Pediatric sedation using dexmedetomidine and remimazolam for magnetic resonance imaging

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The use of magnetic resonance imaging (MRI) in the pediatric population is expanding. Children usually need general anesthesia or sedation to be still for adequate MRI images. While dexmedetomidine has potential benefit for pediatric MRI sedation because of preservation of airway tone, there is not currently consensus for its use for pediatric MRI sedation. In this issue of Journal of Anesthesia, Kim et al. conducted a systematic review and meta-analysis of randomized controlled trials [1], in which they assessed the efficacy and safety of dexmedetomidine sedation for pediatric MRI compared to propofol, ketamine, and midazolam. The authors showed that compared to propofol, ketamine, and midazolam, dexmedetomidine sedation for pediatric MRI resulted in delayed sedation onset [Weighted mean differences (WMD)=8.13 min, 95% CI=4.64–11.63] and recovery times (WMD=5.22 min, 95% CI=0.35–10.09) and decreased heart rate (WMD=−17.34 beats per minute, 95% CI=−22.42 to −12.26). Of note, dexmedetomidine sedation was associated with a lower incidence of desaturation events (RR=0.42, 95% CI=0.20–0.86). There was no difference in sedation quality or incidence of sedation failure. They concluded that dexmedetomidine has the same sedation quality as other drugs but fewer respiratory events.

Meanwhile, delayed sedation onset and recovery times are limitations of dexmedetomidine use for pediatric MRI sedation, but may represent a cautious administration regimen, consistent with the manufacturer's product insert. Since the use of dexmedetomidine for pediatric sedation was officially approved only in pediatric intensive care unit settings thus far [2], there is a multi-country ongoing trial of dexmedetomidine sedation for pediatric MRI in Japan, Canada, and the United States [3].

Procedural sedation is increasingly common in pediatrics [4]. The potential impact of sedative drugs on the pediatric population is important to understand due to developmental concerns [5]. The selection of proper drugs is essential when providing pediatric sedation and ideal features are: rapid predictable onset, short context-sensitive half-time, dose-dependent effect, rapid offset, maintenance of airway tone, spontaneous ventilation and hemodynamic status, no injection pain, and the existence of a reversal. Historically, midazolam and chloral hydrate were popular sedative drugs for pediatric sedation, though recently there is an increasing trend in the use of propofol and dexmedetomidine [4]. There are two existing meta-analyses which compared dexmedetomidine and propofol for pediatric MRI sedation [6, 7]. One study concluded that propofol should be encouraged for pediatric MRI given its better sedative effects and low incidence of emergence delirium [6] while the other study confirmed that dexmedetomidine had a prolonged recovery time [7]. There has been no sedative drug that has all the ideal features for pediatric MRI sedation until recently.

Remimazolam is a brand-new general anesthetic, which is an ultra-short-acting benzodiazepine metabolized by tissue esterases to an inactive compound. Remimazolam has a small steady-state volume of distribution with a short elimination half-life. Researchers strategically designed this novel drug to be metabolized by esterases to provide a preferable sedative profiles [8]. In the United States, European Union,

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Table 1 Ongoing clinical trials of remimazolam in pediatric anesthesia as of May 9th, 2021

Trial name and number	Enrollment	Country	Purpose of trial	Design	Intervention arm	Control arm	Primary outcome	Recruitment status
Intranasal Remimazolam for Premedication in Pediatric Patients: a Double-blinded Randomized Clinical Trial: NCT04720963 [24]	40	China	To investigate whether intranasal remimazolam can reduce anxiety in children before surgery	RCT	Remimazolam	Dexmedetomidine Placebo	The level of anxiety	Recruiting Phase 4
Remimazolam Reduces Emergence Delirium in Preschool Children Undergoing Laparoscopic Surgery by Sevoflurane Anesthesia: a Double-blinded Randomized Clinical Trial: NCT04621305 [25]	120	China	To investigate whether remimazolam can reduce incidence of emergence delirium	RCT	Bolus group Continuous infusion group	Placebo group	The incidence of emergence delirium	Recruiting Phase 4
A Phase 2/3, Prospective, Open-label Trial Evaluating the Efficacy, Safety, and Pharmacokinetics of Remimazolam for Intravenous Sedation in Paediatric Patients Undergoing Diagnostic and/or Therapeutic Procedures: NCT04851717 [26]	100	US Europe	To assess the efficacy of intravenous remimazolam in inducing and maintaining suitable sedation levels for pediatric patients undergoing diagnostic and/or therapeutic procedures	Clinical trial	Remimazolam	Single group	Success of the procedure	Not yet recruiting Phase 2 Phase 3
Effect of Remimazolam Use During Perioperative Period on Postoperative Recovery Indicators: NCT04601350 [27]	60	China	To study the euphoria effect caused by remimazolam during induction of general anesthesia and the postoperative recovery indicators, to further understand the clinical application of remimazolam	RCT	Remimazolam with a dose of 0.05,0.1,0.2,0.3 mg/kg	Remimazolam with a dose of 0.05,0.1,0.2,0.3 mg/kg	Changes in the level of SBP /DBP (MAP) etc	Recruiting Phase NA

DBP diastolic blood pressure, MAP mean arterial pressure, NA not applicable, RCT randomized controlled trial, SBP systolic blood pressure

and China, remimazolam was initially approved for procedural sedation in adults [9–11]. The typical adult dose of remimazolam for procedural sedation is 5 mg via intravenous injection over 1 min and then 2.5 mg via intravenous injection over 15 s as a rescue dose [12, 13]. In Japan and South Korea, remimazolam was approved for general anesthesia in adults [11, 14–16]. The dose of remimazolam recommended for anesthesia induction is at an infusion rate of 12 mg/kg/hour, which is adjustable based on the patient's age and clinical background, and that for the maintenance phase is 1 mg/kg/hour, which is also adjustable to a maximum rate of 2 mg/kg/hour depending on clinical parameters (e.g., heart rate and blood pressure) [17]. Monitoring the electroencephalographic (EEG) index is desirable due to possible interpersonal variability; however, there are no reliable data available for appropriate ranges of EEG index at this point.

Remimazolam does not produce injection site pain which is common in propofol use (18.7% of cases) [17]. The incidence of intraoperative hypotension events is lower with remimazolam (22%) compared with propofol (49.3%) [17]. There is no need for unplanned mechanical ventilation during procedural sedation with using remimazolam [18]. With respect to recovery, the mean time from the end of the procedure to full alertness using remimazolam is shorter [6.0 min (95% CI 5.2–7.1)] compared to midazolam [12 min (95%CI 5.0–15)] [13]. However, the mean time to extubation after discontinuing remimazolam infusion [19.2 min (Standard deviation; SD 10.8)] is longer than after discontinuing propofol [13.1 min (SD 6.5)] [17]. This finding may be a result of less clinical experience with remimazolam and may be overcome using flumazenil, which reverses remimazolam effects. Note there is no recommendation for the dose of flumazenil for remimazolam reversal [19] and it remains unknown whether reversal of remimazolam by flumazenil may or may not cause re-sedation later [19, 20]. The use of flumazenil is not inconsequential or without side effects, so routine reversal of benzodiazepine effects cannot be recommended at this stage. Therefore, future trials are warranted to investigate the efficacy and safety of flumazenil use as a reversal of remimazolam in pediatric sedation.

All evidence cited to this point is from studies in adults. We conducted a comprehensive literature search in MEDLINE, EMASE, and International Pharmaceutical Abstracts (April 21, 2021), containing sets of terms reflecting the medication (remimazolam) without language restriction, which yielded 150 abstracts (Supplementary online resource 1). Of the 150 abstracts, none was in the pediatric population. We further searched ongoing pediatric trials of remimazolam at ClinicalTrials.gov (May 9, 2021) and found 4 ongoing clinical trials of remimazolam in pediatric anesthesia [21], including sedation (summary in Table 1). Three trials are in

China, and one in the U.S. and Europe and is the only trial of pediatric sedation for diagnostic/therapeutic procedures.

Limitations of propofol sedation include injection site pain and respiratory and hemodynamic depression without a reversal agent. Conversely, remimazolam has a reversal agent and no injection site pain, so could be considered as the primary sedative medication for pediatric MRI in the future. Dexmedetomidine is also an option for pediatric MRI, especially for children with obstructive sleep apnea undergoing cine MRI and children requiring magnetoencephalography [22, 23]. Future trials are warranted to investigate the safety and efficacy of remimazolam compared to propofol for pediatric MRI, and to also understand essential perioperative outcomes in children such as emergence delirium, postoperative nausea and vomiting, and respiratory events.

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Declarations

Conflict of interest TE and YS are engaged in an industry trial by Pfizer described in the main text [3], which did not affect this publication. Hence, all authors declare that they have no competing interests related to this publication.

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