Journal of Anesthesia (2024) 38:692–710
https://doi.org/10.1007/s00540-024-03358-w

REVIEW ARTICLE

Remimazolam for anesthesia and sedation in pediatric patients: a scoping review

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Received: 2 February 2024 / Accepted: 27 May 2024 / Published online: 7 June 2024

Abstract

Anesthetic management of pediatric patients poses several challenges and the optimal anesthetic agent for use in this population is still a matter of debate. We systematically searched PubMed/MEDLINE and Google Scholar from their inception for studies that investigated the role and potential applications of remimazolam, a novel ultra-short-acting benzodiazepine, in pediatric patients. Furthermore, in March 2024, an update of the literature search along with an additional post-hoc search on the EMBASE database were performed. A total of fourteen pertinent studies which spanned the 2021–2023 period explored remimazolam as either the primary or adjuvant hypnotic agent for inducing and/or maintaining general anesthesia or sedation. Preliminary evidence derived from these studies highlighted that remimazolam is a safe and effective option for both sedation and general anesthesia in pediatric patients, particularly those with concurrent mitochondrial disorders, myopathic diseases, or at risk for malignant hyperthermia. Moreover, the current evidence suggested that remimazolam may contribute to reducing preoperative anxiety and postoperative delirium in children. Its favorable pharmacodynamic and pharmacokinetic profile demonstrated potential safety, effectiveness, and ease-of-use in various perioperative pediatric contexts, making it suitable for integration into specific protocols, such as intraoperative monitoring of evoked potentials and management of difficult intubation. Notwithstanding these promising findings, further research is essential to determine optimal dosages, establish conclusive evidence of its superiority over other benzodiazepines, and elucidate the impact of genetic factors on drug metabolism.

Keywords General anesthesia · Pediatric patients · Remimazolam · Sedation

Introduction

Up to 60% of children who undergo surgical procedures experience adverse emotions, encompassing vague sensations of worry, nervousness, or unease, which can result in significant cognitive, temperamental and emotional distress [1, 2]. Such negative experiences also exert a high impact on the anesthetic strategy, resulting in extended time required for anesthesia induction as well as an increased need for intraoperative anesthetic and analgesic agents. Moreover, these experiences may lead to postoperative behavioral disturbances (e.g., delirium and agitation), longer hospital stay, more complicated recovery and diminished patients' satisfaction [3, 4].

Historically, general anesthesia (GA) has been the preferred anesthetic approach in children undergoing surgery, with inhalational anesthesia being the prevalently chosen method in the field of pediatric anesthesia [5]. Propofol, short-acting opioids, midazolam, and dexmedetomidine, are also commonly employed for GA induction and maintenance in pediatric patients [6]. However, significant limitations are associated with each of these agents. For instance, sevoflurane is burdened with the risk of postoperative delirium and anxiety, especially during gaseous induction with a facial mask, which may also potentially contribute to long-term psychological trauma in children [6–8]. Propofol administration is linked to lingering pain at the injection site, whereas dexmedetomidine is

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characterized by delayed onset and recovery times [9–11]. Furthermore, both propofol and volatile anesthetics impair mitochondrial activity and fatty acid oxidation chain, and should hence be avoided in children with mitochondrial disorders due to their higher risk for triggering malignant hyperthermia, propofol infusion syndrome, metabolic decompensation, acute encephalopathy and epileptic seizures [12–15].

Remimazolam is a novel hydrosoluble, ultra-short-acting benzodiazepine, currently approved for intravenous administration in GA, procedural sedation, and longer-term sedation in multiple countries [16]. It exhibits a high specificity and affinity for the brain benzodiazepine site on the gamma-aminobutyric acid type A ($GABA_A$) receptor. With its properties such as non-irritating nature, rapid onset, short half-life, predictable sedation levels, swift emergence from anesthesia, kidney- and liver-independent metabolism, minimal residual sedation, and negligible side effects at typical dosages (i.e., cardiovascular and respiratory depression), remimazolam emerges as a promising option for use in children. Furthermore, it does not impair either mitochondrial activity or fatty acid oxidation, and has a specific antagonist (flumazenil).

To date, the administration of remimazolam as the first-choice benzodiazepine for inducing and/or maintaining GA remains rare in pediatric settings. Such limited acceptance may be linked to its approval only in recent years, a lack of consensus on optimal dosages, and unfamiliarity with its application within the scientific community.

The present systematically structured scoping review aims to provide insights into the potential clinical applications of remimazolam for different procedures performed in the pediatric population by summarizing the original data and investigations retrieved from existing literature available to date, ultimately fostering evidence-based clinical decision-making (Fig. 1).

Materials and methods

Search strategy

Based on the guidelines from the Cochrane Collaboration and Centre for Reviews and Dissemination, we conducted a systematically structured scoping review in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (Supplementary Material, Supplementary Table 1) guideline and its extension for scoping reviews [17]. A research protocol for the present scoping review was written and approved by all the authors before study start and is available in the Supplementary material (*Supplementary material, Scoping review Research protocol*). Two experienced and independent investigators (J.D.U. and R.L.) conducted a comprehensive search on PubMed/

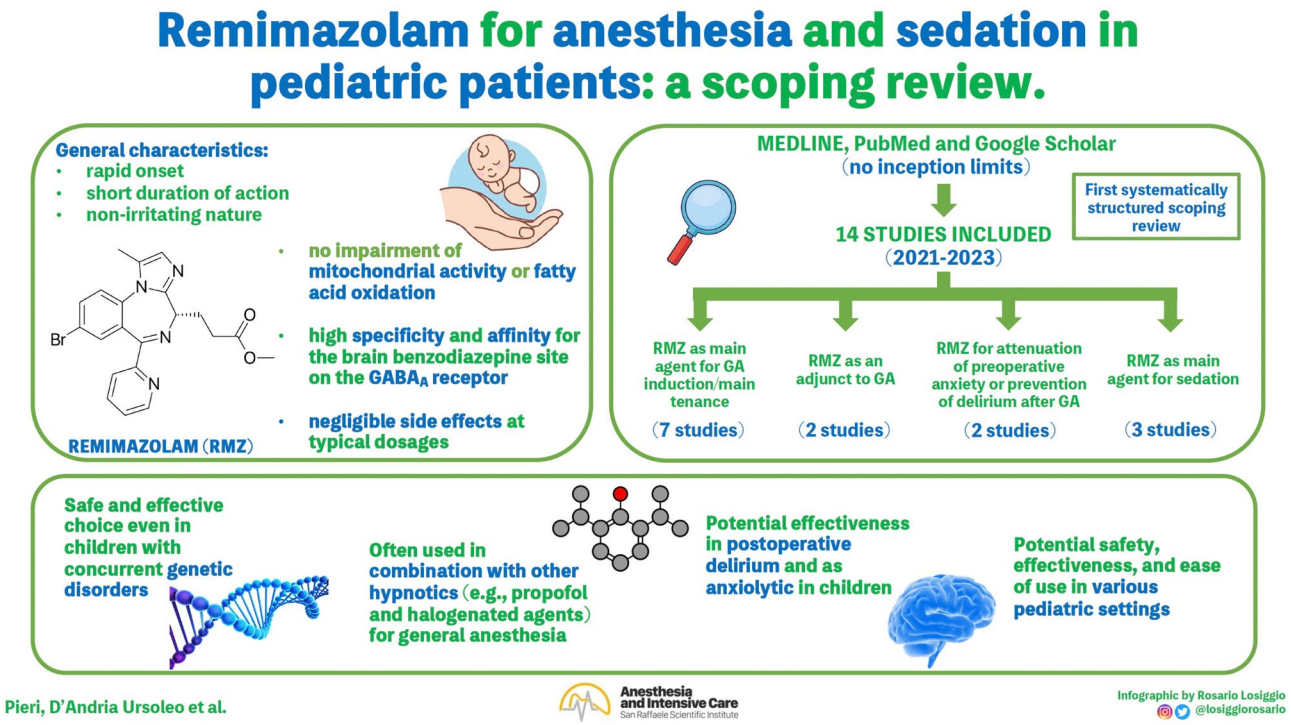

Fig. 1 Visual abstract presenting main article structure, objective, research methodology and results

MEDLINE and Google Scholar databases to identify studies (up to January 15, 2024, without inception limits) pertinent to the research question. Furthermore, on March 23, 2024, an update of the literature search along with an additional post-hoc search on the EMBASE database were carried out. The search string included the commercial names of remimazolam: "Byfavo" (South Korea), "Anerem®" (Japan), "Aptimyda™" (EU), "ByFavo™" (USA) and "Ruima®" (China). Keywords and free terms were combined using the Boolean operator 'OR'. Additional details regarding the search strategy is made available in the supplementary material file (*Supplementary material, Search Strategy*). Duplicate publications were removed using EndNote X9 (Clarivate Analytics) and the resulting citations were uploaded to Rayyan for screening [18]. Notably, both backward and forward snowballing techniques were applied to scrutinize the references of selected articles, aiming to identify additional studies for potential inclusion in the present systematically structured narrative review. Only articles written in English were considered for potential inclusion.

Study selection

Every reference identified through the database search and literature review underwent independent assessment by both investigators, at both title and abstract levels. In cases where concerns or disagreements arose, full-text articles were consulted, and any disagreements were resolved through discussion ultimately involving a third, senior investigator (F.M.).

Inclusion criteria

Studies and case reports or series written in English reporting original experience of remimazolam administration in pediatric patients aged 18 years or less undergoing a variety of procedures either under general anesthesia or sedation were identified and carefully assessed.

Exclusion criteria

Studies concerning the adult population, publications not presenting original data (including reviews, systematic reviews, meta-analyses, commentaries, conference abstracts which had not reached the full publication status, letters, and editorials) and works published in languages other than English were excluded from this review. No additional limitations on the study design were applied.

Data extraction and study characteristics

The PICO (Patient/Population/Problem, Intervention, Comparison/Control, Outcome) approach together with standardized forms were used to carry out data extraction. Specifically, the pediatric population undergoing interventional procedures either under general anesthesia or sedation was considered as the patient group. We assessed interventions involving the administration of remimazolam, solely or in combination with other drugs, vs any comparators when and if present, for sedation or general anesthesia induction and/or maintenance. Extracted information including details on each of the original investigations retrieved, and a summary of the respective main recommendations are summarised in Table 1. The types of anesthesia performed with the related remimazolam dosages are outlined in Table 2.

The risk of bias assessment was performed with the Risk Of Bias In Non-randomised Studies—of Interventions (ROBINS-I) tool for observational studies and the risk-of-bias tool for randomized trials (RoB2) by Cochrane (accessible online at https://www.riskofbias.info), as shown in Fig. 2.

Statistical analysis

We presented the results from individual studies, typically encompassing predictive performance for predefined outcomes. Provided the heterogeneity in the literature, formal data synthesis or analysis were not performed.

Results

Fourteen studies were retrieved for inclusion (Fig. 3), all having been published within the last three years (2021–2023). Eleven studies (79%) were performed in Asian countries and 3 (21%) in the United States. One study was a randomized control trial, 5 studies were observational and 8 were case reports (Supplementary material, Supplementary Table 2).

Existing evidence on remimazolam was categorized into four main clusters: i) as the main anesthetic agent for the induction and/or maintenance of GA, ii) as an adjuvant of GA, and iii) for the attenuation of preoperative anxiety or the prevention of emergence delirium following GA, iv) as the main agent for procedural sedation.

Remimazolam as the main anesthetic agent for the induction and/or maintenance of general anesthesia in children

The published literature on remimazolam as the sole hypnotic agent for both the induction and maintenance of GA is mainly focused on pediatric patients with peculiar genetic mitochondrial diseases, procedures that require intraoperative neurophysiological monitoring (IONM) and myopathic patients.

Remimazolam appeared to provide clear clinical advantages in the context of pediatric patients with mitochondrial

Table 1 Selected studies in the pediatric population with summary of the main reported systemic effect(s) according to the type of remimazolam-based sedation or anesthesia protocol

1st Author[ref], country	Year, type of publication	Sample size (age)	Description of procedure(s)	Type of anesthesia or sedation with remimazolam	Reported effect(s) of remimazolam				Reported adverse effects of remimazolam	Comments
					Blood pressure	Cardiac conduction system alterations	Dysrhythmia occurrence	Postoperative delirium		
Remimazolam as the main anesthetic agent for the induction and/or maintenance of general anesthesia										
Arashiro[28], Japan	2021, Case report	1 pt (17 yr)	Posterior spinal fusion for functional scoliosis in Alström syndrome	General anesthesia	BP stable after remimazolam administration and throughout the perioperative period	None	None	None	None	
Horikoshi[31], Japan	2021, Case report	1 pt (4 yr)	Single-incision LPEC for inguinal hernia and umbilical plasty in Duchenne muscular distrophy	General anesthesia	BP stable after remimazolam administration and throughout the perioperative period	None	None	None	None	
Kamata[27], Japan	2022, Case report	1 pt (12 yr)	Partial resection of an anaplastic astrocytoma in egg allergy	General anesthesia	BP stable after remimazolam administration and throughout the perioperative period	n/a	n/a	None	None	
Kiyokawa[24], Japan	2022, Case report	1 pt (5 yr)	LPEC of an inguinal hernia in Medium-Chain Acyl-CoA Dehydrogenase deficiency	General anesthesia	BP stable after remimazolam administration and throughout the perioperative period	None	None	None	None	

Table 1 (continued)

1st Author[ref], country	Year, type of publication	Sample size (age)	Description of procedure(s)	Type of anesthesia or sedation with remimazolam	Reported effect(s) of remimazolam				Reported adverse effects of remimazolam	Comments
					Blood pressure	Cardiac conduction system alterations	Dysrhythmia occurrence	Postoperative delirium		
Remimazolam as the main anesthetic agent for the induction and/or maintenance of general anesthesia										
Ogino[32], Japan	2023, Case report	1 pt (1 yr)	Laparoscopic gastrostomy in IMNM	General anesthesia	BP stable after remimazolam administration and throughout the perioperative period	None	None	None	None	
Petkus[33], USA	2022, Case report	1 pt (6 yr)	Dental rehabilitation procedure in suspected familiar history for malignant hyperthermia	General anesthesia	n/a	n/a	n/a	None	None	
Yamadori[23], Japan	2022, Case report	1 pt (10 yr)	Open gastrostomy in MELAS and recurrent epilepsy	General anesthesia	n/a	n/a	n/a	None	None	
Remimazolam as an adjunct to general anesthesia										
Gao[35], China	2023, Observational	24 pts (2–6 yr)	General surgery	General anesthesia	Increase of SBP by 10% and of DBP by 15%	None	None	None	None	
Kimoto[34], Japan	2023, Oberva-tional	418 pts (4.6 yr ± 4.52)	Various procedures (most general surgery)	General anesthesia	MAP variation greater than 20% in 75.2% and greater than 30% in 49.3%	None	None	None	Hypotension and hypertension	

Table 1 (continued)

1st Author[ref], country	Year, type of publication	Sample size (age)	Description of procedure(s)	Type of anesthesia or sedation with remimazolam	Reported effect(s) of remimazolam				Reported adverse effects of remimazolam	Comments
					Blood pressure	Cardiac conduction system alterations	Dysrhythmia occurrence	Postoperative delirium		
Remimazolam as the main anesthetic agent for the induction and/or maintenance of general anesthesia										
Remimazolam for the attenuation of preoperative anxiety or the prevention of emergence delirium following general anesthesia										
Xiang[37], China	2023, Observational	80 pts (1–6 yr)	Laparoscopic high-level inguinal hernia ligation	General anesthesia	Minimal decrease of MAP in both groups	None	None	None	None	
Yang[36], China	2022, RCT	104 pts (3–7 yr)	Bilateral tonsillectomy and adenoidectomy	General anesthesia	BP stable after remimazolam administration	None	None	12% in the remimazolam group vs 44% in the placebo group	Postoperative delirium	
Remimazolam as the main agent for procedural sedation										
Hirano[38], Japan	2022, Observational	48 pts (0.1–17.8 yr)	Radiological imaging studies	Sedation	MAP decrease by a median of 22.6% (range: 19.2–58.2%)	None	None	None	Hypotension	
Hughes[40], USA	2023, Case report	1 pt (12 yr)	Fiberoptic intubation in burns and traumatic scars	Sedation	n/a	n/a	n/a	None	None	
Yeh[39], USA	2023, Observational	2 pts (14–16)	Placement of pericardial drain and halo removal	Sedation	Patient 1: BP after remimazolam infusion was 72/55 mmHg Patient 2: BP stable after remimazolam administration and throughout the perioperative period	None	None	None	Hypotentson	2 pediatric patients out of 7 total cases

Table 1 (continued)

1st Author[ref], country	Year, type of publication	Sample size (age)	Description of procedure(s)	Type of anesthesia or sedation with remimazolam	Reported effect(s) of remimazolam				Reported adverse effects of remimazolam	Comments
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Remimazolam as the main anesthetic agent for the induction and/or maintenance of general anesthesia										
1st Author[ref], country	Year, type of publication	Sample size (age)	Description of procedure(s)	Type of anesthesia or sedation with remimazolam	Reported effect(s) of remimazolam				Reported adverse effects of remimazolam	Comments
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Arashiro[28], Japan	2021, Case report	1 pt (17 yr)	Posterior spinal fusion for functional scoliosis in Alström syndrome	General anesthesia	BP stable after remimazolam administration and throughout the perioperative period	None	None	None	None	
Horikoshi[31], Japan	2021, Case report	1 pt (4 yr)	Single-incision LPEC for inguinal hernia and umbilical plasty in Duchenne muscular distrophy	General anesthesia	BP stable after remimazolam administration and throughout the perioperative period	None	None	None	None	
Kamata[27], Japan	2022, Case report	1 pt (12 yr)	Partial resection of an anaplastic astrocytoma in egg allergy	General anesthesia	BP stable after remimazolam administration and throughout the perioperative period	n/a	n/a	None	None	

Table 1 (continued)

1st Author[ref], country	Year, type of publication	Sample size (age)	Description of procedure(s)	Type of anesthesia or sedation with remimazolam	Reported effect(s) of remimazolam				Reported adverse effects of remimazolam	Comments
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Kiyokawa[24], Japan	2022, Case report	1 pt (5 yr)	LPEC of an inguinal hernia in Medium-Chain Acyl-CoA Dehydrogenase deficiency	General anesthesia	BP stable after remimazolam administration and throughout the perioperative period	None	None	None	None	
Ogino[32], Japan	2023, Case report	1 pt (1 yr)	Laparoscopic gastrostomy in IMNM	General anesthesia	BP stable after remimazolam administration and throughout the perioperative period	None	None	None	None	
Petkus[33], USA	2022, Case report	1 pt (6 yr)	Dental rehabilitation procedure in suspected familiar history for malignant hyperthermia	General anesthesia	n/a	n/a	n/a	None	None	
Yamadori[23], Japan	2022, Case report	1 pt (10 yr)	Open gastrostomy in MELAS and recurrent epilepsy	General anesthesia	n/a	n/a	n/a	None	None	
Remimazolam as an adjunct to general anesthesia										
Gao[35], China	2023, Observational	24 pts (2–6 yr)	General surgery	General anesthesia	Increase of SBP by 10% and of DBP by 15%	None	None	None	None	

Table 1 (continued)

1st Author[ref], country	Year, type of publication	Sample size (age)	Description of procedure(s)	Type of anesthesia or sedation with remimazolam	Reported effect(s) of remimazolam				Reported adverse effects of remimazolam	Comments
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Remimazolam for the attenuation of preoperative anxiety or the prevention of emergence delirium following general anesthesia										
Xiang[37], China	2023, Observational	80 pts (1–6 yr)	Laparoscopic high-level inguinal hernia ligation	General anesthesia	Minimal decrease of MAP in both groups	None	None	None	None	
Yang[36], China	2022, RCT	104 pts (3–7 yr)	Bilateral tonsillectomy and adenoidectomy	General anesthesia	BP stable after remimazolam administration	None	None	12% in the remimazolam group vs 44% in the placebo group	Postoperative delirium	
Remimazolam as the main agent for procedural sedation										
Hirano[38], Japan	2022, Observational	48 pts (0.1–17.8 yr)	Radiological imaging studies	Sedation	MAP decrease by a median of 22.6% (range:19.2–58.2%)	None	None	None	Hypotension	
Hughes[40], USA	2023, Case report	1 pt (12 yr)	Fiberoptic intubation in burns and traumatic scars	Sedation	n/a	n/a	n/a	None	None	

Table 1 (continued)

1st Author[ref], country	Year, type of publication	Sample size (age)	Description of procedure(s)	Type of anesthesia or sedation with remimazolam	Reported effect(s) of remimazolam				Reported adverse effects of remimazolam	Comments
					Blood pressure	Cardiac conduction system alterations	Dysrhythmia occurrence	Postoperative delirium		
Remimazolam as the main anesthetic agent for the induction and/or maintenance of general anesthesia										
Yeh[39], USA	2023, Observational	2 pts (14–16)	Placement of pericardial drain and halo removal	Sedation	Patient 1: BP after remimazolam infusion was 72/55 mmHg Patient 2: BP stable after remimazolam administration and throughout the perioperative period	None	None	None	Hypotentson	2 pediatric patients out of 7 total cases

Abbreviations. *pt(s)* patient(s); *yr* years; *BP* blood pressure; *MAP* mean arterial pressure; *LPEC* laparoscopic percutaneous extraperitoneal closure; *IMNM* immune-mediated necrotizing muscle disease; *MELAS* mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; *RCT* randomized clinical trial

Table 2 Summary of pharmacological protocols employed for both anesthesia or sedation induction and maintenance encompassing remimazolam in the selected studies

1st Author[ref], country	Groups	Premedication	Induction agents with resepctive doses	Maintenance agents with respective doses
Remimazolam as the main anesthetic agent for the induction and/or maintenance of general anesthesia				
Arashiro[28], Japan	1	n/a	Sevoflurane 5% in O_2 100% + rocuronium 30 mg IV bolus + remifentanil 0.3 μg/kg/min CI	GA with remimazolam 0.5 mg/kg/h CI + remifentanil 0.3 μg/kg/min CI
Horikoshi[31], Japan	1	None	Remimazolam 3 mg IV bolus + fentanyl 100 μg IV bolus + rocuronium 10 mg IV bolus	GA with remimazolam 15 mg/h CI + remifentanil 1 μg/kg/min CI + rocuronium 10 mg IV bolus + one IV bolus of fentanyl 25 μg
Kamata[27], Japan	1	n/a	Remimazolam 6 mg/kg/h CI + remifentanil 0.5 μg/kg/min CI + rocuronium 30 mg IV bolus	GA with remimazolam 0.8–1.8 mg/kg/h CI + remifentanil 0.3–0.4 μg/kg/min CI
Kiyokawa[24], Japan	1	Diazepam 5 mg OS	Remimazolam 4 mg IV bolus + remifentanil 0.5 μg/kg/min CI + rocuronium 15 mg IV bolus + BINB with 12 mL of levobupivacaine 0.25%	GA with remimazolam 2 mg/kg/h CI + remifentanil 0.5 μg/kg/min CI
Ogino[32], Japan	1	n/a	Remimazolam 10 mg/kg/h CI + fentanyl 3 μg/kg IV bolus + rocuronium 0.6 mg/kg IV bolus	GA with remimazolam 1–2 mg/kg/h CI (total 1.22 mg) + IV boluses of fentanyl 3 μg/kg (total 160 μg) + rocuronium 15 mg IV bolus
Petkus[33], USA	1	n/a	Propofol 4 mg/kg IV bolus	GA with propofol 50 μg/kg/min CI + remimazolam 5–7 μg/kg/min CI
Yamadori[23], Japan	1	None	Remimazolam 0.2 mg/kg IV bolus + remifentanil 0.3 μg/kg/min CI + rocuronium 0.3 mg/kg IV bolus + TAP block with 12 mL of ropivacaine 0.375%	GA with remimazolam 2 mg/kg/h CI + remifentanil 0.1–0.25 μg/kg/min CI + rocuronium 15 mg IV bolus + one IV bolus of fentanyl 25 μg
Remimazolam as an adjunct to general anesthesia				
Gao[35], China	1	n/a	Propofol 2.5 mg/kg IV bolus + fentanyl 3 μg/kg IV bolus + rocuronium 0.6–1 mg/kg IV bolus	GA with sevoflurane 1–3% + IV boluses of fentanyl 1–3 μg/kg + remimazolam 5 mg/kg/h (for 5 min)–1.5 mg/kg/h (for 55 min)
Kimoto[34], Japan	1	n/a	IV or inhalation induction + remimazolam 12 mg/kg/h in CI	GA with TIVA or inhalation anesthetics + remimazolam 1–2 mg/kg/h in CI + intermittent IV boluses of remimazolam 0.2 mg/kg
Remimazolam for the attenuation of preoperative anxiety or the prevention of emergence delirium following general anesthesia				
Xiang[37], China	2	Remimazolam 25 mg IN	Propofol 1.5 mg/kg IV bolus + sufentanil 3 μg/kg IV bolus + rocuronium 0.6 mg/kg	GA with sevoflurane
Yang[36], China	2	None	Sevoflurane 5% in O_2 100% at 6 L/min + propofol 2 mg/kg IV bolus + sufentanil 3 μg/kg IV bolus + mivacurium 0.2 mg/kg IV bolus	Group 1: GA with sevoflurane in a 50% nitrous oxide and 50% O_2 mixture + remimazolam 0.2 mg/kg in 10 mL of 0.9% saline at the end of surgery; Group 2: GA with sevoflurane in a 50% nitrous oxide and 50% O_2 mixture + 10 mL of 0.9% saline at the end of surgery
Remimazolam as the main agent for procedural sedation				
Hirano[38], Japan	1	n/a	Remimazolam 12 mg/kg/h CI	Sedation with remimazolam 1–2 mg/kg/h CI alone or in combination with propofol IV boluses or ketamine in CI or IV boluses or fentanyl IV boluses
Hughes[40], USA	1	Midazolam 2 mg IV bolus + glycopyrrolate 0.4 mg IV bolus	Remimazolam 15 μg/kg/min CI + remifentanil 0.05 μg/kg/min CI	Sedation with remimazolam 15 μg/kg/min CI + remifentanil 0.1 μg/kg/min CI

Table 2 (continued)

1st Author[ref], country	Groups	Premedication	Induction agents with resepctive doses	Maintenance agents with respective doses
Yeh[39], USA	2	n/a	Patient 1: remimazolam 5 mg IV bolus + remimazolam 30 µg/kg/min CI Patient 2: remimazolam 5 mg IV bolus	Patient 1: Sedation with remimazolam 10–15 µg/kg/min CI + fentanyl 100 µg IV bolus Patient 2: three intermittent boluses of remimazolam 2.5 mg + fentanyl 50 µg IV bolus + nitrous oxide for the placement of IV cannula

Abbreviations. *n/a* not specified; *IV* intravenous; *CI* continuous infusion; *GA* general anesthesia; *min* minutes; *h* hours; *OS* oral administration; *BINB* bilateral ilioinguinal nerve block; *IN* intranasal

disorders, in whom commonly used hypnotic drugs (e.g., propofol and halogenated anesthetics) are not indicated [13, 19–21]. Current evidence supports the use and safety of benzodiazepines administration in patients with mitochondrial diseases [21, 22]. Yamadori et al. reported the case of a 10-year old girl with mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS) disease who required open gastrostomy under GA to allow nutrition and improve medication adherence for epileptic seizure control [23]. GA was induced with the administration of a remimazolam bolus (0.2 mg/kg) and subsequently maintained with a continuous infusion of remimazolam (2 mg/kg/h) in combination with remifentanil (0.3 µg/kg/min). The procedure was conducted without complications, and remimazolam was not antagonized by flumazenil, resulting in no delay in patient awakening and no occurrence of respiratory depression.

Remimazolam was used as the sole anesthetic drug also in a 5 year old child with medium-chain acyl-CoA dehydrogenase (MCAD) deficiency undergoing laparoscopic closure of inguinal hernia [24]. GA was performed with a single bolus of 4 mg of remimazolam followed by a continuous infusion (2 mg/kg/h) on top of remifentanil (0.5 µg/kg/min). The perioperative course was uneventful, and again no reversal of remimazolam was deemed necessary. This report highlights that remimazolam may be a valuable option in cases of MCAD deficiency, a disorder impacting mitochondrial fatty acid oxidation, and more broadly in situations where halogenated agents and propofol are relatively contraindicated [15].

Another scenario where remimazolam finds potential application in the pediatric population is during IONM for children at risk of developing perioperative neurological deficits. The heightened risk of neurological injury in pediatric patients during neurosurgical procedures suggests that IONM may exhibit extensive applications in this specific population [25]. However, the utilization of IONM, particularly myogenic motor-evoked potentials (MEPs), necessitates specific halogenated-free anesthetic protocols to minimize interference with alpha-motor neuron excitability [26]. As a result, propofol is frequently selected as the preferred anesthetic agent. Remimazolam proved to be a safe alternative to propofol for GA in a 12 year old girl during supratentorial tumor surgery with MEPs recording [27]. In their investigation, Kamata et al. reported a successful combination of remifentanil (0.5 µg/kg/min) with an escalating titration of remimazolam tailored to the different phases of GA. The induction phase required the administration of 6 mg/kg/h of remimazolam, subsequently reduced to 1.5 mg/kg/h after loss of consciousness was achieved. This was further adjusted to establish a stable anesthetic regimen ensuring consistent recording of MEPs. The remimazolam infusion was maintained at 0.9 mg/kg/h and remifentanil at 0.35 µg/kg/min.

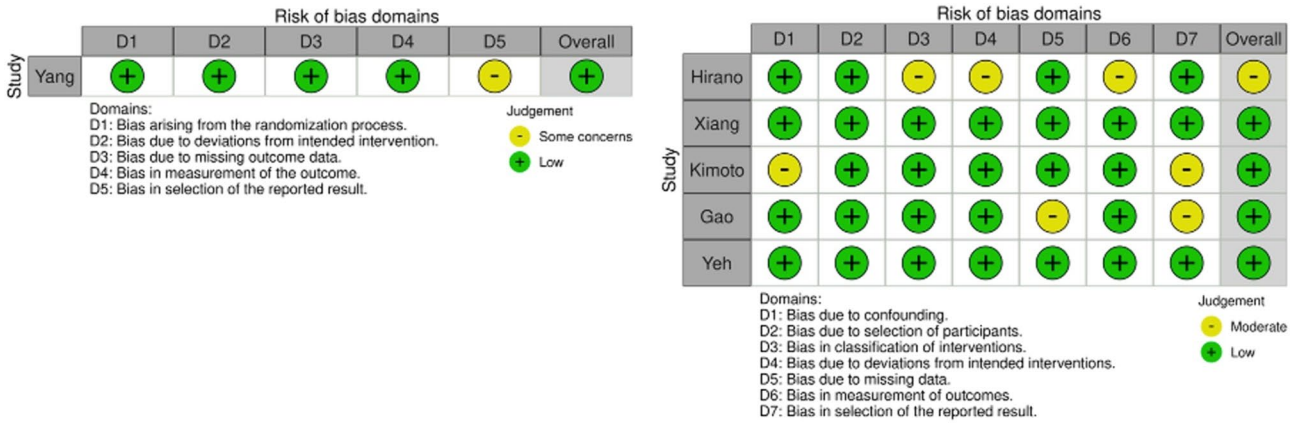

Fig. 2 Risk-of-bias tool for randomized trials (RoB2) evaluation of included randomized trials [36] and Risk Of Bias In Non-randomised Studies—of Interventions (ROBINS-I) evaluation of included observational non – randomised studies [34], [35], [37], [38], [39]

This experience parallels another case involving a 17-year-old patient with Alström syndrome, a rare genetic disorder characterized by obesity, diabetes mellitus, cardiomyopathy and liver dysfunction who underwent spine surgery requiring monitoring of MEPs [28]. The choice of remimazolam over propofol arose from the need to uphold hemodynamic stability in a patient with reduced cardiovascular reserve. Furthermore, remimazolam was chosen as an alternative to midazolam also given the latter's propensity to suppress MEPs [21, 29]. However, additional research is needed to further evaluate whether remimazolam, being a benzodiazepine akin to midazolam, has no effect on MEPs.

Myopathic patients constitute a specific patient sub-group at heightened risk of developing both cardiac and respiratory complications in the perioperative period. Such increased risk results from both muscle weakness and cardiac abnormalities linked to muscular dystrophies and other related disorders [30]. Hence, it is a widely adopted practice to administer total intravenous anesthesia (TIVA), which is considered the safest approach for the majority of patients with myopathies to mitigate the risk of anesthesia-induced rhabdomyolysis. However, administering propofol to individuals with mitochondrial myopathies presents challenges for anesthesiologists due to the potential risk of PRIS. Therefore, avoiding both halogenated agents and propofol opens up the opportunity to use remimazolam in this context as an alternative application. Horikoshi et al. reported the first case of remimazolam use for a single-incision laparoscopic percutaneous extraperitoneal closure under GA in a 4-year-old boy with Duchenne Muscular Dystrophy [31]. They described the use of remimazolam as a 3 mg IV bolus followed by a continuous infusion at a 15 mg/h rate (1 µg/kg/min). Remarkably, the authors reported a conscious recovery within 20 min from the reduction of the remimazolam dose to 5 mg/h in the last 30 min before the end of surgery, without the need for its reversal. This aspect is remarkable, as an extended time for awakening is typically anticipated in such patients.

Ogino et al. reported the case of a 21 months baby with immune-mediated necrotizing muscle disease (IMNM) characterized by proximal weakness and dysphagia in whom GA was induced with remimazolam (10 mg/kg/min), fentanyl (3 µg/kg) and rocuronium (0.6 mg/kg) and maintained with a continuous infusion of remimazolam (1–2 mg/kg/min) and no reversal at the end of surgery [32]. Undeniably, the well-established association between malignant hyperthermia and myopathies discourages GA with volatile anesthetics in these patients. Petkus et al. presented an anecdotal experience involving a 6-year-old girl with a family history of malignant hyperthermia, who underwent dental rehabilitation under total TIVA with remimazolam [33].

Remimazolam as an adjunct to general anesthesia in the pediatric population

Remimazolam widely proved to be more commonly employed as an adjuvant to GA rather than as the sole hypnotic agent. In a study conducted by Kimoto et al. which involved 418 children with a mean age of 4.5 years undergoing surgery under GA, the authors reported their experience using remimazolam upon GA induction with a dose of 12 mg/kg/h, followed by a subsequent infusion of 1–2 mg/kg/h and intermittent boluses (0.2 mg/kg) in accordance with an internal protocol [34]. They reported a median awakening time of 31 min (ranging from 12 to 108 min) from the last dose of remimazolam, with a mean post-anesthesia care unit (PACU) stay time of 13 min. Notably, 75% of the patients experienced a hemodynamic change in mean arterial pressure (either the lowest or highest) from baseline, yet rarely hypotension which required treatment with vasopressors.

To the best of our knowledge, Gao et al. were the first group to investigate the pharmacokinetics of remimazolam

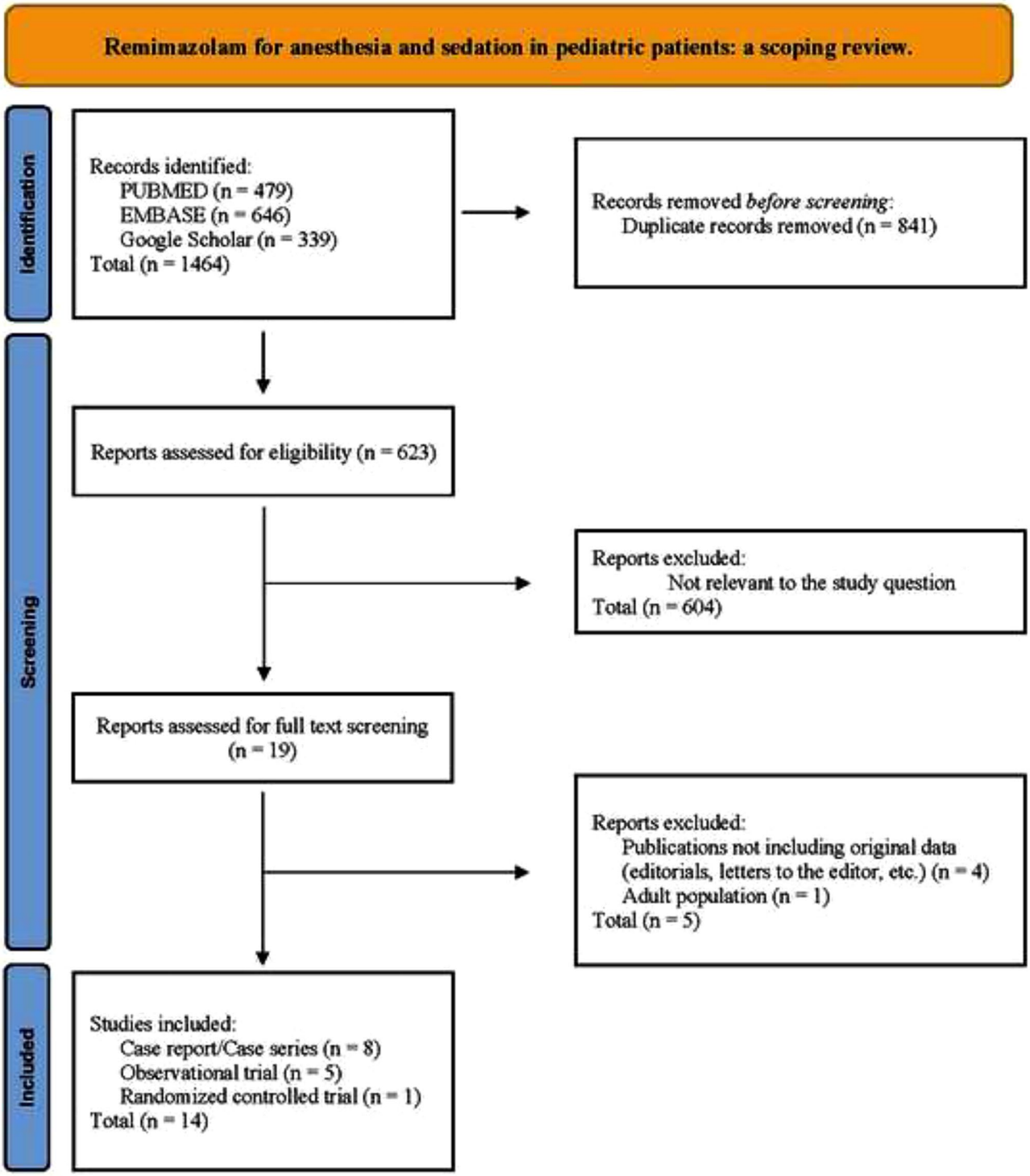

Fig. 3 Flowchart of the studies selection and identification process

after IV infusion over 1 h (5 mg/kg/h for 5 min, followed by 1.5 mg/kg/h for 55 min) in 24 children (aged 2–6 years) undergoing GA with sevoflurane [35]. Upon evaluation of the plasmatic concentrations of remimazolam and its metabolite CNS7054, they found that remimazolam follows a three-compartment model and CNS7054 exhibits a two-compartment model in which the two are connected by a transit compartment. Remimazolam showed a high clearance (median 15.9, 25%, 75% percentile: 12.9, 18.2 mg/kg/min), a small central volume of distribution (median 0.11.

25%,75% percentile: 0.08, 0.14 L.kg^{-1}) and a short terminal half-life (median 67, 25% and 75% percentile 49, 85 min). The context-sensitive half-time after a 4 h infusion was 17 (25%, 75% percentile 12, 21) minutes. On the contrary, the metabolite CNS7054 showed a low clearance of 0.89 (0.33, 1.40) mg/kg/min, a small central volume of distribution of 0.011 (0.005, 0.016) L/kg, and a long terminal half-life of 321 (230, 770) minutes.

Remimazolam for the attenuation of preoperative anxiety or the prevention of emergence delirium following general anesthesia

Given the aforementioned pharmacokinetic and pharmacodynamic characteristics, remimazolam has been administered to mitigate the risk of delirium following GA in children. Yang et al. performed a single-center randomized controlled study on 104 patients aged 3–7 years scheduled for tonsillectomy and adenoidectomy under GA with sevoflurane who were randomly assigned to receive either remimazolam (0.2 mg.kg^{-1} in the intervention group, $n=52$) or placebo (control group, $n=52$) at the end of the procedure [36]. They found a 32% decrease of emergence delirium, defined as a Pediatric Anesthesia Emergence Delirium (PAED) score ≥ 10 in the remimazolam group compared with the placebo ($p<0.001$) [7]. Similarly, the peak PAED scores were lower in the remimazolam group than in the saline group (7 [6–8] vs 9 [8–11], $p<0.001$) and parental satisfaction was improved in the remimazolam group compared with the saline group (9 [8–10] vs 8 [7, 8], $p<0.001$).

Beyond delirium, remimazolam appears effective in mitigating preoperative anxiety as well, as shown by Xiang et al. in a study involving 114 children (early childhood and pre-school age) undergoing laparoscopic high-level inguinal hernia ligation [37]. The study elucidated that the 95% effective dose of a single intranasal infusion of remimazolam to be effective for alleviating preoperative anxiety (defined as modified Yale Preoperative Anxiety Scale, mYPAS < 30) was 1.57 mg/kg (95% confidence interval [CI] 1.45–1.59 mg/kg) in early childhood children and 1.09 mg/kg (95% CI 0.99–1.11 mg/kg) in pre-school children.

Remimazolam as the main agent for procedural sedation

Hirano et al. recently assessed the safety profile of remimazolam at adult protocol dosages when administered for procedural sedation in children [38]. In a cohort of 48 children (mean age 7 years) undergoing diagnostics imaging (e.g., computed tomography or magnetic resonance, radiotherapy, or angiography) the authors observed that remimazolam alone was inadequate to achieve optimal sedation and consequently 95% of patients received other sedatives or analgesics agents (e.g., ketamine, propofol, or fentanyl). The study revealed significant hemodynamic variability, with 88.4% of patients undergoing a ≥ 20% change (increase or decrease) and 62.8% experiencing a ≥ 30% change in mean arterial pressure. Furthermore, a ≥ 20% change in heart rate occurred in 54.3% of patients, with a ≥ 30% change observed in 34.8% of patients.

Similarly, Yeh et al. reported in a case series of 7 patients that remimazolam was satisfactory for achieving an adequate sedation plan during relatively low complexity procedures [39]. Noteworthy, while this case series comprised 7 patients, only 2 were pediatric ones. The first case involved a 14-year-old obese patient undergoing pericardial drainage for recurrent idiopathic pericardial effusion, while the second case involved a 16-year-old boy undergoing Halo removal. Despite both receiving a 5 mg bolus dose of remimazolam, the former received a 30 µg/kg/min continuous infusion for maintenance, which was then titrated down to 10–15 µg/kg/min based on the bispectral index. In contrast, the latter received 3 boluses of 2.5 mg of remimazolam. Both children also received concurrent low-dose fentanyl for analgesia. The procedures lasted less than 30 min in both patients, and no adverse events were recorded, except for a single desaturation episode (peripheral oxygen saturation: 89%) which was promptly managed with increased oxygen supplementation via nasal cannula.

Remimazolam for procedural sedation appears to be potentially integrated into protocols for high-risk clinical scenarios as well. Hughes et al. reported a successful approach encompassing a continuous infusion of remimazolam (15 µg/kg/min) and remifentanil (0.05 µg/kg/min to 0.1 µg/kg/min). This regimen, which was initiated after airway topicalization with nebulized 4% lidocaine and premedication with 2 mg of midazolam, facilitated a successful awake fiberoptic intubation in a 12-year-old patient with an anticipated difficult airway due to burn scars [40].

Discussion

Key findings

This is the first systematically structured scoping review presenting a comprehensive overview of the current clinical landscape surrounding the use of the novel ultra-short-acting benzodiazepine remimazolam in pediatric patients. All studies included in this review were published within the last three years (2021–2023), offering up-to-date insights for contemporary anesthetic and clinical practices. The collective evidence suggests that remimazolam holds promise as a safe and effective option in pediatric settings, whether administered as a standalone drug or in combination with other hypnotics or analgesics, and whether given through

boluses or continuous infusion. Furthermore, while displaying some heterogeneity and being relatively limited due to the novelty of the drug, it also described several successful applications of remimazolam for both sedation and GA. For GA, remimazolam was more often used in combination with other hypnotic drugs, mostly propofol and volatile anesthetics, rather than as the sole agent, and in a single RCT it was reported to be able to mitigate the risk of postoperative delirium [7]. Similar to other benzodiazepines, remimazolam exhibited anxiolytic properties, with dosages adjusted on the age of the pediatric patients [37].

Relationship with previous literature

The present work encompasses all available evidence on the use of remimazolam in children, thus limiting direct comparisons with existing literature to adult studies only mainly due to the recent introduction of remimazolam into clinical practice. The reviewed trials highlighted remimazolam's efficacy in providing sedation while maintaining spontaneous ventilation in various clinical scenarios, ranging from gastrointestinal endoscopy to airway procedures like bronchoscopy [41, 42]. Compared to propofol, remimazolam exhibited a more favorable pharmacokinetic and pharmacodynamic profile, with a lower incidence of respiratory depression and overall adverse events [43, 44]. In bronchoscopy sedation, remimazolam demonstrated equivalent efficacy to a dexmedetomidine–remifentanil combination, boasting a faster onset and recovery time and a lower incidence of hemodynamic effects [45].

GA with remimazolam has shown promise in various clinical settings, with notable evidence accumulating in adult patients undergoing cardiac surgery, a high-risk population with reduced cardiovascular reserve prone to perioperative complications [10, 41, 46]. Despite the likelihood that the observed favorable hemodynamic stability could be credited to the anesthetic protocol as a whole rather than solely to remimazolam, its unique pharmacokinetic profile has positioned it as a potential aid in high-risk or unstable patients, although evidence in this context remains limited [47].

Furthermore, delayed awakening and respiratory depression, that are commonly observed when other benzodiazepines are administered (e.g., midazolam) and not promptly reversed, may be overcome with the administration of remimazolam in light of its rapid metabolism by plasmatic esterases. While flumazenil is the available antagonist for reversing benzodiazepines, it may still potentially increase the risk of epileptic seizures, particularly in pediatric patients, who exhibit a lower physiological threshold for seizures compared to the adult population. Given these considerations, remimazolam emerges as safe and promising anesthetic option for also for children with MELAS and epilepsy.

It's also crucial to acknowledge that existing literature lacked exploration of the impact of altered organ metabolism and interaction with concomitant treatments in clinical practice.

Implications for clinical practice and future research

This scoping review provides contemporary patient data that could significantly inform daily practices in modern anesthesia and clinical care. Our findings indicate that remimazolam can be regarded as a safe pharmacological option, with no safety concerns identified in any of the included studies. It emerges as an attractive alternative within the broader benzodiazepine family, particularly in peculiar scenarios, given its ease of handling due to its ultra-short acting pharmacokinetic profile. In comparison to midazolam, which constitutes the most commonly used benzodiazepine in the pediatric population, remimazolam's rapid offset counter-balances the need for flumazenil reversal. This is particularly significant, as the routine use of flumazenil should be avoided due to its associated risk of triggering cardiac arrhythmias and epileptic seizures [48]. Remimazolam can be employed either as an adjunct to GA or as the primary hypnotic agent for GA, although evidence supporting the latter application is still limited. Indeed, it may find a specific niche in the context of GA for pediatric patients with specific genetic comorbidities, (i.e., mitochondrial diseases, myopathies, and at risk of malignant hyperthermia), where other anesthetic drugs are contraindicated.

In such scenarios, indeed, anesthetic regimens involving propofol or volatile anesthetics are deemed unsuitable due to their potential to trigger propofol infusion syndrome (PRIS) and malignant hyperthermia related to inhaled anesthetics, respectively [13, 19, 20]. The anxiolytic properties of remimazolam may also have further clinical applications in alleviating preoperative anxiety in children. Moreover, preliminary evidence indicating the potential of remimazolam in reducing postoperative delirium is promising, though further validation is needed.

Conversely, there remain numerous unm needs in the use of remimazolam in pediatric populations. First, there is a lack of consensus regarding the optimal doses of remimazolam for various clinical situations. Similarly, specific regimens for remimazolam administration (i.e., target-controlled infusion, TCI) are lacking. While the dosage protocols adopted in the studies included in the present review were mostly extrapolated from the adult setting, pediatric patients exhibit several peculiarities that complicate direct extrapolation. In addition, whether remimazolam is administered as a bolus or continuous infusion, the hemodynamic and respiratory effects of both approaches concerning different anesthesia types should be more thoroughly elucidated. Second, no direct comparisons were made between

remimazolam and other currently used short-acting benzodiazepines (e.g., midazolam). The evidence suggesting the superiority of remimazolam over placebo is insufficient to advocate for its use when other short-acting drugs of the same class are already successfully employed in clinical practice. Drug metabolism, influenced by factors such as ethnicity, genetics, and the environment, may also play a crucial role in the widespread adoption of novel drugs in anesthetic practice. Hence, large, multi-center prospective studies are still required to better evaluate the impact of remimazolam on preventing postoperative delirium and agitation in the pediatric population.

Strengths and limitations

The strengths of this study include a comprehensive literature search, alignment with prior research reports into the pharmacokinetic and pharmacodynamic profiles of remimazolam, demonstrating their superiority when compared to those of other commonly used anesthetic agents in routine practice (e.g., volatile anesthetics and propofol). Nevertheless, this study presents some limitations.

First, the geographic origin of the studies and, consequently, patient data is limited. With 95% of the studies originating from Asian regions, data generalization becomes less reliable. In addition and as previously emphasized, methodological concerns exist within the studies included in our investigation, given that the majority of evidence available to date originated from observational studies with limited sample size and case reports. In addition, considering the pharmacological nature of the intervention under investigation in this scoping review, an additional search was conducted on the EMBASE database to ensure inclusivity of potentially pertinent studies published in non-strictly medical journals (i.e., pharmaceutical journals). However, as this was done post-hoc rather than as part of the initial research plan, it led to a disparity between the databases searched for mentioned in the present scoping review and the pre-planned ones outlined in the original research protocol. Despite these limitations, the data reported in the present review encompass the entire, albeit unique, experience currently available on remimazolam in daily pediatric anesthesiology practice.

Second, the clinical scenarios for remimazolam use varied widely among the studies retrieved for inclusion. Such heterogeneity resulted in the adoption of a systematically structured scoping review instead of a meta-analysis.

Moreover, a comparative analysis between remimazolam and other short-acting benzodiazepines (e.g., midazolam) is lacking. This information is crucial to fully elucidate the role, viability and superiority of remimazolam in the context of pediatric anesthesia.

Finally, since the majority of the included studies were case reports or observational, they may be influenced by unmeasured confounders or selection bias. Consequently, all of our findings should be considered as hypothesis-generating only.

Conclusions

Remimazolam exhibits promising potential for application in pediatric anesthesiology. Its favorable pharmacokinetic and pharmacodynamic characteristics, coupled with the prompt availability of its antagonist (i.e., flumazenil), render it a potentially safe and versatile option for use as the primary agent or adjunct during GA induction and/or maintenance, even in patients in whom routinely used anesthetic agents are contraindicated. Nevertheless, several gaps in our understanding of this novel anesthetic agent still persist (e.g., optimal dosages for diverse clinical situations, conclusive evidence of superiority compared to other short-acting benzodiazepines, the impact of genetic, environmental factors, and ethnicity on drug metabolism in patients) which warrant further investigation in future research, aiming to enhance a better integration of remimazolam into routine clinical practice.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00540-024-03358-w.

Acknowledgements The authors would like to thank Kate Gralton for English language editing.

Collaborators: Ludovica Giannetti, Stefano Lazzari, Carolina Faustini, Niki Kaufman-Donetskii, Viviana Teresa Agosta, Chiara Cimmino, Emanuele Ghirardi

Authors' contribution **Marina Pieri:** investigation, methodology, data curation and writing—review and editing. **Jacopo D'Andria Ursoleo:** conceptualization, study design, investigation, methodology and writing—original draft. **Ambra Licia Di Prima:** investigation, methodology, writing—original draft. **Samuele Bugo:** methodology, writing—original draft. **Gaia Barucco:** supervision, data curation and writing—review and editing. **Margherita Licheri:** supervision, data curation and writing—review and editing. **Rosario Losiggio:** investigation, writing—original draft. **Giovanna Frau:** supervision and writing—original draft. **Fabrizio Monaco:** supervision, data curation and writing—review and editing.

Funding This manuscript did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability Further information is available from the corresponding authors upon reasonable request.

Declarations

Conflict of interest The authors declare that they have no competing interests.

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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