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Review

Pharmacological strategies to reduce perioperative anxiety in children – a narrative review

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Abstract /Summary

Preoperative anxiety is common among children, resulting in negative postoperative behavior and increased postoperative pain. This review focuses on the practical use, safety, and efficacy of pharmacological strategies to reduce perioperative anxiety in children. The PubMed® database was searched using MeSH terms: ((care, preoperative) AND (children) AND (anti-anxiety drugs); (medication, preanesthetic) AND (child, preschool). An in-dept assessment was performed after which 85 articles were retrieved. Benzodiazepines (midazolam, diazepam), zolpidem, melatonin, opioids (fentanyl, butorphanol), alpha-2-adrenergic receptor agonists (clonidine, dexmedetomidine), ketamine and antihistamines (hydroxyzine, promethazine) were reviewed. Their pharmacological properties, routes of administration, doses, efficacy and (dis)advantages are discussed in this review. Based upon the results of our review, some suggestions can be made. Oral midazolam, oral clonidine, intranasally dexmedetomidine and the combination of oral ketamine and midazolam are recommendable products. Some other products like oral diazepam, butorphanol, ketamine intranasal s-ketamine + midazolam and hydroxyzine can be considered because of their proper safety profile and benefits.
Further research should focus on patient selection for specific pharmacological and non-pharmacological interventions to achieve a tailored approach. Standardized assessment of anxiety, clinical significancy and feasibility should be included in the objectives of these studies.

Keywords: **Medication, preanesthetic, care, perioperative, children.**

Introduction

Anesthesiologists are confronted daily with children scheduled for diagnostic or surgical procedures requiring general anesthesia. For most children this results in high anxiety and often non-cooperative behavior. Perioperative anxiety associated with to negative postoperative behavior and an increase in postoperative pain[1]. A lot of strategies to diminish periprocedural anxiety in children have been described. These include non-pharmacological methods (information and education, parental presence, distraction techniques) and pharmacological methods (under the form of premedication). This review focuses on the practical use, safety, and efficacy of pharmacological approaches.

Methods

Approval from the academic Ethics Committee was obtained on March 17th, 2021 (identifier: MP017638). The recommendations and checklist of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) were followed to conduct this review[2]. The PubMed® database was searched using following Medical Subject Headings terms (MeSH): ((care,

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This review will be submitted for and presented at BeSARPP Graduation Day, June 10th, 2023 (Best Master Work competition).

preoperative) AND (children) AND (anti-anxiety drugs); (medication, preanesthetic) AND (child, preschool). The search was restricted to articles written in English, Dutch, French or German. Older articles – defined as published before January 1st, 2000 – were excluded by automation. Prospective and retrospective clinical trials on children, case series, meta-analysis, systematic reviews, or observational studies were selected for inclusion. Records were screened by reviewing titles and abstracts on the relevancy of its content. Due to practical and financial considerations, articles not freely available via institutional login, were excluded. Selected articles underwent full-text review and references were screened for further studies not identified by the initial search.

Results

A – identification of studies

One-thousand two-hundred ninety records (n=1290) were obtained in the PubMed® database. More than seventy percent of them (n=965) were excluded by automation. After screening by title and abstract, 78 articles were left for full text review, of which 9 were marked as not relevant. After searching by citation, 16 studies were added to our review. The final analysis included 85 references. (See Table I. PRISMA flow diagram).

Drugs include midazolam (n=49), clonidine (n=19), dexmedetomidine (n=18), ketamine (n=16), opioids (n=3), diazepam (n=4), zolpidem (n=1), melatonin (n=6) and antihistamines (n=3). Preoperative effect was studied in the most of these records (n=69), whereas others focused on the postoperative effects and emergence behavior (n=28).

B – drugs

(See Table II. - Summary of studies.)

B-1. Benzodiazepines

B-1.1 Midazolam

Midazolam, a short-acting benzodiazepine, is the most studied anxiolytic of the last twenty years. It is extensively used as premedication for children and can be found on the World Health Organization Model List of Essential Medicines for Children[3]. Midazolam is a GABAergic agent which suppresses consciousness by reducing corticothalamic integration[4]. This results in an altered mental state (sedation), anxiolysis and anterograde amnesia.

Oral administration

Midazolam can be administered in different ways. Oral administration is a very easy, non-invasive, and therefore most common way of premedication. Fruit-flavored syrup preparations are available in certain countries (brand name Versed® - midazolam hydrochloride 2mgml^{-1}). Doses as low as 0,25mgkg^{-1} are effective for preoperative sedation and anxiolysis within 10 minutes[5].

Commercially available formulations are expensive and not available throughout the world[6]. Oral preparations can also be generated from intravenous solutions. Due to its intrinsic bitterness, multiple additives have been studied. When solved in Syrpalta (a commercially available pharmaceutical vehicle syrup) - plasma levels of midazolam where higher than pre-made syrup preparations with better clinical outcomes[7]. The addition of sodium citrate may have the same effect. It improves drug compliance and produces a deeper level of sedation compared to addition of Pepsi® Cola, pomegranate

Table I. — PRISMA flow diagram.

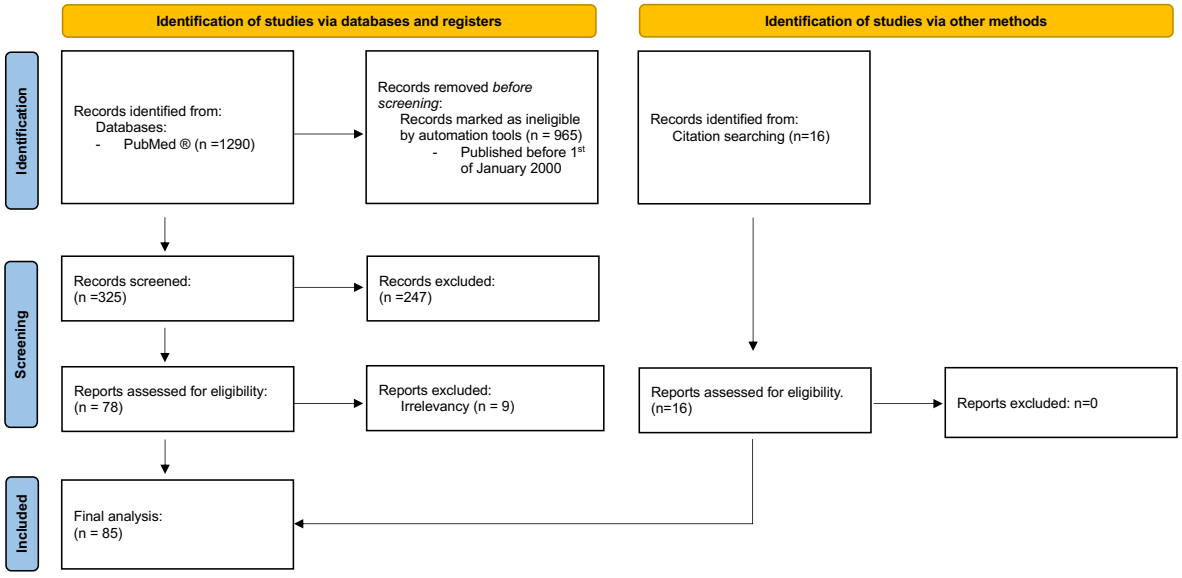

Table II. — Summary of studies. Publications marked in red are mentioned more than once.

author	year	type of study	number of subjects	population	intervention	comparison intervention	outcome parameters	conclusion
Midazolam								
Kogan A, et al.[30]	2002	Double-blind, randomized trial	119	1,5-5 year(s) old, ASA I-II	Oral midazolm 0,5mgkg^{-1}	Intranasal midazolam 0,3mgkg^{-1}; Rectal midazolam 0,5mgkg^{-1}; Sublingual midazolam 0,3mgkg^{-1}	Efficacy, onset time, safety, acceptability to parents	All routes of administration are equal
Lam C, et al.[35]	2005	Single-blind, retrospective randomized trial	23	2-9 year(s) old, ASA I	Intranasal midazolam 0,2mgkg^{-1}	Intramuscular midazolam 0,2mgkg^{-1}	Efficacy, sedation, anxiolysis	Favors intramuscular midazolam 0,2mgkg^{-1}
Oral midazolam								
Buffett-Jerrott SE, et al.[50]	2003	Double-blind, randomized-controlled trial	40	4-6 year(s) old, undergoing myringotomy	Oral midazolam 0,5mgkg^{-1} + acetaminophen 15mgkg^{-1}	Oral acetaminophen 15mgkg^{-1}	Memory, sedation, attention	Midazolam impairs memory, not only due to sedation/ inattention
Coté CJ, et al.[5]	2002	Double-blind, randomized trial	405	6 months – 16 year(s) old, ASA I-III	Commercially available oral midazolam syrup 0,25mgkg^{-1}	Commercially available oral midazolam 0,50mgkg^{-1}; Commercially available midazolam 1mgkg^{-1}	Level of sedation, anxiolysis, onset time	Favors 0,25mgkg^{-1}, little effect with higher doses
Golden L, et al.[102]	2006	Single-blind, randomized trial	100	3-6 year(s) old, ASA I-II, undergoing elective ambulatory surgery	Giving toy 5 min prior to oral midazolam 0,5mgkg^{-1} administration	Oral midazolam 0,5mgkg^{-1} administration	Anxiety prior to oral administration of midazolam	Favors giving a toy
Masue T, et al.[29]	2003	Randomized trial	193	4 old – 2 year(s) old, congenital heart disease	Oral midazolam 1,0mgkg^{-1}; Oral midazolam 1,5mgkg^{-1}	Oral midazolam 0,5mgkg^{-1}	Level of sedation, safety	Favors oral midazolam 1,5mgkg^{-1}
Mehrdad S, et al.[28]	2011	Randomized-controlled trial	90	2-8 year(s) old, ASA I-II	Oral midazolam 0,5mgkg^{-1}; Oral midazolam 1mgkg^{-1}	Oral placebo	Anxiolysis, parental separation, mask acceptance, preparation of intravenous line	Favors oral midazolam 1mgkg^{-1}
Sola C, et al.[46]	2017	Single-blind, randomized trial	135	2-12 year(s) old,	Handheld DVD-player; Oral midazolam 0,4mgkg^{-1} + handheld DVD-player	Oral midazolam 0,4mgkg^{-1}	Efficacy	All strategies are effective
Zand F, et al.[17]	2011	Single-blind, randomized trial	167	2-7 year(s) old, ASA I-II, undergoing outpatient surgery	Sevoflurane + oral midazolam 0,5mgkg^{-1}; Halothane + oral midazolam 0,5mgkg^{-1}	Sevoflurane + parental presence (no premedication); Halothane + parental presence (no premedication)	Postoperative agitation	Equally effective after inhaled sevoflurane, favors midazolam after inhaled halothane
Additives to oral midazolam								
Brosius KK, et al.[7]	2003	Double-blind, randomized trial	50	2-10 year(s) old, ASA I-II	Versed® syrup 0,5mgkg^{-1}	Mixture of IV midazolam 0,5mgkg^{-1} + Syrpalta syrup	Level of sedation, plasma levels	Favors IV midazolam + Syrpalta syrup

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Isik B, et al.[8]	2008	Double-blind, randomized-controlled trial	75	2-8 year(s) old, ASA I, undergoing dental treatment, compliance was determined as 3-4 with the Frankl Behavior Scale.	Oral administration of injectable midazolam + Pepsi Cola or + 10% Sodium citrate or + fresh pomegranate juice or + grapefruit juice	Oral administration of injectable midazolam	Tolerability, efficacy, safety	Favors IV midazolam + sodium citrate
Lammers CR, et al.[9]	2002	Double-blind, randomized-controlled trial	40	2-6 year(s) old, ASA I-II	Oral midazolam 0,5mgkg^{-1} + sodium citrate	Oral midazolam 0,5mgkg^{-1} + Hawaiian fruit punch	Onset of sedation, anxiolysis, parental separation, induction conditions	Favors oral midazolam 0,5mgkg^{-1} + sodium citrate due to shortening of sedation, but no difference in other factors
Salman S, et al.[10]	2018	Double-blind, randomized trial	150	3-16 year(s) old	Oral midazolam in chocolate-based tablet 0,5mgkg^{-1}	Oral midazolam 0,5mgkg^{-1}	Tolerability, efficacy	Favors oral midazolam in chocolate-based tablet 0,5mgkg^{-1}
Oral midazolam-clonidine								
Almenrader N, et al.[24]	2007	Open-label, randomized trial	64	1-6 year(s) old, ASA I-II	Oral midazolam 0,5mgkg^{-1}	Oral clonidine 4µgkg^{-1}	Tolerability, efficacy, postoperative recovery, parental satisfaction	Favors oral clonidine
Fazi L, et al.[16]	2001	Double-blind, randomized-controlled trial	134	4-12 year(s) old, undergoing tonsillectomy	Oral placebo + oral midazolam 0,5mgkg^{-1}	Oral clonidine 4µgkg^{-1} + placebo	Preoperative behavior, postoperative recovery	No clinically important benefits
Mikawa K, et al.[74]	2002	Letter to the editor – report of clinical trial	175	2-11 year(s) old, undergoing minor surgery	Oral midazolam 0,5mgkg^{-1}; Oral placebo	Oral clonidine 2µgkg^{-1} ; Oral clonidine 4µgkg^{-1}	Sevoflurane-related agitation, discharge times	Favors oral clonidine
Zhang CMD, et al.[20]	2013	Meta-analysis (12 randomized-controlled trials)	1214	0,5-10 year(s) old	0,2-0,5 mgkg^{-1} oral midazolam premedication; 0,75-3µkg^{-1} epidural/intravenous clonidine intraoperatively	Placebo	Sevoflurane-related emergence agitation	Favors both interventions
Oral midazolam - dexmedetomidine								
Özcengiz D, et al.[21]	2011	Randomized-controlled trial	100	3-9 year(s) old, ASA I-II, undergoing esophageal dilatation	Oral midazolam 0,5mgkg^{-1}; Oral placebo	Oral melatonin 0,1mgkg-1; Oral dexmedetomidine 2,5µgkg^{-1}	Postoperative agitation	Equally effective compared to placebo
Sathyamoorthy M, et al.[19]	2019	Single-blind, randomized trial	75	>5 year(s) old, >20kg scheduled for dental procedures	Oral midazolam 0,5mgkg^{-1}	Intranasal dexmedetomidine 2µgkg^{-1}	Sedation, parental separation, mask acceptance, safety	Favors intranasal dexmedetomidine

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Yuen VM, et al.[48]	2008	Double-blind, randomized-controlled trial	96	2-12 year(s) old, ASA I-II, undergoing minor surgery	Intranasal placebo + oral midazolam 0,5mgkg^{-1} + oral acetaminophen 20mgkg^{-1}	Intranasal dexmedetomidine 0,5µgkg^{-1} + oral acetaminophen 20mgkg^{-1}; Intranasal dexmedetomidine 1µgkg^{-1} + oral acetaminophen 20mgkg^{-1}	Sedation, parental separation	Equally effective
Oral midazolam - ketamine								
Darlong V, et al.[47]	2004	Single-blind, randomized trial	78	1-9 year(s) old, ASA I-II, undergoing ophthalmic surgery	Oral midazolam 0,5mgkg^{-1}	Oral ketamine 6mgkg^{-1}; Oral ketamine 3mgkg^{-1} + oral midazolam 0,25mgkg^{-1}	Efficacy, side effects, onset time, recovery profile	Favors combination of oral ketamine with oral midazolam
Ghai B, et al.[95]	2004	Double-blind, randomized trial	100	10months - 6year(s) old, ASA I-II	Oral midazolam 0,5mgkg^{-1}	Oral midazolam 0,25mgkg^{-1} + ketamine 2,5mgkg^{-1}	Efficacy, safety, sedation, parental separation, mask acceptance, recovery profile	Equally effective, but favors combination of oral midazolam + ketamine
Horiuchi T, et al.[25]	2005	Single-blind, randomized trial	55	2-6year(s) old, ASA I-II	Oral midazolam 0,5mgkg^{-1}	Transmucosal (Lollipop) ketamine 50mg	Sedation, efficacy	Favors oral midazolam
Trabold B, et al.[96]	2002	Double-blind, randomized trial	79	1-8 year(s) old, ASA I-II	Oral midazolam 0,5mgkg^{-1}	Oral midazolam 0,5mgkg^{-1} + ketamine 1,8mgkg^{-1}, oral ketamine 3mgkg^{-1}	Emergence and recovery times	No difference
Oral midazolam - other								
Arai YCP, et al.[56]	2005	Single-blind, randomized-controlled trial	42	1-7 year(s) old, ASA I-II, undergoing adenotonsillectomy	Oral midazolam 0,5mgkg^{-1} + diazepam 0,25mgkg^{-1}; Oral midazolam 0,5mgkg^{-1}	No premedication	Pre-induction conditions, emergence condition	Favors combination of oral midazolam + diazepam
Gitto E, et al.[59]	2016	Pilot study: double-blind, randomized trial	92	5-14 year(s) old, undergoing elective surgery	Oral midazolam 0,5mgkg^{-1}	Oral melatonin 0,5mgkg^{-1}	Required infusion of propofol, sedation, emergence	Equally effective
Hanna AH, et al.[14]	2018	Non inferiority, randomized trial	86	2-9 year(s) old, ASA I-II	Oral midazolam 0,5mgkg^{-1}	Oral zolpidem syrup (± 0,25mgkg^{-1})	Anxiolysis, mask acceptance	Favors oral midazolam
Isik B, et al.[103]	2008	Single-blind, randomized-controlled trial	60	3-8 year(s) old, ASA I, undergoing dental treatment	Oral midazolam 0,75mgkg^{-1}	Oral melatonin 3mg; Oral melatonin 0,5mgkg^{-1}; Oral placebo	Sedation, safety	Favors midazolam
Kain Z, et al.[64]	2009	Double-blind, randomized trial	148	2-8 year(s) old, ASA I-II, undergoing outpatient elective surgery	Oral midazolam 0,5mgkg^{-1}	Oral melatonin 0,05mgkg^{-1}; Oral melatonin 0,2mgkg^{-1} ; Oral melatonin 0,4mgkg^{-1}	Anxiolysis at induction	Favors midazolam
Kurdi M, et al.[63]	2016	Double-blind, randomized-controlled trial	100	5-15 year(s) old, ASA I-II	Oral midazolam 0,5mgkg^{-1}	Oral placebo; Oral melatonin 0,5mgkg^{-1} ; Oral melatonin 0,75mgkg^{-1}	Anxiolysis, cognitive and psychomotor functions	Favors oral melatonin 0,75mgkg^{-1}
Martinez JL, et al.[6]	2002	Double-blind, randomized trial	154	4 months - 18 year(s) old, undergoing upper endoscopy	Oral midazolam 0,5mgkg^{-1} + IV meperidine 2mgkg^{-1}	Oral diazepam 0,3mgkg^{-1} + IV meperidine 2mgkg^{-1}	Efficacy, safety, cost	Equally effective, but lower cost with diazepam

Table II. — Summary of studies. Publications marked in red are mentioned more than once.

Nadri S, et al.[18]	2020	Double-blind, randomized-controlled trial	93	3-9 year(s) old, ASA I-II, undergoing ambulatory surgery	Oral midazolam 0,5mgkg^{-1}; Oral placebo	Oral promethazine 0,3mgkg^{-1}	Sedation, anxiolysis	Equally effective, significant different to placebo
Singh V, et al.[23]	2005	Double-blind, randomized trial	60	2-10 year(s) old, ASA I-II	Oral midazolam 0,5mgkg^{-1}	Oral butorphanol 0,2mgkg^{-1}	Sedation, anxiolysis, parental separation, IV-puncture, postoperative pain	Favors oral butorphanol
Sinha C, et al.[68]	2012	Double-blind, randomized trial	60	2-12 year(s) old, ASA I-II	Oral midazolam 0,5mgkg^{-1}	Oral butorphanol 0,2mgkg^{-1}	Sedation, anxiolysis, parental separation, IV-puncture, mask acceptance	Favors oral butorphanol (sedation), but midazolam superior as anxiolytic during venipuncture and mask application
Stewart B, et al.[51]	2019	Single-blind, randomized trial	102	4-12 year(s) old, ASA I-II, scheduled for outpatient surgery	Oral midazolam 0,3mgkg^{-1}	Tablet-based interactive distraction (TBID)	Anxiolysis, parental separation, mask acceptance	Favors TBID
Intranasal midazolam								
Akin A, et al.[32]	2012	Double-blind, randomized trial	90	2-9 year(s) old, ASA I, undergoing adenotonsillectomy	Intranasal midazolam 0,2mgkg^{-1}	Intranasal dexmedetomidine 1µgkg^{-1}	Anxiolysis, parental separation, mask acceptance	Favors intranasal midazolam
Baldwa NM, et al.[33]	2012	Single-blind, randomized trial	60	1-12 year(s) old, ASA I-II	Atomized intranasal midazolam 0,2mgkg^{-1}	Atomized intranasal midazolam 0,3mgkg^{-1}	Onset of sedation, parental separation, mask acceptance	Favors intranasal midazolam 0,3mgkg^{-1}
Weber F. et al.[34]	2003	Double-blind, randomized trial	90	6 months - 6 year(s) old, ASA I-II	Intranasal midazolam 0,2mgkg^{-1}	Intranasal S-ketamine 1mgkg^{-1} + midazolam 0,2mgkg^{-1}; Intranasal S-ketamine 2mgkg^{-1} + midazolam 0,2mgkg^{-1}	Onset time, sedation, anxiolysis	Favors nasal administration of s-ketamine + midazolam
Buccal midazolam								
Millar K, et al.[39]	2007	Double-blind, randomized-controlled trial	179	5-10 year(s) old, ASA I-II, dental extraction under general anesthesia	Commercially available buccal midazolam 0,2mgkg^{-1}	Buccal placebo	Postoperative cognitive function	Favors placebo
Millar K, et al.[40]	2009	Double-blind, randomized-controlled trial	181	5-10 year(s) old, ASA I-II, undergoing dental extractions	Buccal midazolam 0,2mgkg^{-1}	Buccal placebo	Dental anxiolysis, pre-induction conditions, postoperative psychological morbidity, subsequent attendance	No benefit

Table II. — Summary of studies. Publications marked in red are mentioned more than once.

Sublingual midazolam								
Pant D, et al.[38]	2014	Double-blind, randomized trial	100	1-12 year(s) old, ASA I-II, undergoing outpatient urological surgery	Sublingual midazolam 0,25mgkg^{-1}	Sublingual dexmedetomidine 1,5µgkg^{-1}	Efficacy, sedation, conditions at induction and awakening	Favors sublingual dexmedetomidine
Nebulized midazolam								
Abdel-Ghaffar HS, et al.[36]	2018	Double-blind, randomized trial	90	3-7 year(s) old, ASA I-II, undergoing bone marrow aspiration	Nebulized midazolam 0,2mgkg^{-1}	Nebulized ketamine 2mgkg^{-1}, nebulized dexmedetomidine 2µgkg^{-1},	Sedation, tolerability, anxiolysis, recovery time, postoperative agitation	Favors nebulized dexmedetomidine
Rectal midazolam								
Bergendahl HTG, et al.[42]	2004	Double-blind, randomized trial	104	1-11 year(s) old, ASA I, undergoing adenoidectomy or tonsillectomy	Rectal midazolam 0,3mgkg^{-1} + atropine 40µgkg^{-1}	Rectal clonidine 5µgkg^{-1} + atropine 40µgkg^{-1}	Sedation, postoperative pain, postoperative vomiting, shivering, postoperative confusion	Favors rectal clonidine
Constant I, et al.[43]	2004	Double-blind, randomized trial	40	2-10 year(s) old, ASA I, undergoing tonsillectomy	Rectal midazolam 0,4mgkg^{-1}	Oral clonidine 4µgkg^{-1}	Agitation during sevoflurane induction	Favors oral clonidine
Marhofer P, et al.[94]	2001	Double-blind, randomized trial	62	Children, 3-20kg	Rectal midazolam 0,75mgkg^{-1}	Rectal S(+)-ketamine 1,5mgkg^{-1}; Rectal S(+)-ketamine 0,75mgkg^{-1} + 0,75mgkg^{-1} rectal midazolam	Efficacy, mask acceptance, side effects	Equally effective, no benefit of addition of rectal S(+)-ketamine
Tanaka M, et al.[45]	2000	Single-blind, randomized trial	66	7-61 months old, ASA I, undergoing minor urological surgery	Rectal midazolam 1mgkg^{-1}	Rectal ketamine 5mgkg^{-1}; Rectal ketamine 7mgkg^{-1}; Rectal ketamine 10mgkg^{-1}	Sedation, analgesia, emergence	Favors rectal midazolam
Wang X, et al.[97]	2010	Double-blind, randomized trial	67	2 months - 2year(s) old, undergoing surgery >60 minutes	Rectal midazolam 0,5mgkg^{-1} + ketamine 4mgkg^{-1} + atropine 0,02mgkg^{-1}	Rectal midazolam 0,5mgkg^{-1} + ketamine 8mgkg^{-1} + atropine 0,02mgkg^{-1}	Sedation, parental separation	Favors rectal ketamine 8mgkg^{-1} + midazolam 0,5mgkg^{-1} + atropine 0,02mgkg^{-1}
Intravenous/intramuscular midazolam								
Golparvar M, et al.[49]	2004	Double-blind, randomized-controlled trial	706 (24 with paradoxical reaction)	6 months - 6 year(s) old, ASA I-II	Intravenous (IV) midazolam 0,1mgkg^{-1} extra after observation of paradoxical reaction following IV midazolam 0,1mgkg^{-1}; IV ketamine 0,5mgkg^{-1} after paradoxical reaction	Intravenous placebo after paradoxical reaction	Response after paradoxical reaction	Favors intravenous ketamine

Table II. — Summary of studies. Publications marked in red are mentioned more than once.

Verghese ST, et al.[52]	2003	Single-blind, randomized trial	80	1-3 year(s) old, ASA I-II, undergoing bilateral myringotomy and tube insertion (ambulatory)	Intramuscular midazolam 0,1mgkg^{-1} + ketamine 2mgkg^{-1}; Intramuscular midazolam 0,2mgkg^{-1} + ketamine 2mgkg^{-1}; Intramuscular midazolam 0,2mgkg^{-1} + ketamine 1mgkg^{-1}	Intramuscular ketamine 2mgkg^{-1}	Recovery, discharge	Not recommendable
Diazepam								
Arai YCP, et al.[56]	2005	Single-blind, randomized-controlled trial	42	1-7 year(s) old, ASA I-II, undergoing adenotonsillectomy	Oral midazolam 0,5mgkg^{-1} + diazepam 0,25mgkg^{-1}; Oral midazolam 0,5mgkg^{-1}	No premedication	Pre-induction and emergence conditions	Favors combination of oral midazolam and oral diazepam
Filatov SM, et al.[57]	2000	Double-blind, randomized-controlled trial	100	1,1-4,4 year(s) old, 10-15kg, ASA I, scheduled for adenoidectomy	EMLA-cream + rectal diclofenac 12,5mg + rectal diazepam 0,5mgkg^{-1} + oral placebo + IV glycopyrrolate 5µgkg^{-1}; EMLA-cream + rectal diclofenac 12,5mg + rectal diazepam 0,5mgkg^{-1} + oral placebo + IV placebo; Placebo cream + rectal placebo + oral ketamine 6mgkg^{-1} + IV glycopyrrolate 5µgkg^{-1}	Placebo cream + rectal placebo + oral ketamine 6mgkg^{-1} + Intravenous (IV) placebo	Efficacy, safety	Favors rectal diclofenac + rectal diazepam
Martinez JL, et al.[6]	2002	Double-blind, randomized trial	154	4 months - 18 year(s) old, undergoing upper endoscopy	Oral diazepam 0,3mgkg^{-1} + IV meperidine 2mgkg^{-1}	Oral midazolam 0,5mgkg^{-1} + IV meperidine 2mgkg^{-1}	Efficacy, safety, cost	Equally effective, but lower cost with diazepam
Sakurai Y, et al.[58]	2010	Nonrandomized trial	40	1-7 year(s) old, ASA I	Rectal diazepam 0,7mgkg^{-1}	Buccal dexmedetomidine 3-4µgkg^{-1}	Sedation	Favors buccal dexmedetomidine
Zolpidem								
Hanna AH, et al.[14]	2018	Non inferiority, randomized trial	86	2-9 year(s) old, ASA I-II	Oral zolpidem syrup (± 0,25mgkg^{-1})	Oral midazolam 0,5mgkg^{-1}	Anxiolysis, mask acceptance	Favors oral midazolam

Table II. — Summary of studies. Publications marked in red are mentioned more than once.

Melatonin								
Almenrader N, et al.[60]	2013	Double-blind, randomized trial	87	1-5 year(s) old, ASA I-II, undergoing minor surgery	Oral melatonin 0,3mgkg^{-1}	Oral clonidine 4µgkg^{-1}	Success of steal induction, safety, postoperative pain	Clonidine more successful for steal induction, melatonin safer, clonidine better in reducing postoperative pain
Gitto E, et al.[59]	2016	Pilot study: double-blind, randomized trial	92	5-14 year(s) old, undergoing elective surgery	Oral melatonin 0,5mgkg^{-1}	Oral midazolam 0,5mgkg^{-1}	Required infusion of propofol, sedation, emergence	Equally effective
Isik B, et al.[103]	2008	Single-blind, randomized-controlled trial	60	3-8 year(s) old, ASA I, undergoing dental treatment	Oral melatonin 3mg; Oral melatonin 0,5mgkg^{-1}; Oral midazolam 0,75mgkg^{-1}	Oral placebo	Sedation, safety	No effect of oral melatonin compared to placebo, favors midazolam
Kain Z, et al.[64]	2009	Double-blind, randomized trial	148	2-8 year(s) old, ASA I-II, undergoing outpatient elective surgery	Oral melatonin 0,05mgkg^{-1}; Oral melatonin 0,2mgkg^{-1}; Oral melatonin 0,4mgkg^{-1}	Oral midazolam 0,5mgkg^{-1}	Anxiolysis	Favors midazolam
Kurdi M, et al.[63]	2016	Double-blind, randomized-controlled trial	100	5-15 year(s) old, ASA I-II	Oral melatonin 0,5mgkg^{-1}; Oral melatonin 0,75mgkg^{-1}	Oral midazolam 0,5mgkg^{-1}; Oral placebo	Anxiolysis, cognitive and psychomotor functions	Favors oral melatonin 0,75mgkg^{-1}
Özcengiz D, et al.[21]	2011	Randomized-controlled trial	100	3-9 year(s) old, ASA I-II, undergoing esophageal dilatation	Oral melatonin 0,1mgkg^{-1}	Oral dexmedetomidine 2,5µgkg^{-1}; Oral midazolam 0,5mgkg^{-1} ; Oral placebo	Postoperative agitation	Equally effective compared to placebo
Sury MRJ, et al.[62]	2006	Double-blind, randomized-controlled trial	98	5-40kg, undergoing MRI	Oral melatonin 3mg (<15kg) or oral melatonin 6mg (>15kg) 10 minutes before routine sedation (chloralhydrate/temazepam)	Oral placebo 10 minutes before routine sedation (chloralhydrate/temazepam)	Sedation	No effect
Oral transmucosal fentanyl citrate (OTFC)								
Binstock W, et al.[66]	2004	Double-blind, randomized-controlled trial	125	2-10 year(s) old, ASA I-II, undergoing ambulatory surgery	OTFC (oral transmucosal fentanyl citrate) 10µgkg^{-1} + IV ondansetron 0,1mgkg^{-1}; OTFC 10-15µgkg^{-1} + IV placebo	Oral placebo + IV ondansetron 0,1mgkg^{-1}; Oral placebo + IV placebo	Early postoperative agitation, adverse events	OTFC showed decrease in postoperative agitation but has important side effects

Table II. — Summary of studies. Publications marked in red are mentioned more than once.

Butorphanol								
Singh V, et al.[23]	2005	Double-blind, randomized trial	60	2-10 year(s) old, ASA I-II	Oral butorphanol 0,2mgkg^{-1}	Oral midazolam 0,5mgkg^{-1}	Sedation, anxiolysis, parental separation, IV-puncture, postoperative pain	Favors oral butorphanol
Sinha C, et al.[68]	2012	Double-blind, randomized trial	60	2-12 year(s) old, ASA I-II	Oral midazolam 0,5mgkg^{-1}	Oral butorphanol 0,2mgkg^{-1}	Sedation, anxiolysis, parental separation, IV-puncture, mask acceptance	Favors oral butorphanol (sedation), but midazolam superior as anxiolytic during venipuncture and mask application
Clonidine								
Homma M, et al.[76]	2006	Study on pharmacokinetics	23	1-11 year(s) old, ASA I, undergoing adenoidectomy or tonsillectomy	Oral clonidine disintegrating tablets 4µgkg^{-1}	Clonidine lollipop 4µgkg^{-1}	Sedation, plasma concentration, safety	Favors orally disintegrating tablets
Oral clonidine								
Gulhas N, et al.[73]	2003	Double-blind, randomized trial	80	3-12 year(s) old, ASA I, undergoing strabismus surgery	Oral clonidine 4µgkg^{-1}	Oral placebo	Postoperative nausea and vomiting	Not effective
Inomata S, et al.[79]	2000	Single-blind, randomized-controlled trial	90	2-8 year(s) old, ASA I, undergoing inguinal hernia repair	Oral clonidine 2µgkg^{-1}; Oral clonidine 4µgkg^{-1}	Oral placebo	MACEI (endotracheal intubation), MAC (skin incision)	Reduction of MACEI and MAC in dose-dependent way
Larsson P, et al.[70]	2011	Study on pharmacokinetics	8	3-10 year(s) old, ASA I, undergoing adenotonsillectomy	Oral clonidine 4µgkg^{-1}	/	Pharmacokinetics	Higher doses (per kg) necessary compared to adults
Nader ND, et al.[80]	2001	Double-blind, randomized-controlled trial	18	Adults, undergoing lower extremity revascularization	Oral clonidine 0,2mg (in 2 doses), Oral clonidine 0,4mg (in 2 doses)	Oral placebo	Catecholamine release (central and peripheral)	Decrease in catecholamine release
Yaguchi Y, et al.[71]	2002	Single-blind, randomized-controlled trial	60	2-9 year(s) old, ASA I, undergoing inguinal hernia repair	Oral clonidine 4µgkg^{-1}; Oral clonidine 2µgkg^{-1}	Oral placebo	MAC-ex (endotracheal extubation), emergence time, airway related complications	Decrease in MAC-ex, no adverse effects
Oral clonidine - midazolam								
Almenrader N, et al. [24]	2007	Open-label, randomized trial	64	1-6 year(s) old, ASA I-II	Oral clonidine 4µgkg^{-1}	Oral midazolam 0,5mgkg^{-1}	Tolerability, efficacy, postoperative recovery, parental satisfaction	Favors oral clonidine
Constant I, et al.[43]	2004	Double-blind, randomized trial	40	2-10 year(s) old, ASA I, undergoing tonsillectomy	Oral clonidine 4µgkg^{-1}	Rectal midazolam 0,4mgkg^{-1}	Agitation during sevoflurane induction	Favors oral clonidine

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Fazi L, et al.[16]	2001	Double-blind, randomized-controlled trial	134	4-12 year(s) old, undergoing tonsillectomy	Oral clonidine 4μgkg^{-1} + placebo	Oral placebo + oral midazolam 0,5mgkg^{-1}	Preoperative behavior, postoperative recovery	No clinically important benefits
Mikawa K, et al.[74]	2002	Letter to the editor – report of clinical trial	175	2-11 year(s) old, undergoing minor surgery	Oral clonidine 2μgkg^{-1}; Oral clonidine 4μgkg^{-1}	Oral midazolam 0,5mgkg^{-1}; Oral placebo	Sevoflurane-related agitation, discharge times	Favors oral clonidine
Oral clonidine - midazolam - dexmedetomidine								
Schmidt AP, et al.[22]	2007	Open-label, randomized trial	60	7-12 year(s) old, ASA I-II, ambulatory procedures	Oral clonidine 4μgkg^{-1}	Oral midazolam 0,5mgkg^{-1}, transmucosal dexmedetomidine 1μgkg^{-1}	Postoperative anxiolysis, sedation, sympathetic stimulation, postoperative pain	Favors alpha-agonists
Oral clonidine - melatonin								
Almenrader N, et al.[60]	2013	Double-blind, randomized trial	87	1-5 year(s) old, ASA I-II, undergoing minor surgery	Oral clonidine 4μgkg^{-1}	Oral melatonin 0,3mgkg^{-1}	Success of steal induction, safety, postoperative pain	Clonidine more successful for steal induction, melatonin safer, clonidine better in reducing postoperative pain
Intranasal clonidine								
Almenrader N, et al.[77]	2009	Study on pharmacokinetics	13	22-84 months old, ASA I, undergoing minor urologic surgery	Intranasal clonidine 4μgkg^{-1} after induction	/	Pharmacokinetics	Not recommendable
Larsson P, et al.[78]	2012	Double-blind, randomized-controlled trial	60	6 months - 6 year(s) old, ASA I-II, undergoing minor ambulatory surgery	Intranasal clonidine 3-4μgkg^{-1}; Intranasal clonidine 7-8μgkg^{-1}	Intranasal placebo	Pre- and postoperative sedation	Inadequate preoperative sedation, no prolonging of postoperative sedation
Rectal clonidine								
Bergendahl HTG, et al.[42]	2004	Double-blind, randomized trial	104	1-11 year(s) old, ASA I, undergoing adenoidectomy or tonsillectomy	Rectal clonidine 5μgkg^{-1} + atropine 40μgkg^{-1}	Rectal midazolam 0,3mgkg^{-1} + atropine 40μgkg^{-1}	Sedation, postoperative pain, postoperative vomiting, shivering, postoperative confusion	Favors rectal clonidine
Intravenous clonidine								
Kulka PJ, et al.[26]	2001	Double-blind, randomized-controlled trial	49	2-7 year(s) old, ASA I-II, undergoing circumcision	Intravenous clonidine 2μgkg^{-1} intraoperative	Intravenous placebo intraoperative	Sevoflurane-related emergence agitation	Favors intravenous clonidine
Larsson PG, et al.[72]	2015	Observational study (nonrandomized)	1507	0,02-18 year(s) old	IV clonidine 1-2μgkg^{-1}; Oral clonidine 3-6μgkg^{-1}	No premedication	Incidence of bradycardia	Low incidence of bradycardia

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Zhang CMD, et al.[20]	2013	Meta-analysis (12 randomized-controlled trials)	1214	0,5-10 year(s) old	0,2-0,5 $mgkg^{-1}$ oral midazolam premedication; 0,75-3μkg^{-1} epidural/intravenous clonidine intraoperatively	Placebo	Sevoflurane-related emergence agitation	Favors both interventions
Transmucosal clonidine								
Sumiya K, et al.[75]	2003	Study on pharmacokinetics	16	1-11 year(s) old, ASA I	Clonidine lollipop 2 μgkg^{-1}	Clonidine lollipop 4μgkg^{-1}	Plasma concentrations, sedation, safety	No significant difference in plasma concentrations, correlation between plasma concentration and sedation, no adverse effects
Dexmedetomidine								
Anttila M, et al.[87]	2003	Study on pharmacokinetics	12	20-27 year(s) old, healthy men	Buccal dexmedetomidine 2μgkg^{-1}	IV dexmedetomidine 2μgkg^{-1}, IM dexmedetomidine 2μgkg^{-1}, oral dexmedetomidine 2μgkg^{-1},	Bioavailability	Buccal dexmedetomidine is well absorbed through oral mucosa
Cimen ZS, et al.[83]	2013	Double-blind, randomized trial	62	2-6 year(s) old, ASA I-II, undergoing minor elective surgery	Oral dexmedetomidine 1μgkg^{-1}	Intranasal dexmedetomidine 1μgkg^{-1}	Onset of action, sedation	Favors intranasal dexmedetomidine
Koo E, et al.[90]	2014	Animal in vivo study	20	Pregnant cynomolgus monkeys	Intramuscular ketamine 20$mgkg^{-1}$ + 20-50$mgkg^{-1}$/h; IV dexmedetomidine 3μgkg^{-1} + 3μgkg^{-1}/h; IV dexmedetomidine 30μgkg^{-1} + 30μgkg^{-1}/h	No anesthetic	Neuro-apoptosis, cellular degeneration	No effect of dexmedetomidine on neuro-apoptosis or cellular degeneration
Sanders RD, et al.[89]	2010	In vitro study, In vivo animal study	/	In vitro mice neuro-cortices, in vivo: rat pups	Various doses of dexmedetomidine	/	Cortical apoptosis	Dexmedetomidine prevents cortical apoptosis in vitro and in vivo
Sun L, et al.[91]	2014	Meta-analysis (15 randomized-controlled trials)	661	1-10 year(s) old	Dexmedetomidine intraoperatively	Placebo intraoperatively	Sevoflurane-related emergence agitation	Decreased incidence of sevoflurane related emergence agitation
Zub D, et al.[88]	2005	Retrospective cohort study	13	4-14 year(s) old	Oral dexmedetomidine	/	Efficacy, complication, parental satisfaction	Dexmedetomidine may be an effective oral premedication

Table II. — Summary of studies. Publications marked in red are mentioned more than once.

Intranasal dexmedetomidine								
Akin A, et al.[32]	2012	Double-blind, randomized trial	90	2-9 year(s) old, ASA I, undergoing adenotonsillectomy	Intranasal dexmedetomidine 1µgkg^{-1}	Intranasal midazolam 0,2mgkg^{-1}	Anxiolysis, parental separation, mask acceptance	Favors intranasal midazolam
Jia JE, et al.[86]	2013	Single-blind, randomized trial	160	2-6 year(s) old, ASA I-II	Intranasal dexmedetomidine 1µgkg^{-1} + oral ketamine 3mgkg^{-1}; Intranasal dexmedetomidine 1µgkg^{-1} + oral ketamine 5mgkg^{-1}; Intranasal dexmedetomidine 2µgkg^{-1} + oral ketamine 3mgkg^{-1}	Intranasal dexmedetomidine 2µgkg^{-1} + oral ketamine 5mgkg^{-1}	Tolerability, onset time, sedation, parental separation, face mask acceptance, IV cannulation, side-effects	Favors 2 µgkg^{-1} intranasal dexmedetomidine + 3 mgkg^{-1} oral ketamine
Lin YMD, et al.[85]	2016	Single-blind, randomized-controlled trial	98	1-8 year(s) old, 9-38kg, ASA I-II, undergoing cataract surgeries	Intranasal dexmedetomidine 1µgkg^{-1}; Intranasal dexmedetomidine 2µgkg^{-1}	Intranasal placebo	Face mask acceptance, emergence agitation, discharge time, complications	Favors dexmedetomidine
Sathyamoorthy M, et al.[19]	2019	Single-blind, randomized trial	75	>5 year(s) old, >20kg scheduled for dental procedures	Intranasal dexmedetomidine 2µgkg^{-1}	Oral midazolam 0,5mgkg^{-1}	Sedation, parental separation, face mask acceptance, safety	Favors intranasal dexmedetomidine
[84]Yuen VM, et al.	2012	Double-blind, randomized trial	123	1-8 year(s) old, ASA I-II	Intranasal dexmedetomidine 1µgkg^{-1}	Intranasal dexmedetomidine 2µgkg^{-1}	Sedation, adverse effects	Favors intranasal dexmedetomidine 2µgkg^{-1}
Yuen VM, et al.[48]	2008	Double-blind, randomized-controlled trial	96	2-12 year(s) old, ASA I-II, undergoing minor surgery	Intranasal dexmedetomidine 0,5µgkg^{-1} + oral acetaminophen 20mgkg^{-1}; Intranasal dexmedetomidine 1µgkg^{-1} + oral acetaminophen 20mgkg^{-1}	Intranasal placebo + oral midazolam 0,5mgkg^{-1} + oral acetaminophen 20mgkg^{-1}	Sedation, parental separation, mask induction	Intranasal dexmedetomidine 1µgkg^{-1} was equally effective as oral midazolam 0,5mgkg^{-1}
Yuen VM, et al.[104]	2007	Double-blind, randomized-controlled trial (cross-over study)	18	18-36 year(s) old, ASA I	Intranasal dexmedetomidine 1µgkg^{-1}; intranasal dexmedetomidine 1,5µgkg^{-1}	Intranasal placebo	Efficacy, onset, tolerability	Favors dexmedetomidine
Nebulized dexmedetomidine								
Abdel-Ghaffar HS, et al.[36]	2018	Double-blind, randomized trial	90	3-7 year(s) old, ASA I-II, undergoing bone marrow aspiration	Nebulized dexmedetomidine 2µgkg^{-1}	Nebulized ketamine 2mgkg^{-1}, nebulized midazolam 0,2mgkg^{-1}	Sedation, tolerability, anxiolysis, recovery time, postoperative agitation	Favors nebulized dexmedetomidine

Table II. — Summary of studies. Publications marked in red are mentioned more than once.

Oral dexmedetomidine								
Özcengiz D, et al.[21]	2011	Randomized-controlled trial	100	3-9 year(s) old, ASA I-II, undergoing esophageal dilatation	Oral dexmedetomidine 2,5µgkg^{-1}	Oral midazolam 0,5mgkg^{-1}; Oral melatonin 0,1mgkg^{-1}; Oral placebo	Postoperative agitation	Equally effective compared to placebo
Transmucosal dexmedetomidine								
Schmidt AP, et al.[22]	2007	Open-label, randomized trial	60	7-12 year(s) old, ASA I-II, ambulatory procedures	Transmucosal dexmedetomidine 1µgkg^{-1}	Oral clonidine 4µgkg^{1}; Oral midazolam 0,5mgkg^{-1}	Postoperative anxiolysis, sedation, sympathetic stimulation, postoperative pain	Favors alpha-agonists
Pant D, et al.[38]	2014	Double-blind, randomized trial	100	1-12 year(s) old, ASA I-II, undergoing outpatient urological surgery	Sublingual dexmedetomidine 1,5µgkg^{-1}	Sublingual midazolam 0,25mgkg^{-1}	Efficacy, sedation, conditions at induction, awakening	Favors sublingual dexmedetomidine
Sakurai Y, et al.[58]	2010	Nonrandomized trial	40	1-7 year(s) old, ASA I	Buccal dexmedetomidine 3-4µgkg^{-1}	Rectal diazepam 0,7mgkg^{-1}	Sedation	Favors buccal dexmedetomidine
Ketamine								
Cheng C, et al.[93]	2021	Retrospective, nonrandomized trial	383	3-10 year(s) old, >12kg	Oral ketamine 10mgkg^{-1}; Nebulized ketamine 3mgkg^{-1}	Apple juice	Sedation, postoperative pain, safety, postoperative nausea and vomiting, adverse effects	Favors nebulized ketamine
Oral ketamine								
Darlong V, et al.[47]	2004	Single-blind, randomized trial	78	1-9 year(s) old, ASA I-II, undergoing ophthalmic surgery	Oral ketamine 6mgkg^{-1}; Oral ketamine 3mgkg^{-1} + oral midazolam 0,25mgkg^{-1}	Oral midazolam 0,5mgkg^{-1}	Efficacy, onset time, side-effects, recovery profile	Favors combination of oral ketamine + midazolam
Filatov SM, et al.[57]	2000	Double-blind, randomized-controlled trial	100	1,1-4,4 year(s) old, 10-15kg, ASA I, scheduled for adenoidectomy	EMLA-cream + rectal diclofenac 12,5mg + rectal diazepam 0,5mgkg^{-1} + oral placebo + IV glycopyrrolate 5µgkg^{-1}; EMLA-cream + rectal diclofenac 12,5mg + rectal diazepam 0,5mgkg^{-1} + oral placebo + IV placebo; Placebo cream + rectal placebo + oral ketamine 6mgkg^{-1} + IV glycopyrrolate 5µgkg^{-1}	Placebo cream + rectal placebo + oral ketamine 6mgkg^{-1} + Intravenous (IV) placebo	Efficacy, safety	Favors rectal diclofenac + rectal diazepam

Table II. — Summary of studies. Publications marked in red are mentioned more than once.

Ghai B, et al.[95]	2004	Double-blind, randomized trial	100	10months - 6year(s) old, ASA I-II	Oral midazolam 0,25mgkg^{-1} + ketamine 2,5mgkg^{-1}	Oral midazolam 0,5mgkg^{-1}	Efficacy, safety, sedation	Favors combination of oral ketamine + midazolam
Jia JE, et al.[86]	2013	Single-blind, randomized trial	160	2-6 year(s) old, ASA I-II	Intranasal dexmedetomidine 1µgkg^{-1} + oral ketamine 3mgkg^{-1}; Intranasal dexmedetomidine 1µgkg^{-1} + oral ketamine 5mgkg^{-1}; Intranasal dexmedetomidine 2µgkg^{-1} + oral ketamine 3mgkg^{-1}	Intranasal dexmedetomidine 2µgkg^{-1} + oral ketamine 5mgkg^{-1}	Tolerability, onset time, sedation, parental separation, face mask acceptance, IV cannulation, side-effects	Favors 2 µgkg^{-1} intranasal dexmedetomidine and 3 mgkg^{-1} oral ketamine
Kararmaz A, et al.[92]	2004	Double-blind, randomized-controlled trial	80	3-6 year(s) old, ASA I-II, undergoing adenotonsillectomy	Oral ketamine 6mgkg^{-1}	Oral placebo	Emergence agitation after desflurane anesthesia, emergence	Favors oral ketamine 6mgkg^{-1}
Trabold B, et al.[96]	2002	Double-blind, randomized trial	79	1-8 year(s) old, ASA I-II	Oral midazolam 0,5mgkg^{-1} + ketamine 1,8mgkg^{-1}, oral ketamine 3mgkg^{-1}	Oral midazolam 0,5mgkg^{-1}	Emergence and recovery times	No difference
Nebulized ketamine								
Abdel-Ghaffar HS, et al.[36]	2018	Double-blind, randomized trial	90	3-7 year(s) old, ASA I-II, undergoing bone marrow aspiration	Nebulized ketamine 2mgkg^{-1}	Nebulized dexmedetomidine 2µgkg^{-1}, nebulized midazolam 0,2mgkg^{-1}	Sedation, tolerability, anxiolysis, recovery time, postoperative agitation	Favors nebulized dexmedetomidine
Intravenous/Intramuscular ketamine								
Golparvar M, et al.[49]	2004	Double-blind, randomized-controlled trial	706 (24 with paradoxical reaction)	6 months - 6 year(s) old, ASA I-II	Intravenous (IV) midazolam 0,1mgkg^{-1} extra after observation of paradoxical reaction following IV midazolam 0,1mgkg^{-1}; IV ketamine 0,5mgkg^{-1} after paradoxical reaction	Intravenous placebo after paradoxical reaction	Response after paradoxical reaction	Favors intravenous ketamine
Koo E, et al.[90]	2014	Animal in vivo study	20	Pregnant cynomolgus monkeys	Intramuscular ketamine 20mgkg^{-1} + 20-50mgkg^{-1}/h; IV dexmedetomidine 3µgkg^{-1} + 3µgkg^{-1}/h; IV dexmedetomidine 30µgkg^{-1} + 30µgkg^{-1}/h	No anesthetic	Neuro-apoptosis, cellular degeneration	No information on effects of intramuscular ketamine

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Verghese ST, et al.[52]	2003	Single-blind, randomized trial	80	1-3 year(s) old, ASA I-II, undergoing bilateral myringotomy and tube insertion (ambulatory)	Intramuscular ketamine 2mgkg^{-1} + midazolam 0,1mgkg^{-1}; Intramuscular ketamine 2mgkg^{-1} + midazolam 0,2mgkg^{-1}; Intramuscular ketamine 1mgkg^{-1} + midazolam 0,2mgkg^{-1}	Intramuscular ketamine 2mgkg^{-1}	Recovery, discharge	Not recommendable
Transmucosal/Intranasal ketamine								
Horiuchi T, et al.[25]	2005	Single-blind, randomized trial	55	2-6year(s) old, ASA I-II	Transmucosal (Lollipop) ketamine 50mg	Oral midazolam 0,5mgkg^{-1}	Sedation, efficacy	Favors oral midazolam
Weber F. et al.[34]	2003	Double-blind, randomized trial	90	6 months - 6 year(s) old, ASA I-II	Intranasal S-ketamine 1mgkg^{-1} + midazolam 0,2mgkg^{-1}; Intranasal S-ketamine 2mgkg^{-1} + midazolam 0,2mgkg^{-1}	Intranasal midazolam 0,2mgkg^{-1}	Onset time, sedation, anxiolysis	Favors nasal S-ketamine + midazolam
Rectal ketamine								
Marhofer P, et al.[94]	2001	Double-blind, randomized trial	62	Children, 3-20kg	Rectal S(+)-ketamine 1,5mgkg^{-1}; Rectal S(+)-ketamine 0,75mgkg^{-1} + 0,75mgkg^{-1} rectal midazolam	Rectal midazolam 0,75mgkg^{-1}	Efficacy, mask acceptance, side effects	Equally effective, no benefit of addition of rectal S(+)-ketamine
Tanaka M, et al.[45]	2000	Single-blind, randomized trial	66	7-61 months old, ASA I, undergoing minor urological surgery	Rectal ketamine 5mgkg^{-1} ; Rectal ketamine 7mgkg^{-1} ; Rectal ketamine 10mgkg^{-1}	Rectal midazolam 1mgkg^{-1}	Sedation, analgesia, emergence	Favors rectal midazolam
Wang X, et al.[97]	2010	Double-blind, randomized trial	67	2 months - 2year(s) old, undergoing surgery >60 minutes	Rectal ketamine 4mgkg^{-1} + midazolam 0,5mgkg^{-1} + atropine 0,02mgkg^{-1}	Rectal ketamine 8mgkg^{-1} + midazolam 0,5mgkg^{-1} +atropine 0,02mgkg^{-1}	Sedation, parental separation	Favors rectal ketamine 8mgkg^{-1} + midazolam 0,5mgkg^{-1} + atropine 0,02mgkg^{-1}
Hydroxyzine								
Faytrouny M, et al.[101]	2007	Single-blind, randomized trial	30	31-10 month(s) old, ASA I, uncooperative children undergoing dental treatment	Oral hydroxyzine 20mgkg^{-1} 24h before procedure + 3,7mkg^{-1} oral hydroxyzine 1 hour before operation	3,7mkg^{-1} oral hydroxyzine 1 hour before procedure	Sedation	No benefit of administration 24h before procedure

Table II. — Summary of studies. Publications marked in red are mentioned more than once.

Trifa M, et al.[100]	2010	Single-blind, randomized-controlled trial	100	1-9 year(s) old, ASA I-II, undergoing outpatient surgery	Oral hydroxyzine 1mgkg^{-1}	Placebo	Mask acceptance	Favors hydroxyzine
Promethazine								
Nadri S, et al.[18]	2020	Double-blind, randomized-controlled trial	93	3-9 year(s) old, ASA I-II, undergoing ambulatory surgery	Oral midazolam 0,5mgkg^{-1}; Oral placebo	Oral promethazine 0,3mgkg^{-1}	Sedation, anxiolysis	Equally effective, significant different to placebo

juice, fresh grapefruit juice or placebo[8]. Despite this promising result, a double blinded controlled trial by Lammers et al. could only show a significant ($p<0,05$) decrease in onset time, but no statistical difference in anxiety at any moment[9]. A chocolate-based 0,5mgkg^{-1} formulation improved tolerability while remaining as efficient and fast as the oral solution in the same dose[10]. Newer formulations like ADV6209 are oral solutions, based on gamma-cyclodextrin which reduces the bitterness of midazolam and enhances its solubility[11]. This leads to rapid absorption of 77% of the midazolam dose 30 minutes after oral administration.

Oral doses ranging from 0,25mgkg^{-1} to 1,5mgkg^{-1} have been studied with different results in efficacy. This might be depending on age. Toddlers (1-3 years old) possibly require a higher dose (1mgkg^{-1}) whereas 0,75mgkg^{-1} seems sufficient for >95% of children more than 3 years old[5,12,13]. Most studies use 0,5mgkg^{-1} as a 'golden standard'[14-26] and this is believed to be the most effective dose with least side effects[27].

Some authors endeavor higher doses of oral midazolam. A randomized controlled double-blind trial by Mehrdad et al. concluded that children premedicated with 1mgkg^{-1} had a significant ($p<0,01$) lower level of anxiety and agitation[28]. In a randomized trial among children with congenital heart disease, 1,5mgkg^{-1} was more effective than lower doses (1mgkg^{-1} or 0,5mgkg^{-1}). Only 4% of these children showed agitation compared to 14% and 26% respectively. This is translated into better safety since agitation in these children can result in an increased oxygen demand and anoxic spells[29].

Onset and duration after oral administration

The onset of sedation in oral midazolam is dose dependent. A lower dose results in a slower onset[15,27]. First changes in mental and behavioral state are seen 10 to 30 minutes[5,12,16,23,24,27] after oral administration. Peak sedative effects are seen within 20 to 32min[15,24,27,29,30]. Theoretically, midazolam has an elimination half-life of approximately 2,5h[31].

Oral midazolam has a theoretical first pass effect, as it is metabolized in the liver. Other routes of administration in which this effect is bypassed include the intravenous, intramuscular, intranasal, rectal sublingual, and buccal route.

Intranasal administration

The most common intranasal dose ranges from 0,2 to 0,3mgkg-1[13,15,30,32-35]. The latter dose (via atomized intranasal spray) leads to faster onset, better mask acceptance (33% vs 16,6%) and less anxiety or agitation (16,6% vs 46,6%) with a small number of complications[33]. Intranasal administration of midazolam however causes an unpleasant burning sensation in the nasal cavity and is for that reason not always accepted by the child. In a comparative study, 77% of the children cried after given intranasal midazolam. This is substantially more compared to other routes of administration[30]. In another trial, only 23,4% of the children had good acceptance of the intranasal form (drops via syringe) whereas 43,3% and 33,4% had rather fair or poor acceptance[35]. For this reason, some authors suggest nebulized midazolam. An atomizer or mask nebulization increases comfort and theoretically maximizes surface area, enabling rapid absorption[36]. Chiaretti et al. used intranasal lidocaine 10mg one minute prior to intranasal midazolam via atomizer device. This prevented any nasal discomfort or pain reported by parents[37].

Studies show a high heterogeneity regarding onset time. Some studies describe an onset after 10 to 20 minutes (intranasal drops via syringe as well as atomized spray)[12,15,32,33]. Weber et al. described an improved condition for parental separation after only 5 minutes when 0,2mgkg-1 was administered intranasally (drops via syringe)[34]. Compared to other methods of dispensing, intranasal midazolam resulted faster in an altered mental state (drowsy or asleep) and adequate sedation. It is not described whether this administration occurred via atomizing or intranasal drops[30].

Sublingual/buccal administration

Sublingual and buccal dosage of midazolam is comparable to the intranasal dose: 0,2-0,3mgkg^{-1} [15,38-40]. Peak sedative effects are seen at 29.8±5.8min[30]. Buccolam® (midazolam hydrochloride) is an approved oromucosal preparation for pediatric patients with acute, prolonged convulsive seizures. It has a rapid onset of action (<10min) due to its high lipophilicity[41]. No clinical studies were found on its use in preoperative sedation and whether this is substantially different from non-commercial preparations.

Rectal administration

Rectal administration of drugs is quite invasive and therefore no more accepted in some cultures. Dosages of rectal midazolam are very diverse among different study designs (0,3 to 1mgkg^{-1})[15,42-45]. Although 1mgkg^{-1} is more effective, inadequate sedation still occurs frequently. Higher doses might also result in prolonged paradoxical agitation[44]. One major disadvantage of rectal administration of any kind of premedication is its unreliable absorption due to spill and unknown venous resorption (upper rectal vein which drains into the hepatic portal system). This might be an explanation for its low reliability. Only one study mentioned the onset of action which was 33.7±3.4min[30]. Rectal midazolam is often combined with rectal ketamine, as will be discussed later.

Intramuscular administration

Although quite invasive, intramuscular midazolam 0,2mgkg^{-1} is an option for preprocedural sedation. Compared to intranasal, intramuscular midazolam allowed for more reliable sedation in a pilot study[35].

Efficacy

Multiple reviews have described midazolam as an 'effective' strategy to relieve perioperative anxiety[27,46]. Compared to placebo, oral midazolam significantly ($p<0,05$) reduced crying, stress during induction, improved mask acceptance and parental separation[18,28]. Two studies reported satisfactory mask induction in 86% and 75% of children treated with oral midazolam 0,5mgkg^{-1} [24,47]. Akin et al. reported this achievement in 82,2% of children premedicated with intranasal midazolam 0,2mgkg^{-1} [32]. Others report less patients with favorable conditions for induction: 63% (intranasal drops of midazolam 0,2mgkg^{-1}, sedation scores at induction)[34], 33,3% (intranasal atomized midazolam 0,3mgkg^{-1}, mask acceptance)[33], 18,8% (oral midazolam 0,5mgkg^{-1}, satisfactory sedation at induction) 48 to less than 12% (intranasal atomized midazolam 0,2mgkg^{-1}, mask acceptance)[33]. Higher doses of oral midazolam might have an additional effect: only 4% of infants and children who received 1,5mgkg^{-1} oral midazolam showed preoperative agitation. This contrasts with 14% and 26% of those who received 1,0mgkg^{-1} or 0,5mgkg^{-1} respectively[29].

Advantages

Preoperative midazolam decreases propofol requirements, resulting in easier laryngeal mask insertion[12]. In a meta-analysis, preoperative oral midazolam also significantly ($p<0,05$) reduced the incidence of emergence agitation compared to placebo (OR=0,45[95% CI, 0,29-0,70])[20].

Disadvantages

Sedation with midazolam may produce some other minor side effects: loss of balance and head control, blurred visions[4] and hiccups after rectal administration[15]. These are nonspecific and relative harmless. Paradoxical reactions like restlessness, violent behavior and need for restraints have been described. After intravenous midazolam premedication, these reactions occur in about 3,4% [95% CI, 2–4.7%] of cases[49]. They take place after an initial sedation of a few minutes, and some suggest that they are rather temperamental behavior from impulsive children than a reflection of anxiety at all. This would imply that anxiolytic treatment has no place in these children[27]. Long term postoperative maladaptive behavior after midazolam administration have been investigated but remains unproven[12,27,38,44]. Midazolam impairs children's explicit memory and cognitive function on a short term (48h)[39,50]. The long-term effects are not yet clear but might affect a child's well-being after day-care procedure. Retrograde amnesia can be beneficial for some. However without memory of preceding inductions, subsequent experiences might seem 'new' and more distressful[27].

The effect on emergence delay and discharge is debatable[12,15]. Increasing the dose of oral midazolam from 0,5mgkg^{-1} to 0,75mgkg^{-1}, might result in delayed emergence[4]. Compared to non-pharmacological interventions (distraction or hypnosis), midazolam leads to a considerable delay in recovery time, but not in discharge[27,51] Adding 0,1mgkg^{-1} or 0,2mgkg^{-1} intramuscular midazolam to intramuscular ketamine, significantly delayed recovery and discharge ($p=0,001$ and $p=0,007$ respectively)[52]. In this research, no studies observed delayed discharge in children premedicated with oral midazolam.

The variable bioavailability of midazolam, especially when administered orally, apparently results more in inadequate sedation than serious adverse events. In a study comparing three

different doses of oral midazolam, 4% of the cases who received 1,5mgkg^{-1} oral midazolam, showed upper airway complications[29]. In a comparative study of oral premedication with midazolam and clonidine, postoperative desaturation (SpO_2 < 95%) occurred more frequently in the midazolam group after tonsillectomy[16]. Some authors suggest that this might be a result of the decrease of the upper airway tone. Nonetheless, limited research suggests that midazolam premedication was not associated with higher incidence of complications in children with obstructive sleep apnea or Down syndrome[53-55].

B-1.2 Diazepam

Diazepam is another benzodiazepine with twice the potency of midazolam as an anxiolytic in children[56]. It can be administrated orally and rectally in doses of 0,3mgkg^{-1} or 0,5-0,75mgkg^{-1} respectively[6,57]. The onset of sedation after oral administration is about 30 to 60 minutes. Oral diazepam 0,25mgkg^{-1} can be combined with midazolam 0,25mgkg^{-1}. This combination does provide a more adequate preinduction condition and more tranquil emergence compared to placebo and midazolam 0,5mgkg^{-1} alone[56]. This prolonged postoperative effect is probably caused by the longer half-life of diazepam (more than 20 hours) compared to midazolam. This can lead to a hangover-effect in some children, with more postoperative sleeping and excessive sedation 56. In one study, rectal administration of 0,5mgkg^{-1} diazepam combined with rectal diclofenac 20 minutes before induction provided calm parental separation and good preoperative sedation[57]. This is contrary to another trial in which rectal administration of diazepam 0,7mgkg^{-1} did not provide adequate induction conditions 60 minutes later[58]. As discussed earlier, rectal administration of any drug might be associated with unreliable absorption.

B-2 Zolpidem

Zolpidem is a more selective GABA-A-receptor agonist. It has a relative short acting time of 6 to 8 hours. This product is only available in tablets for adults, but it is water-soluble. One non-inferiority trial in this database compared the effectiveness of zolpidem and midazolam. Oral zolpidem 0,25mgkg^{-1} was administered 30 minutes before parental separation. This study did not find any significant difference between oral zolpidem and midazolam regarding anxiety scores or postoperative behavior. Mask-acceptance scores were significantly (p=0,03) worse in the zolpidem-group. Five participants in the zolpidem group (n=42) showed minor adverse reactions: double vision, visual hallucinations, dysphoria, involuntary tongue movements and excessive sleepiness[14].

B-3 Melatonin

Melatonin is a neurohormone involved in sleep-wake cycle and circadian rhythm. Synthetically produced melatonin has sedative effects, with relative low evidence for use in sleep disorders[59]. In children it is effective for idiopathic chronic sleep-onset insomnia[60]. It is a relative short-acting drug with an elimination half-life of about 45 minutes[61]. Melatonine can be given orally, which is well tolerated by children[62]. As premedication, investigated doses vary from 0,05mgkg^{-1} to 0,75mgkg^{-1}. Sedation starts after an average 35 minutes (15-60 minutes)[60].

Efficacy

The efficacy of melatonin is debatable. Depending on the primary outcome, studies showed different results. In a study of oral melatonin 0,5mgkg^{-1}, it was found to be as effective in anxiolysis as oral midazolam 0,5mgkg^{-1} [59]. Doses up to 0,5mgkg^{-1} or even 0,75mgkg^{-1} in children aged 5 to 15 years old, showed effective anxiolysis, but did not produce sedation[63]. Other authors conclude that melatonin improved sleepiness, but not sedation, or that the efficacy was not statistically significant compared to placebo[8,62]. In a trial that compared three different doses of melatonin (0,05mgkg^{-1}, 0,2mgkg^{-1} and 0,4mgkg^{-1}) to oral midazolam (0,5mgkg^{-1}) Kain et al. concluded that melatonin in any dose did not reduce anxiety at induction, whereas midazolam did[64]. A substantial difference between oral melatonin, dexmedetomidine 2,5µgkg^{-1} or midazolam 0,5mgkg^{-1} has not been demonstrated[21].

Advantages

Melatonin is effective in 75% of children for steal induction in a dose of 0,3mgkg^{-1} [60]. Steal induction is a technique where the premedicated child is asleep when arriving at the operating theatre. The child is not touched or disturbed. Inhalational induction is than accomplished by holding the mask near the child's face. Subgroup analysis of the 25% participants in which this failed, showed that failure was more frequent in early morning[60]. So, the authors concluded that there might be a diurnal effect of melatonin. Melatonin shows a dose-response effect on emergence agitation[64]. In contrast with midazolam, melatonin showed no derangement of psychomotor or cognitive function[63,65].

B-4 Opioids

B-4.1 Fentanyl

Opioids are used widely used in the perioperative setting for quick and adequate pain relief. Fentanyl is a highly lipid soluble synthetic opioid. Therefore,

it has a rapid onset of action when administered transmucosal. Oral transmucosal fentanyl citrate (OTFC) was the first sedating drug approved by the Food and Drug Administration (FDA) for the use in children. Most of the studies on intranasal opioids as a premedication were published more than twenty years ago and are – for this reason – excluded from this review.

OTFC can be prepared in a candy-based matrix in the form of a lollypop or lozenge and given preoperatively. A single oral administration of 10-15µgkg^{-1} results in sedation 30 to 45 min after consumption[15]. Although OTFC has a sedative effect, it does not lead to anxiolysis or improved cooperation[15,66]. OTFC reduces postoperative opioid requirements and significantly ($p<0,05$) reduces immediate postoperative agitation[66]. This effect is also observed when intranasal fentanyl is administered intraoperatively[12]. OTFC is associated with a significant ($p<0,05$) increase in preoperative and a postoperative nausea and vomiting. Sedation is often accompanied by dose-related facial pruritus[15,66]. Opioids, including OTFC lead to respiratory depression and increase the risk of intra- and postoperative respiratory events[12,66]. Misuse of fentanyl lollipops have been reported and need awareness, given the current opioid crisis[67].

B-4.2 Butorphanol

Butorphanol is a synthetic opioid, which possesses partial agonist and antagonist activity at the µ-receptor. This leads to less hypoventilation, compared to other opioids. Only two small trials (2x n=60) studied the effect of oral butorphanol, where 0,2mgkg^{-1} was administered 20 minutes before parental separation or 30 minutes before induction. Compared to oral midazolam 0,5mgkg^{-1}, it led to better sedation at induction in both studies. One study found more amnesia and less recall of venipuncture 25 minutes after administration[23], while Sinha et al. stated that midazolam proved to be a better anxiolytic during face mask application and venipuncture[68]. Children in the butorphanol group required less rescue analgesia intra- and postoperatively, cried less, and showed no serious adverse events[23]. The pharmacodynamic effects of butorphanol premedication on other intra-operative opioids has not been noted.

B-5 Alpha-2-adrenergic receptor agonists

B-5.1 Clonidine

Clonidine is an alpha-2-adrenergic receptor agonist. It antagonizes the effects of norepinephrine in the brainstem's locus coeruleus. This produces a sedative and anxiolytic effect. Influencing the descending tracts of the spinal cord, the product has an additional analgetic effect[69]. Clonidine can be administered orally, intranasally, rectally, or intravenously.

Oral administration

Dosage of oral administration differs among studies, but most frequently 4µgkg^{-1} [4,16,22, 24,43,60,69-74] is used. Bioavailability of oral clonidine is approximately 55%. This implies that oral doses are double of the intravenous dose 70. No studies regarding clinical dose-response on anxiety were found. Bergendahl et al. mentioned an older study that reported a benefit of 4µgkg^{-1} oral clonidine over 2µgkg^{-1} oral clonidine regarding parental separation, mask acceptance and sedation[44]. Clonidine is tasteless and odorless and leads to less refusal to take the drug compared to midazolam[24]. To improve tolerance, clonidine lollipops 2-4µgkg^{-1} and orally disintegrating tablets have been made[75,76]. Lollipops can be used for preoperative sedation in patients aged 4 to 11 years old. Younger children might not take the lollipop completely, resulting in inadequate plasma concentrations and less sedation[75]. Orally disintegrating tablets (clonidine in a fixed dose of 40µg or 60µg) may be of benefit in these younger patients. With less variety of plasma concentrations, these tablets led to better sedation than lollipops without an increase in adverse events[76]. Onset of sedation after oral clonidine is around 38 minutes, while it reaches its peak sedative effect around 46 minutes, 1 hour or even 105-120 minutes[24,70,75]. This correlates with maximum concentration in blood samples taken 1 hour or 90-120 minutes after oral administration[70,75].

Rectal administration

Rectal administration of clonidine results in a higher bioavailability. One trial compared rectal clonidine 5µgkg^{-1} to rectal midazolam 0,3mgkg^{-1} [42]. Both were combined with rectal atropine 40µgkg^{-1}. This addition is recommended due to cases of severe bradycardia in the past[44]. Rectal clonidine leads to significant ($p<0,05$) better pain relief and prolonged calmness during 24 postoperative hours, compared to midazolam[42]. Peak plasma concentration after rectal administration is reached after 50 minutes[15].

Efficacy

The efficacy of clonidine premedication varies among studies. Most trials compare oral clonidine to oral midazolam. Although none of these trials could prove a significant better mask acceptance, level of sedation and higher parental satisfaction were significantly ($p<0,05$) better after oral clonidine[24]. When children are adequately sedated, a steal

induction could be performed in about 66% to 88,4% after oral clonidine[24,60]. Another trial among 4-12 years old children (n=134), was not able to prove a benefit of oral clonidine over oral midazolam as it caused a more intense anxiety on parental separation and mask appliance[16]. Clonidine, dexmedetomidine and midazolam reduce postoperative anxiety levels equally[22].

Advantages

Clonidine premedication improves speed of induction since it lowers anesthetic requirements. Minimum Alveolar Concentration (MAC-ex) of sevoflurane to reach clinically adequate anesthetic dept, is significantly ($p<0,05$) less (1,9% ± 0,1 vs 2,9% ± 0,1) after clonidine (4µgkg^{-1}) premedication[71,79]. This reduction is dose-dependently and shortens the time for emergence with 1,5 minutes compared to oral midazolam ($p<0,05$)[16]. However, a study in ambulatory pediatric surgery failed to support this result but preoperative administration of alpha-2 agonists resulted in lower postoperative pain scores and are therefore favorable[22]. This is supported by other authors[42,44,80]. Intravenous clonidine intraoperative is known to decrease postoperative sevoflurane-induced agitation[26], which might as well be the case with oral clonidine premedication[69]. A trend towards better or at least similar recovery compared to benzodiazepines is seen, without prolonging discharge times[16,24]. Children pretreated with oral clonidine, show less psychomotor impairments, less need for oxygen supplementation and fewer paradoxical reactions[12,16]. Its effects on postoperative nausea and vomiting are a topic of debate. Early studies found a meaningful reduction in postoperative vomiting after oral premedication with clonidine[81,82] but this could not be reproduced[16,26,42,73].

Disadvantages

In a study on the incidence of bradycardia after clonidine, oral doses up to 6µgkg^{-1} were used. This resulted in a low incidence of significant (lower than 85% of lower limit of the normal range –reference values from Fleming et al.) decrease in heart rate compared to controls but did not result in any life-threatening bradycardia[72]. The elimination half-life of clonidine is long: 12-16 hours after oral administration[31]. Clonidine is considered a safe product, without major side-effects.

B-5.2 Dexmedetomidine

Dexmedetomidine is an alpha-2-receptor agonist which specificity (for alpha-2 over alpha^{-1} receptors) is eightfold greater than clonidine[12]. Its sedation state is similar to that of natural non-REM-sleep[4]. Its higher specificity leads to less side effects. Compared to clonidine, dexmedetomidine has a shorter elimination half-life (2-5 hours)[31].

Intranasal administration

Dexmedetomidine can be administered intranasally, which is the most common, noninvasive way. It is a colorless and odorless substance. Most commonly, doses of 1µgkg^{-1} (drops via syringe)[12,32,83] or 2µgkg^{-1} (atomizer/nebulization)[19,36] are used for intranasal administration. The lowest dose assessed in this review was 0,5µgkg^{-1}. But compared to 1µgkg^{-1} dexmedetomidine (both administered via intranasal drops), children were more easily aroused with external stimulation[48,84]. Doubling the dose of intranasal dexmedetomidine from 1µgkg^{-1} (diluted drops) to 2µgkg^{-1} (undiluted drops) resulted in more satisfactory sedation in older children (aged 5-8years old) but not in those aged 4 years or less[84]. A possible explanation for this non-intuitive finding, might be the smaller intranasal surface area of younger children, which limits drug absorption[84]. Another trial that did not distinguish between age groups, did not find a significant difference in efficacy between these two doses[85]. Although intranasal administration can occur via drops in a syringe, using an atomizer device might theoretically improve effectiveness as this maximizes surface area, enabling rapid drug absorption[36]. No studies comparing this nebulized administration and classic intranasal drops were found. Some authors advocate the use of undiluted 100µgmL^{-1} intranasal drops since over-dilution leads to partial oral administration[19]. Onset of sedation is comparable between different doses of intranasal drops of dexmedetomidine and is about 20 to 30 minutes[84,85]. Its peak sedative effect is after 90 to 105 minutes[32]. This is a long interval, but adequate sedation is already achieved after 45 minutes to 1 hour[32,48,83,84]. When combined with oral ketamine, onset time is shorter: 15-20 minutes. This combination might be a more practical way for adequate and quick sedation or anxiolysis[86].

Oral administration

Like clonidine, dexmedetomidine can also be administered orally. Its bioavailability is very low (16%)[87]. Zub et al. suggest oral doses of 3-4µgkg^{-1}, which provides adequate sedation after 20 to 30 minutes[88]. Other authors suggest 2µgkg^{-1}, resulting in an onset time of 45 to 90 minutes[13].

Transmucosal administration

Due to its poor bioavailability, buccal administration of dexmedetomidine provides a more reliable blood concentration[87]. However, this route requires more patient cooperation because children must hold

the drug for 5 minutes in their mouth without swallowing[88]. Compared to the intranasal way, buccal administration of 1µgkg^{-1} dexmedetomidine is slower and less effective[83]. Sublingual administration of dexmedetomidine 1,5µgkg^{-1} led to more effective sedation after 55 minutes compared to sublingual midazolam[38].

Efficacy

The efficacy of dexmedetomidine is indisputable. In a single-blinded, randomized, placebo-controlled clinical comparison study, intranasal drops of dexmedetomidine 1µgkg^{-1} and 2µgkg^{-1} significantly ($p<0,001$) reduced anxious behavior at mask induction[85]. Intranasal administration dexmedetomidine 1µgkg^{-1} (either via atomization of intranasal drops) led to good or excellent mask induction in approximately 80% of children[19,83]. Intranasal or transmucosal dexmedetomidine is considered equally[19,22,48] or more[12,4]8 effective in preoperative sedation and relief of perioperative anxiety than oral midazolam. Additionally, when both agents are administered sublingually or nebulized, dexmedetomidine 2µgkg^{-1} seems to be superior to midazolam 0,2mgkg^{-1} regarding sedation, recovery time and postoperative agitation[36,38]. Only one trial found an advantage of midazolam over intranasal drops of dexmedetomidine regarding behavior at mask induction, while they were equally effective in decreasing anxiety at parental separation[32].

Advantages

As with clonidine, alpha-2 agonist may decrease intraoperative requirements for inhaled anesthetics and opioids, although a study of Schmidt et al. failed to prove this in ambulatory pediatric anesthesia[22]. Dexmedetomidine might be neuroprotective as well. In an experiment among rodents and fetal monkeys, it prevented cortical apoptosis[89,90]. Unlike midazolam, dexmedetomidine does not impair explicit memory. A meta-analysis of 15 randomized controlled trials concluded that dexmedetomidine significantly reduced (pooled RR= 0,351 [95%CI: 0,275-0,449]) the incidence of sevoflurane-related emergence agitation[91]. This is possible without prolonging discharge times 85. One trial even noticed shorter recovery times compared to midazolam or ketamine[36]. Factors in this improved postoperative flow might be less postoperative pain 22 and nausea and vomiting[86]. Dexmedetomidine might be especially useful in older and larger combative patients, as it holds a substantial benefit over midazolam[19].

Disadvantages

Dexmedetomidine leads to a reduction in heart rate and mean arterial pressure before and during surgery[4,22,32,38,48,85]. Nonetheless, no record revealed clinically significant hemodynamic fluctuations that required an intervention.

B-6 Racemic ketamine

Ketamine is a water-soluble arylcycloalkylamine known for its sedative, dissociative effects. It also produces amnesia and analgesia, depending on the dose. Ketamine antagonizes the NMDA-receptor, resulting in a potent anesthetic effect. For that reason, it is included in the World Health Organization list of Essential Medicines for Children[3]. Ketamine can be administered orally, transmucosal, intranasally, rectally and intramuscular and has an elimination half-life of 1-2 hours in children[31].

Oral administration

Oral preparations of doses ranging from 3mgkg^{-1} to 10mgkg^{-1} are administered. Some articles advocate small doses of 3mgkg^{-1} since side effects are dose dependent[15] but most commonly, 5mgkg^{-1} to 6mgkg^{-1} is used[12,47,57,92]. One trial used 10mgkg^{-1} oral racemic ketamine. Surprisingly, compared to placebo this did not improve sedation [93].

Transmucosal/intranasal administration

Transmucosal administration in the form of a lollipop containing a fixed dose of racemic ketamine has been tested, but this resulted in calmness in only 26% of participants[25]. Racemic ketamine can be administered intranasally in a dose of 3 to 5mgkg^{-1} [15]. To improve uptake by expanding the area, a nebulized form can be used. Based on limited research, doses of 2 or 3mgkg^{-1} are acceptable. Nebulizing might induce nose irritation but leads to better sedation and less perioperative opioid requirements than oral ketamine[93].

Rectal administration

In a comparative study between 5mgkg^{-1}, 7mgkg^{-1}, 10mgkg^{-1} rectal racemic ketamine and 1mgkg^{-1} rectal midazolam, dose-related sedation was noted. As 75% of participants in the ketamine 5mgkg^{-1} group required restraints to achieve induction versus none in the 10mgkg^{-1} group, 5mgkg^{-1} is not an appropriate dose. Rectal racemic ketamine 7mgkg^{-1} and 10mgkg^{-1} prolongs postoperative discharge but decreases the need for rescue analgesics[45].

Intramuscular administration

Intramuscular administration is an invasive method but sometimes the only solution in very combative

children. Doses ranging from 2 to 5mgkg^{-1} are used[12,13,15,52]. This results in an onset time of 5 to 10 minutes[12,13].

S-Ketamine

In all the previous studies, racemic ketamine was used. The S-enantiomer of ketamine might have less disadvantages: less psychomimetic effects and less salivation. It is more potent and thus requires a lower dose. Marhofer et al. studied the effects of rectal S-ketamine (to a dose of 1,5mgkg^{-1}) but did not find any advantage over 0,75mgkg^{-1} rectal midazolam. S-ketamine causes prolonged excitation during induction, which might be problematic[94].

Ketamine plus midazolam

Ketamine is frequently mixed with midazolam, to attenuate side effects of both drugs. Ketamine can be half dosed this way. For oral administration this would mean: 1,8mgkg^{-1} to 3mgkg^{-1} racemic ketamine plus 0,25mgkg^{-1} to 0,3mgkg^{-1} midazolam[12,47,95,96]. This combination results in less sedation, but more awake, calm, and quiet children preoperatively[95]. Moreover, this results in a faster onset (approximately 20 minutes vs 30 minutes with ketamine 6mgkg^{-1} alone), minimal side effects and a more rapid recovery[47]. Wang et al. used the combination of rectal racemic ketamine and midazolam but did not half the dose of ketamine (8mgkg^{-1} vs 4mgkg^{-1}). This resulted in more children being unconscious in the high dose group, although most patients were calm during parental separation in both groups[97]. No adverse effects were seen as atropine 0,02mgkg^{-1} was used systematically. Nasal administration of drops of S-ketamine 2mgkg^{-1} plus midazolam 0,2mgkg^{-1} shows a very rapid onset of action (2,5 min) and a significantly ($p<0,0001$) better sedation compared to drops of midazolam alone[34]. One side effect was noted in this study: all patients complained of its bitter taste immediately after drug administration[34]. Combination of intramuscular racemic ketamine (1mgkg^{-1} or 2mgkg^{-1}) and intramuscular midazolam (0,1mgkg^{-1} or 0,2mgkg^{-1}) resulted in a very quick onset of satisfactory sedation in all patients. But this was at the expense of clinically unacceptable prolonged recovery and discharge times[52].

Efficacy

It is difficult to assess the efficacy of ketamine, as there are not many trials that compare ketamine premedication to placebo. Oral ketamine 10mgkg^{-1} did not produce significant effects on preoperative sedation score, compared to placebo (anxiety scores 4.31±0.79 vs 4.21±0.79, $p=0,002$) but it was successful in the reduction of perioperative pain[93]. In another trial, 60% percent of patients had calm parental separation after 6mgkg^{-1} ketamine. A mixture of oral ketamine 3mgkg^{-1} and midazolam 0,25mgkg^{-1} had the same result, but this was achieved earlier[47]. Funk et al. reported a success rate (anxiolysis, behavior at separation) of 90% with the combination of oral ketamine 3mgkg^{-1} and midazolam 0,25mgkg^{-1} versus 70% and 51% with respectively midazolam 0,5mgkg^{-1} and ketamine 6mgkg^{-1} alone[98]. Nebulized ketamine was able to provide effective sedation but did not have any advantage over nebulized dexmedetomidine as mask acceptance was lower[36,93]. However, the combination of oral ketamine 3mgkg^{-1} and intranasal dexmedetomidine 2µgkg^{-1} is promising as this combines the onset time of ketamine with the reliability of dexmedetomidine[86]. Rectal ketamine 8mgkg^{-1} plus midazolam 0,5mgkg^{-1} resulted in 62% of patients being asleep at parental separation 30 minutes later[97]. Ten mgkg^{-1} rectal ketamine was found to be equally effective as 1mgkg^{-1} rectal midazolam[45]. Nasal administration of 2mgkg^{-1} S-ketamine shows good conditions for induction in 63% of patients. This happens within 2,5 minutes, which is very fast[34]. Rectal appliance of S-ketamine either alone or combined with midazolam does not show any advantages over rectal midazolam[94].

Advantages-disadvantages

Ketamine does not cause hemodynamic or respiratory depression, which is an advantage[15]. Side effects are vomiting, sialorrhea, bronchial secretions requiring anticholinergics which makes ketamine not suitable for upper airway surgery[13,15,57]. The incidence of postoperative nausea and vomiting is proportional to oral dose administered[86]. The effect of ketamine on emergence delirium is disputable. Kararmaz et al. found that oral ketamine 6mgkg^{-1} successfully reduced the incidence of emergence agitation[92], while Trabold et al. stated that oral ketamine combined with midazolam does not have a significant benefit over midazolam alone[96]. Nevertheless, ketamine might be an adequate treatment in children with paradoxical reactions or emergence agitation after midazolam premedication[49,99]. Some of the benefits might be the result of the intrinsic analgesic effect of ketamine, which lasts postoperatively. Children premedicated with either 10mgkg^{-1} rectal ketamine or oral/inhaled ketamine showed less postoperative pain, compared to controls[45,93]. This effect of ketamine goes together with delayed emergence 45 and even discharge[15,52] which is especially the case for operations shorter than 30 minutes. Side effects can be attenuated by using combinations with other drugs as described above.

Table III. — Recommendations.

Recommendation	*Product*	*Route of administration*	*Tolerance*	*Recommended dose*	*Onset time*	*Onset*	*Efficacy*	*Safety and side effects*
recommendable	*midazolam*	*oral*	*high*	*1mgkg-1 (1-3years old); 0,75mgkg-1 (>3j old)*	*10-30min*	*fast-moderate*	*debatable*	*safe, minor side effects, paradoxical reactions, impairment of cognition*
recommendable	*clonidine*	*oral*	*high*	*4µgkg-1, 40-60µg (young children)*	*38min*	*slow*	*good*	*safe, bradycardia (not requiring intervention)*
recommendable	*dexmedetomidine*	*intranasal*	*high*	*1µgkg-1 (<5 years old), 2µgkg-1 (>5years old)*	*20-30min*	*moderate*	*high*	*very safe, limited reduction of heart rate and mean arterial pressure*
recommendable	*ketamine + midazolam*	*oral*	*high*	*4mgkg-1 + 0,25mgkg-1*	*20 min*	*moderate*	*good-high*	*safe, minor side effects*
considerable	*diazepam + midazolam*	*oral*	*high*	*0,25mgkg-1 + 0,25mgkg-1*	*45min*	*slow*	*high*	*safe, minor side effects*
considerable	*butorphanol*	*oral*	*unknown*	*0,2mgkg-1*	*20-30min*	*moderate*	*debatable*	*limited studies*
considerable	*ketamine*	*oral*	*high*	*5-6mgkg-1*	*10-20min*	*fast*	*good*	*major side effects: nausea, vomiting, sialorrhea*
considerable	*s-ketamine + midazolam*	*intranasal*	*low*	*2mgkg-1 + 0,2mgkg-1*	*2,5min*	*extremely fast*	*good*	*limited studies*
considerable	*hydroxyzine*	*oral*	*high*	*1mgkg-1*	*105min*	*very slow*	*unknown*	*very safe, limited studies*
not recommendable	*midazolam*	*intranasal*	*low*	*-*	*5-20min*	*(very) fast*	*debatable*	*burning sensation, low tolerance*
not recommendable	*midazolam*	*sublingual/ buccal*	*moderate*	*-*	*29,8±5,8min*	*moderate*	*debatable*	*limited studies*
not recommendable	*midazolam*	*rectal*	*low*	*-*	*33,7±3,4min*	*slow*	*unknown*	*not reliable*
not recommendable	*midazolam*	*intramuscular*	*low*	*-*	*5-10min*	*fast*	*high*	*invasive*
not recommendable	*diazepam*	*oral*	*high*	*-*	*30-60min*	*(very) slow*	*unknown*	*minor side effects (hangover effect)*
not recommendable	*diazepam*	*rectal*	*low*	*-*	*?*	*unknown*	*debatable*	*not reliable*
not recommendable	*zolpidem*	*oral*	*high*	*-*	*15 min*	*fast*	*low*	*low efficacy, some side effects*
not recommendable	*melatonin*	*oral*	*high*	*-*	*15-60min*	*fast-very slow*	*debatable*	*not reliable, high safety*
not recommendable	*OTFC*	*oral transmucosal*	*high*	*-*	*30-45min*	*slow*	*low*	*major safety issues: r espiratory depression*
not recommendable	*clonidine*	*intranasal*	*high*	*-*	*?*	*unknown*	*low*	*low efficacy*
not recommendable	*clonidine*	*rectal*	*low*	*-*	*50min*	*very slow*	*unknown*	*major side effects: bradycardia*
not recommendable	*dexmedetomidine*	*oral*	*high*	*-*	*45-90min*	*very slow*	*(very)low*	*(very) low efficacy*
not recommendable	*dexmedetomidine*	*buccal/ sublingual*	*moderate*	*-*	*>45 min*	*very slow*	*unknown*	*difficult administration, very slow onset*
not recommendable	*ketamine*	*transmucosal*	*high*	*-*	*30min*	*moderate*	*low*	*low efficacy*
not recommendable	*ketamine*	*intranasal*	*low*	*-*	*<10min*	*very fast*	*unknown*	*limited studies*
not recommendable	*ketamine*	*nebulized*	*moderate*	*-*	*30min*	*moderate*	*good-low*	*limited studies*

Table III. — Recommendations.

not recommendable	*ketamine*	*rectal*	*low*	-	*20-30min*	*moderate*	*very low - low*	*prologs postoperative discharge*
not recommendable	*ketamine*	*intramus-cular*	*low*	-	*5-10min*	*very fast*	*unknown*	*invasive*
not recommendable	*s-ketamine*	*rectal*	*low*	-	*?*	*unknown*	*low*	*major side effects: prolongs excitation*
not recommendable	*ketamine + midazolam*	*rectal*	*low*	-	*30min*	*moderate*	*good*	*limited studies*
not recommendable	*ketamine + midazolam*	*intramus-cular*	*low*	-	*5-10min*	*very fast*	*good*	*invasive*
not recommendable	*promethazine*	*oral*	*low*	-	*?*	*unknown*	*debatable*	*low tolerance, minor side effects*
Recommendation			*Toler-ance*		*Onset time*	*Onset*	*Efficacy*	*Efficacy*
not recommendable			*low*		*<5 min*	*extremely fast*	*<25%*	*very low*
considerable			*moderate*		*5-10 min*	*very fast*	*25-50%*	*low*
recommendable			*high*		*10-20min*	*fast*	*50-75%*	*good*
highly recommandable					*20-30min*	*moderate*	*>75%*	*high*
					30-45min	*slow*	*≠*	*debatable*
					>45 min	*very slow*	*?*	*unknown*
					?	*unknown*		

B-7 Antihistamine

B-7.1 Hydroxyzine-promethazine

Hydroxyzine and promethazine are antihistamines with sedating properties. Hydroxyzine can be administered orally as a syrup or as a tablet. Three different doses of hydroxyzine were found: 1mgkg^{-1} [100], 3,7mgkg^{-1} and a fixed dose of 20mg[101]. Oral promethazine is administered in a dose of 0,3mgkg^{-1} [18]. Compared to placebo, administration of oral hydroxyzine 1mgkg^{-1} and promethazine 1¾ hour prior to induction respectively resulted in a significant ($p<0,05$) better tolerance of inhalational induction[18,100]. Promethazine was equally effective compared to oral midazolam 0,5mgkg^{-1} regarding stress reduction at parental separation and induction[18]. Administration of 20mg oral hydroxyzine one day before dental treatment had no additional anxiolytic or sedative effect[101]. Advantages of these antihistamines are their price, their availability and intrinsic anti-emetic and little to no side effects[18,101]. However, promethazine might cause a stinging sensation in the children's mouth[18].

Discussion

The perfect premedication for children is a non-invasive, safe, and reliable anxiolytic, with a quick onset time and little to no adverse effects. Postoperative decrease of emergence agitation is a benefit. Different products have different properties and therefore unique advantages. Based upon the results of our review, some suggestions can be made(See Table III. Recommendations).

Oral midazolam has been the golden standard for long, with a fast to moderate onset time, high tolerance and few side effects. Efficacy of oral midazolam is dependent on the outcome parameter that has been used (anxiety versus sedation versus ease of mask induction) and is therefore a topic of debate. Oral clonidine in a dose of 4µgkg^{-1} is slower, but considered equally effective to oral midazolam, with higher parental satisfaction. Orally disintegrating tablets and lollipops and additives are promising but need further research. Intranasally dexmedetomidine is the most reliable product, but this is at the expense of a relative onset time and peak effect. The combination of oral ketamine and midazolam on the other hand is faster, well tolerated with a high efficacy. Some other products like oral diazepam, butorphanol, ketamine intranasal s-ketamine + midazolam and hydroxyzine can be considered because of their proper safety and benefits. A tailored approach to the use of different premedications must be made based on the child's needs and comorbidities, the anesthesiologist's goals, and availability of each product. Non-pharmacological interventions were not studied but are nonetheless non-invasive and safe and should therefore be considered in most children.

A major limitation of this review is the large variability in study designs and results of all included studies. Different endpoints, study populations and various tools to assess perioperative anxiety make interstudy comparison difficult. Agents have a different onset time, which was not taken in account in studies that compared different types of premedications. This might lead to suboptimal assessment of anxiety (too early – i.e., before onset time, or too late – i.e., after peak sedative effect). Bias was not analyzed in this review.

Further research in this topic should focus on patient selection to choose a suitable intervention. Standardized assessment of anxiety, clinical significancy and feasibility should be included in the objectives of these studies.

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