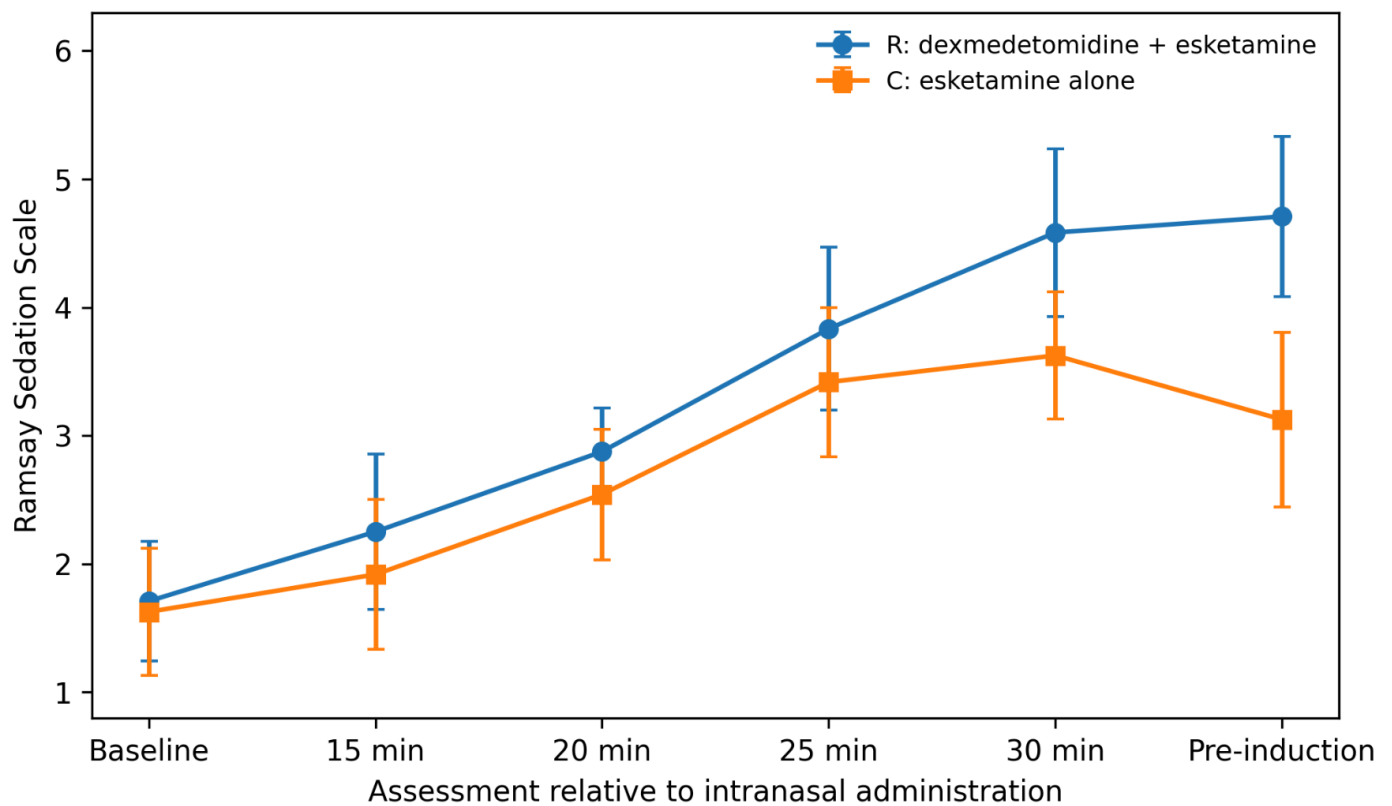


Figure 2

Ramsay Sedation Scale before and after intranasal premedication

Points show observed means and error bars show standard deviations across 24 children per regimen. These are descriptive, unadjusted trajectories. T0 is the same-session baseline; T1–T4 are 15, 20, 25 and 30 min after administration; T5 is immediately before induction and is event-defined. The assessment categories are equally spaced for display and do not imply equal elapsed intervals. Adjusted treatment contrasts are reported in the tables. R, intranasal dexmedetomidine plus esketamine; C, intranasal esketamine alone.

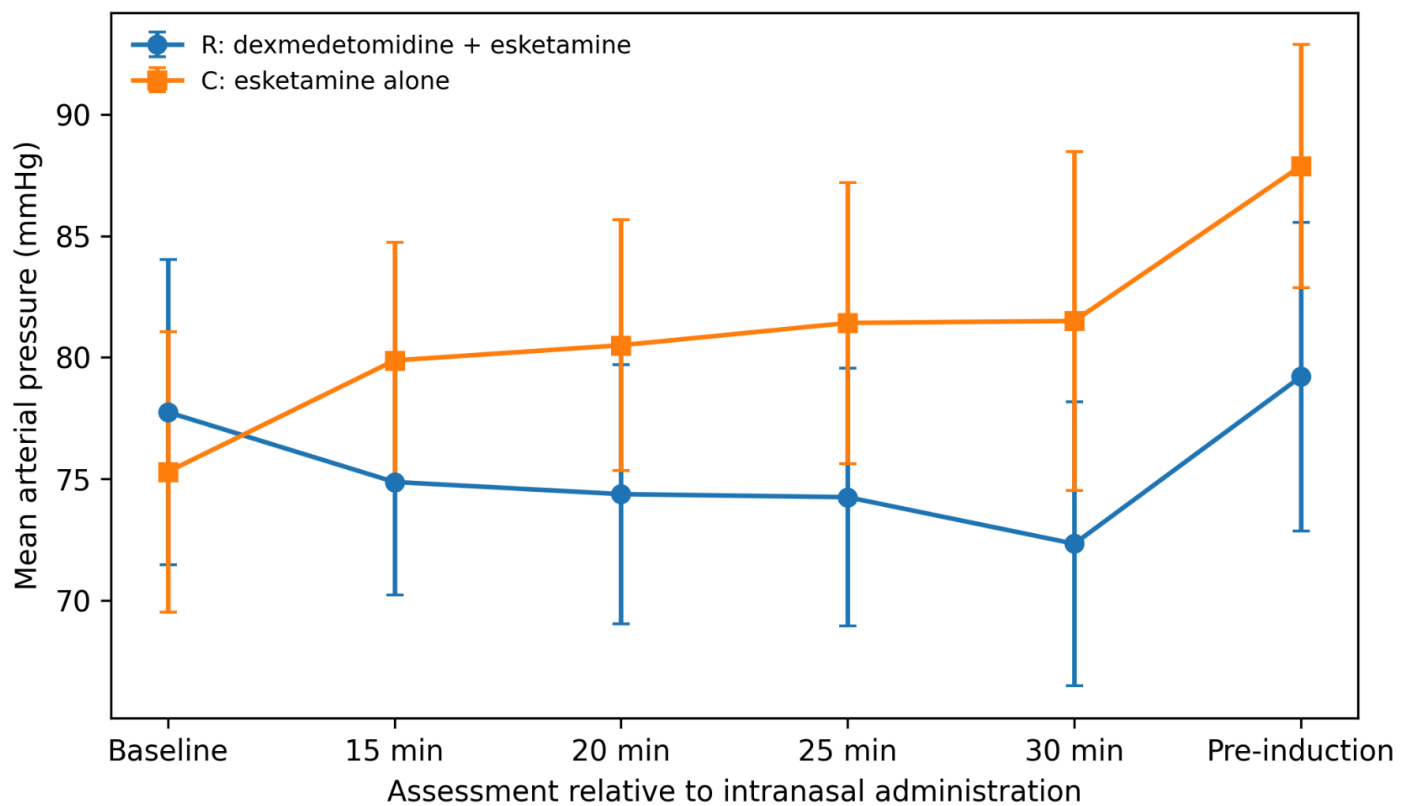


Figure 3

Mean arterial pressure before and after intranasal premedication

Points show observed means and error bars show standard deviations across 24 children per regimen. These are descriptive, unadjusted trajectories. T0 is the same-session baseline; T1–T4 are 15, 20, 25 and 30 min after administration; T5 is immediately before induction and is event-defined. The assessment categories are equally spaced for display and do not imply equal elapsed intervals. Adjusted treatment contrasts are reported in the tables. R, intranasal dexmedetomidine plus esketamine; C, intranasal esketamine alone.

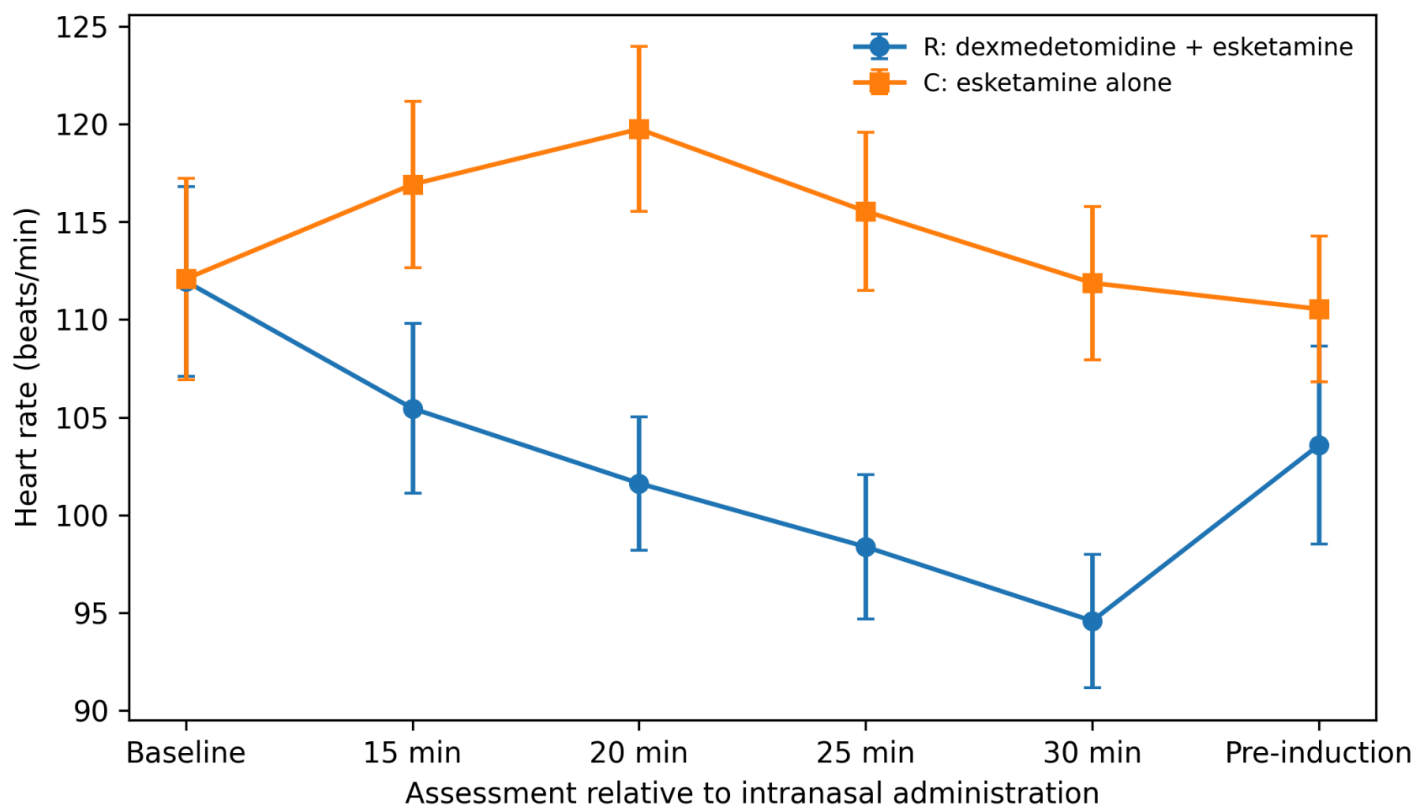


Figure 4

Heart rate before and after intranasal premedication

Points show observed means and error bars show standard deviations across 24 children per regimen. These are descriptive, unadjusted trajectories. T0 is the same-session baseline; T1–T4 are 15, 20, 25 and 30 min after administration; T5 is immediately before induction and is event-defined. The assessment categories are equally spaced for display and do not imply equal elapsed intervals. Adjusted treatment contrasts are reported in the tables. R, intranasal dexmedetomidine plus esketamine; C, intranasal esketamine alone.

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