Supplementary material 2

Supplementary Table 1. Results.

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| Author/Year | Study design | Number of patients and age | Type of sedation/Groups | Time when anxiety was measured | Side effects reported | Patient recovery | Parent satisfaction | Type of anxiety measurement (sedation) | |
| Biological factors and vital signs assessed | Surveys |
| Elkhatib *et al.* [15], 2024 | RCT | 72 patients aged 4–6 years | Group 1 (n = 24): 5 μg/kg nebulized DEX  Group 2 (n = 24): 3 μg/kg DEX + 0.3 mg/kg nebulized MID  Group 3 (n = 24): 0.5 mg/kg nebulized MID | Before, during and until discharge | Not evaluated | Not evaluated | Not evaluated | - | MOAASS (sedation)  FLACC (pain)  Ease of completing treatment |
| El-Rouby *et al.* [16], 2024 | RCT | 56 patients aged 3–5 years | Group 1 (n = 28): 2 μg/kg oral DEX + 2 mg/kg KET  Group 2 (control, n = 28): 4 μg/kg oral DEX | Before, during and until discharge | No significant amnestic effect found (*p* > 0.05) | DEX-KET fastest recovery | Not evaluated | SBP  DBP  HR  SatO2  Salivary sIgA | OSUBRS |
| Dubey *et al.* [23], 2024 | Cross-over RCT | 47 patients aged 3–9 years | Group 1 (n = 47): 7 mm/kg IN KET  Group 2 (n = 47): 0.3 mg/kg IN MID + 3 μg/kg IN DEX | Before, during and until discharge | No significant adverse effects found | KET fastest recovery (*p* < 0.001) | Not evaluated | SBP  DBP  HR  SatO2 | UMSS  MRAAPD (ease of completing treatment) |
| Janiani *et al.* [26], 2024 | Cross-over RCT | 14 patients aged 6–8 years | Group 1 (n = 14): 1 μg/kg IN DEX  Group 2 (n = 14): 0.3 mg/kg IN MID  Group 3 (n = 14): N2O | Before, during and until discharge | Sneezing and coughing (*p* < 0.001) | Not evaluated | Not evaluated | HR  SatO2 | Ramsay |
| Isik *et al.* [27], 2024 | RCT | 69 patients aged 3–7 years | Group 1 (control, n = 23): 20–60 μg/kg/min IV propofol  Group 2 (n = 23): IV ketofol 1:3 (50 mg KET + 150 propofol)  20–60 μg/kg/min  Group 3 (n = 23): IVketofol 1:4(50 mg KET + 200 propofol) 20–60 μg/kg/min | Before, during and until discharge | No significant adverse effects found | Ketofol 1:3 significant longer recovery than Propofol (*p* < 0.001) and Ketofol 1:4 (*p* = 0.002) | Not evaluated | SCL  BIS  RSS  SBP  DBP  HR  SpO2 | Ramsay |
| Ansari *et al.* [6], 2024 | Cross-over RCT | 26 patients aged 2–6 years | Group 1 (n = 26): 10 mg/kg IN KET  Group 2 (n = 26): 5 mg/kg IM KET | Before, during and until discharge | No significant adverse effects found (nausea and vomiting) | MID IN recovery was in shorter time than IM | Preferred IM | - | Houpt |
| Nie *et al.* [24], 2024 | RCT | 83 patients aged 3–12 years | Group 1 (n = 43): 0.5 mg/kg oral MID + IN placebo  Group 2 (n = 40): 0.5 mg/kg oral MID + 2 μg/kg IN DEX | Before, during and until discharge | No significant adverse effects found (*p* = 0.660), except for lethargy (*p* = 0.023) | Not evaluated | Very satisfied Group 2 *vs.* Group 1 (*p* = 0.001) | - | Ramsay  Houpt  Frankl |
| Janiani *et al.* [18], 2023 | Cross-over RCT | 32 patients aged 3–5 years | Group 1 (n = 32): 0.3 mg/kg IN MID  Group 2 (n = 32): N2O | During | Not evaluated | Not evaluated | Not evaluated | - | OSUBRS |
| Alhaidari *et al.* [25], 2022 | Cross-over RCT | 32 patients aged 3–6 years | Group 1 (n = 32): 0.7 mg/kg oral MID + IN placebo  Group 2 (n = 32): 0.7 mg/kg oral MID + 1 μg/kg IN FEN | Before, during and until discharge | No significant adverse effects found (*p* = 0.70) | Better recovery in MID + FEN Group | Not evaluated | - | MOAASS  Behavioral scale |
| Rehman *et al.* [22], 2021 | RCT | 30 patients aged 2–5 years | Group 1 (n = 15): 1 mg/kg IV Propofol + saline  Group 2 (n = 15): 1 mg/kg IV propofol + 1 μg/kg IV DEX | Before, during and until discharge | No significant adverse effects found | Similar recovery time (*p* > 0.05) | Not evaluated | NIBP  HR  RR  SpO2 | Houpt |
| Shaat *et al.* [19], 2022 | Cross-over RCT | 42 patients aged 5–7 years | Group 1 (n = 42): IN DEX 1 μg/kg  Group 2 (n = 42): sublingual DEX 1 μg/kg | Before and during | Not evaluated | Not evaluated | Not evaluated | - | Venham |
| Haider *et al.* [21], 2022 | Cross-over RCT | 30 patients aged 2–6 years | Group 1 (n = 30): 1 μg/kg  IV DEX + 0.5 mg/kg IV KET  Group 2 (n = 30): 1 μg/kg  DEX | Before, during and until discharge | No significant adverse effects found (*p* = 0.483) | Group 1: 28.67  Group 2: 21.67  *p* = 0.866 | Using Likert scale of satisfaction (*p* = 1) | HR  NIBP  RR  SpO2 | Houpt  Venham |
| Hammadyeh *et al.* [20], 2019 | RCT | 40 patients aged 2–6 years | Group 1 (n = 20): 1 μg/kg  IV DEX + 0.2 μg/kg continuous infusion  Group 2 (n = 20):2 mg/kg IV KET + 0.01 mg/kg Atropine | Before, during and until discharge | No side effects were reported | Shorter recovery time in DEX Group (15) than in KET (17), but not statistically significant values  (*p* = 0.1) | Not evaluated | - | OSUBRS |
| El-Rouby *et al.* [17], 2024 | RCT | 56 patients aged 3–5 years | Group 1 (n = 28): 2 μg/kg DEX + 2 mg/kg oral KET  Group 2 (n = 28):4 μg/kgoralDEX | Before, during and until discharge | No significant adverse effects found | DEX-KET showed a shorter recovery time than DEX (*p* = 0.0001) | Not evaluated | - | MOAASS  FLACC  Houpt |

HR: Heart Rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; SatO2: Arterial Oxygen Saturation; sIgA: Secretory Immunoglobulin A; SCLs: Saliva Cortisol Levels; BIS: Bispectral Index; RR: Respiratory Rate; NIBP: Non-Invasive Blood Pressure; RCT: Randomized Controlled Trial; DEX: Dexmedetomidine; MID: Midazolam; MOAASS: Modified Observer Assessment of Alertness and Sedation Scale; FLACC: Face, Legs, Activity, Cry, Controllability; KET: Ketamine; OSUBRS: Ohio State University Behavioral Rating Scale; N2O: Nitrous Oxide; SpO2: Pulse Oxygen Saturation; IM: Intramuscular; IN: Intranasal; UMSS: University of Michigan Sedation Scale; MRAAPD: Modified Recommendations American Academy of Pediatric Dentistry; IV: Intravenous; RSS: Ramsey Sedation Scale.

Supplementary Table 2. Biological factors and vital signs assessed.

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| Article | Type of sedation used | Biological factors and vital signs assessed | Main results |
| El-Rouby *et al.* [16], 2024 | Group 1 (n = 28): 2 μg/kg oral DEX + 2 mg/kg KET  Group 2 (control, n = 28): 4 μg/kg oral DEX | HR  SBP  DBP  SatO2  Salivary sIgA | HR  Group 1: 104.38  Group 2: 104.85  *p* = 0.899 |
| SBP  Group 1: 95.35  Group 2: 98.46  *p* = 0.523 |
| DBP  Group 1: 64.96  Group 2: 65.85  *p* = 0.830 |
| SatO2  Group 1: 98.08  Group 2: 98.04  *p* = 0.865 |
| Salivary sIgA  Group 1: 0.27  Group 2: 0.12  *p* = 0.556 |
| Dubey *et al.* [23], 2024 | Group 1 (n = 47): 7 mg/kg IN KET  Group 2 (n = 47): 0.3 mg/kg IN MID + 3 μg/kg IN DEX | HR  SBP  DBP  SatO2 | HR  Group 1: 131.51  Group 2: 118.79 |
| SBP  Group 1: 129.00  Group 2: 112.06 |
| DBP  Group 1: 70.59  Group 2: 62.70 |
| SatO2  Group 1: 99.57  Group 2: 98.33 |
| Janiani *et al.* [26], 2024 | Group 1 (n = 14): 1 μg/kg IN DEX  Group 2 (n = 14): 0.3 mg/kg IN MID  Group 3 (n = 14): N2O | HR  SatO2 | HR  Group 1: 95.14  Group 2: 96.71  Group 3: 96.92 |
| SatO2  Group 1: 99.14  Group 2: 97.71  Group 3: 99.07  *p* = 0.001 |
| Isik *et al.* [27], 2024 | Group 1 (control, n = 23): 20–60 μg/kg/min IV propofol  Group 2 (n = 23): IV ketofol 1:3 (50 mg ketamine + 150 propofol)  20–60 μg/kg/min  Group 3 (n = 23): IVketofol 1:4(50 mg ketamine + 200 propofol) 20–60 μg/kg/min | SCL  BIS  HR  SBP  DBP  SpO2 | SCL (postoperative)  Group 1: 16.2  Group 2: 27.8  Group 3: 41.3  *p* = 0.001 |
| BIS (at 25 min)  Group 1: 55  Group 2: 57  Group 3: 65  *p* < 0.001 |
| HR (at 15 min)  Group 1: 97.1  Group 2: 115.2  Group 3: 107.5 |
| SBP (at 15 min)  Group 1: 89  Group 2: 92.2  Group 3: 93.2 |
| DBP  Group 1: 49.2  Group 2: 51.7  Group 3: 53.9 |
| SpO2  Group 1: 98.8  Group 2: 97.9  Group 3: 97.7 |
| Rehman *et al.* [22], 2021 | Group 1 (n = 15): 1 mg/kg IV propofol + saline  Group 2 (n = 15): 1 mg/kg IV propofol + 1 μg/kg IV DEX | HR  SBP  DBP  RR  SpO2 | HR (at 15 min)  Group 1: 119.2  Group 2: 108.87 |
| SpO2 (at 15 min)  Group 1: 98.67  Group 2: 98.67 |
| RR (at 15 min)  Group 1: 20.67  Group 2: 21.27 |
| SBP (at 15 min)  Group 1: 91.87  Group 2: 93.4 |
| DBP (at 15 min)  Group 1: 51.83  Group 2: 51.83 |
| Haider *et al.* [21], 2022 | Group 1 (n = 30): 1 μg/kg  DEX IV + 0.5 mg/kg IV KET  Group 2 (n = 30):1 μg/kg  DEX | HR  NIBP  RR  SpO2 | HR (at 15 min)  Group 1: 121  Group 2: 116 |
| NIBP (at 15 min)  Group 1: 90  Group 2: 83 |
| RR (at 15 min)  Group 1: 23.2  Group 2: 20.8 |
| SpO2 (at 15 min)  Group 1: 97.5  Group 2: 97.9 |

HR: Heart Rate; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; SatO2: Arterial Oxygen Saturation; sIgA: Secretory Immunoglobulin A; SCLs: Saliva Cortisol Levels; BIS: Bispectral Index; RR: Respiratory Rate; NIBP: Non-Invasive Blood Pressure; DEX: Dexmedetomidine; MID: Midazolam; KET: Ketamine; N2O: Nitrous Oxide; SpO2: Oxygen Saturation; IN: Intranasal; IV: Intravenous.

Supplementary Table 3. Measures using scales/surveys.

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| Article | Type of sedation used | Measures used | Main results |
| Elkhatib *et al.* [15], 2024 | Group 1 (n = 24): 5 μg/kg nebulized DEX  Group 2 (n = 24): 3 μg/kg DEX + 0.3 mg/kg nebulized MID  Group 3 (n = 24): 0.5 mg/kg nebulized MID | MOAASS (sedation)  FLACC (pain)  Ease of completing the treatment | MOAASS (during treatment)  Group 1: 3.33  Group 2: 2.79  Group 3: 2.99  *p* = 0.045 |
| FLACC  Group 1: 3.75  Group 2: 3.29  Group 3: 4.80  *p* = 0.20 |
| Ease of completing the treatment  Group 1: 3.67  Group 2: 3.58  Group 3: 2.78  *p* = 0.03 |
| El-Rouby *et al.* [16], 2024 | Group 1 (n = 28): 2 μg/kg oral DEX + 2 mg/kg KET  Group 2 (control, n = 28): 4 μg/kg oral DEX | OSUBRS | OSUBRS (with local anesthesia)  Group 1: 2  Group 2: 4  *p* = 0.017  (during treatment)  Group 1: 2  Group 2: 3  *p* = 0.037 |
| Dubey *et al.* [23], 2024 | Group 1 (n = 47): 7 mg/kg IN KET  Group 2 (n = 47): 0.3 mg/kg IN MID + 3 μg/kg IN DEX | UMSS  MRAAPD (ease of completing the treatment) | UMSS  Group 1: 2.04  Group 2: 1.51  *p* = 0.001 |
| MRAAPDP  Group 1: 28.04  Group 2: 36.04  *p* < 0.001 |
| Janiani *et al.* [26], 2024 | Group 1 (n = 14): 1 μg/kg IN DEX  Group 2 (n = 14): 0.3 mg/kg IN MID  Group 3 (n = 14): N2O | Ramsay | Ramsay  Group 1: 1.86  Group 2: 2.35  Group 3: 1.35  *p* = 0.001 |
| Isik *et al.* [27], 2024 | Group 1 (control, n = 23): 20–60 μg/kg/min IV propofol  Group 2 (n = 23): IV ketofol 1:3 (50 mg KET + 150 propofol)  20–60 μg/kg/min  Group 3 (n = 23):IV ketofol 1:4(50 mg KET + 200 propofol) 20–60 μg/kg/min | Ramsay | Ramsay (at 15 min)  Group 1: 5  Group 2: 5  Group 3: 5  *p* = 0.907 |
| Ansari *et al.* [6], 2024 | Group 1 (n = 26): 10 mg/kg IN KET  Group 2 (n = 26): 5 mg/kg IM KET | Houpt | Houpt (at 15 min)  Group 1: 19.2  Group 2:92.3  *p* < 0.05 |
| Nie *et al.* [24], 2024 | Group 1 (n = 43): 0.5 mg/kg oral MID + IN placebo  Group 2 (n = 40): 0.5 mg/kg oral MID + 2 μg/kg IN DEX | Ramsay  Frankl  Houpt | Ramsay  Group 1: 2  Group 2: 4  *p* < 0.05 |
| Frankl  Group 1: 2  Group 2: 3  *p* = 0.008 |
| Houpt  Group 1: 4  Group 2: 5  *p* = 0.033 |
| Janiani *et al.* [18], 2023 | Group 1 (n = 32): 0.3 mg/kg IN MID  Group 2 (n = 32): N2O | OSUBRS | OSUBRS (with local anesthesia)  Group 1: 1.47  Group 2:1.94  *p* < 0.14 |
| Alhaidari *et al.* [25], 2022 | Group 1 (n = 32): 0.7 mg/kg oral MID oral + IN placebo  Group 2 (n = 32): 0.7 mg/kg oral MID + 1 μg/kg IN FEN | MOAASS  Behavioral scale | MOAASS (at 15 min)  Group 1: 5.04  Group 2: 5.38  *p* = 0.012 |
| Behavioral scale (at 15 min)  Group 1: 2.52  Group 2: 2.63  *p* = 0.125 |
| Rehman *et al.* [22], 2021 | Group 1 (n = 15): 1 mg/kg IV propofol + saline  Group 2 (n = 15):1 mg/kg IV propofol + 1 μg/kg IV DEX | Houpt | Houpt (with local anesthesia)  Group 1: 5.13  Group 2:4.6 |
| Shaat *et al.* [19], 2022 | Group 1 (n = 42): IN DEX 1 μg/kg  Group 2 (n = 42):sublingual DEX 1 μg/kg | Venham | Venham (with local anesthesia)  Group 1: 1  Group 2:1  *p* = 0.44 |
| Haider *et al.* [21], 2022 | Group 1 (n = 30): 1 μg/kg  IV DEX + 0.5 mg/kg IV KET  Group 2 (n = 30): 1 μg/kg  DEX | Venham  Houpt | Venham  Group 1: 4.53  Group 2: 5.00  *p* = 0.004 |
| Houpt (with local anesthesia)  Group 1: 4.9  Group 2: 3.8 |
| Hammadyeh *et al.* [20], 2019 | Group 1 (n = 20): 1 μg/kg  IV DEX + 0.2 μg/kg continuous infusion  Group 2 (n = 20): 2 mg/kg IV KET + 0.01 mg/kg Atropine | OSUBRS | OSUBRS  Group 1: 1.2  Group 2: 2.3  *p* = 0.03 |
| El-Rouby *et al.* [17], 2024 | Group 1 (n = 28): 2 μg/kg DEX + 2 mg/kg oral KET  Group 2 (n = 28): 4 μg/kg oral DEX | MOAASS  FLACC  Houpt | MOAASS  Group 1: 3.50  Group 2: 2.50  *p* = 0.064 |
| FLACC (with local anesthesia)  Group 1: 2.50  Group 2: 5  *p* = 0.057 |
| Houpt  Group 1: 4  Group 2:3  *p* = 0.048 |

DEX: Dexmedetomidine; MID: Midazolam; FLACC: Face, Legs, Activity, Cry: Controllability; KET: Ketamine; OSUBRS: Ohio State University Behavioral Rating Scale; N2O: Nitrous Oxide; MOAASS: Modified Observer Assessment of Alertness and Sedation Scale; UMSS: University of Michigan Sedation Scale; IN: Intranasal; MRAAPD: Modified Recommendations American Academy of Pediatric Dentistry; IV: Intravenous; IM: Intramuscular.