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Masterthesis / Review

Total intravenous anesthesia for the pediatric patient: a narrative review

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Abstract

Objective: **To undertake a database and registry search of scientific literature of the past ten years (2014-2024) and review findings in the format of a narrative review.**
Methods: **A literature search was carried out using the following databases and registries: NIHM Pubmed, The Cochrane Library, Wiley Online Library. Searches were performed using the following search terms in title and abstract: (anesthesia, intravenous) AND (anesthesia, pediatric) AND ((total intravenous anesthesia) OR (target controlled infusion)). Results were then filtered to show records published between the years 2014 and 2024. Inclusion criteria were: research on TIVA or comparing TIVA to IHA; a pediatric study population; systematic review, meta-analysis or randomized controlled trial. 34 studies of the last ten years pertaining to TIVA practice in pediatric anesthesiology were retained. Based on these articles a narrative review was conducted.**
Summary: **Total Intravenous Anesthesia (TIVA) has been proven safe and its use by anesthesiologists in the pediatric population is rising. In this review, established evidence, known advantages and disadvantages of TIVA in the pediatric population are first summarized. Recent findings in different topics pertaining to TIVA are then explored: facilitating intravenous induction in the pediatric patient by (non)pharmacological means; anesthetic drug development, its hurdles in pediatric practice; pharmacokinetic/pharmacodynamic modeling; developmental neurology; electroencephalographic guided anesthesia practice; emergence delirium; TIVA use in different clinical contexts; environmental and economic impact of TIVA; immune response to surgery and anesthesia and finally a short foray into genetics brings us to a tie-in of this broad subject, along with some concrete avenues for future research.**
The manuscript aims to give an overview of up-to-date information in order to provide inspiration and a springboard for research into the coming years.

Keywords: **Anesthesia, Intravenous, Pediatric Anesthesia, Review.**

Introduction

Total intravenous anesthesia (TIVA) is a technique for induction and maintenance of general anesthesia using solely intravenous (IV) anesthetic agents. Though intravenous administration of drugs with anesthetic effect in animals was described as early as 1656[1], modern anesthesia practice in humans developed initially using inhaled agents[2]. With development of technologies and pharmaceutical compounds - and especially with the introduction of propofol in the 1980's[3] - over the last couple of decades the use of TIVA has increased. As a technique it is already well-known and utilized in both adult and pediatric populations[4,5]. Proponents for either technique (general anesthesia using inhalational anesthesia (IHA) versus TIVA) exist[6]. However each technique has its advantages and disadvantages, with - as of yet - no clear superiority for either when it comes to safety or long term outcomes[7]. It appears that for now choice of modality is dependent on experience of the practicing anesthetist, surgical and patient factors (e.g. shared airway or malignant hyperthermia), economic, geographical and environmental factors[6,8-11]. There are several arguments as to why TIVA may have a favorable profile in the pediatric population[12]. Innovation in areas such as pharmacokinetic/pharmacodynamic (PK/PD) modeling, developmental neurology, novel drugs, as well as regard for topics such as plastic waste and environmental pollution drive changes in medical practice[13-16].

In this review, the author aims to summarize new evidence of the last ten years with respect to TIVA technique in the pediatric population, focusing on meta-analysis, systematic review, randomized trials (RCT).

Methods

This narrative review was not eligible for registry in a review database. The recommendations and checklist of the PRISMA statement (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) were used as a guideline to conduct this review[17].

A literature search was carried out using the following databases and registries: NIHM Pubmed, The Cochrane Library and Wiley Online Library. Searches were performed using the following search terms in title and abstract: (anesthesia, intravenous) AND (anesthesia, pediatric) AND ((total intravenous anesthesia) OR (target controlled infusion)). Results were then filtered to show records published between the years 2014 and 2024. Searches were performed in January of 2024. 631 studies were identified following the initial literature search. Following screening, retrieval of reports and report assessment, 34 studies were retained as eligible for inclusion. Inclusion criteria were: research on TIVA or comparing TIVA to IHA; a pediatric study population; systematic review, meta-analysis or randomized controlled trial (see Figure I - PRISMA flow diagram; see Table I - List of included studies.) A narrative review was undertaken on the subject matter of TIVA advances and practice in pediatric anesthesia based on these 34 articles. In order to maximize

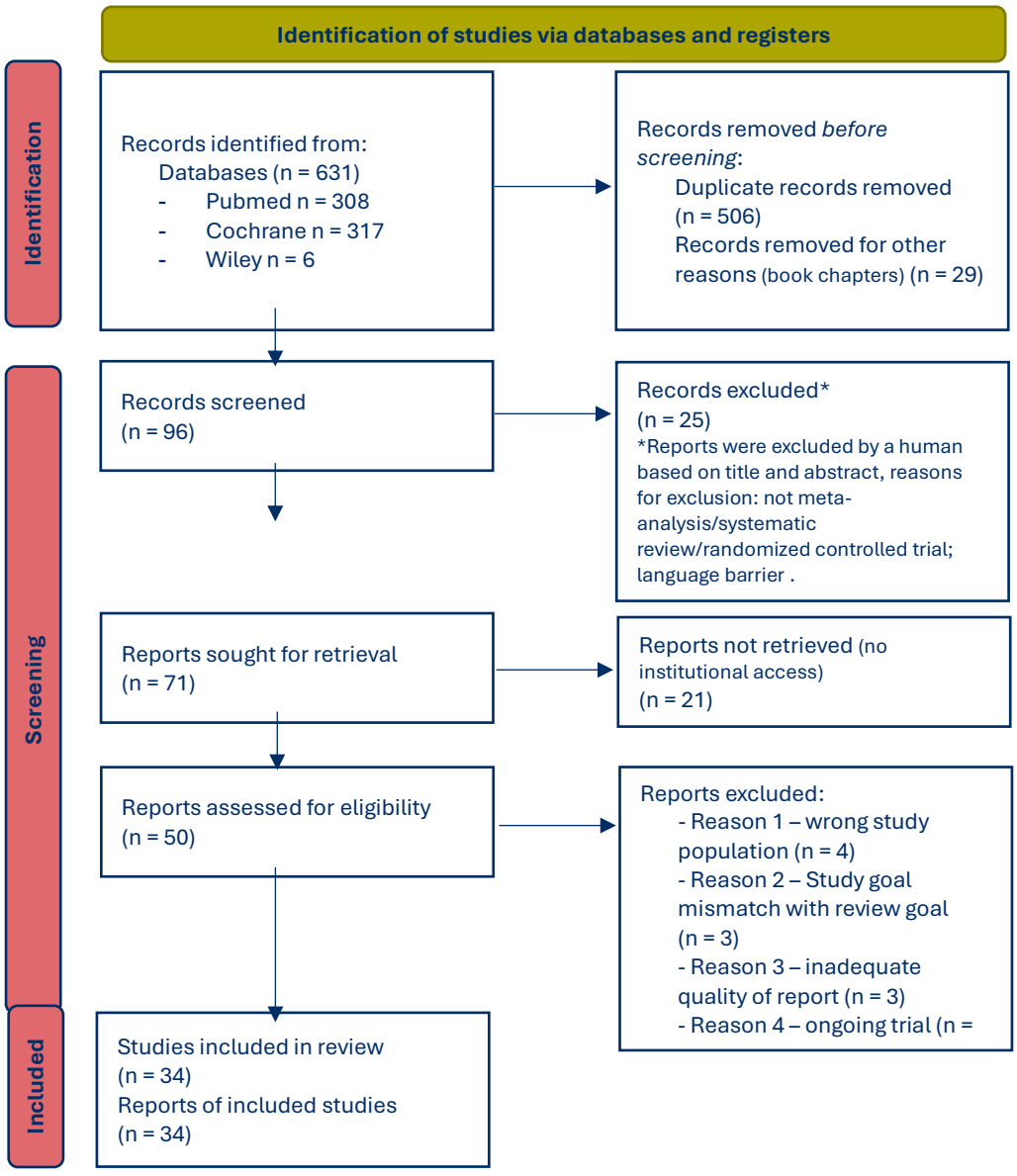

Fig. 1 — PRISMA flow diagram.
Adapted from: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71 10.

Table I. — List of included studies after initial literature search.

	Author, year of publication	Title	Study Design	Study setting and Study Population	Key Findings
1	Xess et al. (2024) [1]	"Effect of CoolSense and EMLA Cream on Pain During Intravenous Cannulation in Pediatric Population: A Randomized, Controlled Trial"	Randomized Controlled Trial, Double-Blinded Level 2 evidence	140 ASA I and II children of 6-12 years old. Divided into two groups of 70.	"There was a significant reduction in pain scores during intravenous cannulation in the CoolSense group compared to the EMLA cream group (mean pain score 7.14±4.322 versus 29.32±8.95, p value 0.001). Comparison of pre- and postprocedural anxiety levels showed a decrease in the anxiety level in the CoolSense group (p value=0.003)"
2	Jones Oguh et al. (2024) [2]	"Implementation of an electroencephalogram-guided propofol anesthesia practice in a large academic pediatric hospital: A quality improvement project"	Reporting on a Quality Improvement Project Level 6 evidence	Quality improvement project in a large academic pediatric anesthesia practice	"After four Plan-Do-Study-Act cycles, electroencephalogram-guided total intravenous anesthesia increased from 5% to 75% and was sustained at 72% 9 months after project completion. Total intravenous anesthesia cases/month and number of perioperative emergency activations did not change significantly from start to end of the project, while emergence time for electroencephalogram-guided total intravenous anesthesia was greater statistically but not clinically (total intravenous anesthesia without electroencephalogram [16±10 min], total intravenous anesthesia with electroencephalogram [18±9 min], sevoflurane [17±9 min] p<.001)"
3	Abdelaal et al. (2024) [3]	"The effects of dexmedetomidine on intraoperative neurophysiologic monitoring modalities during corrective scoliosis surgery in pediatric patients: A systematic review"	Systematic Review Level 1 evidence	PubMed, Scopus, and Cochrane Library were searched on January 1, 2022 and included randomized controlled trials, observational cohort and case-control studies and case series investigating dexmedetomidine in the population of interest and comparing against a standardized anesthesia regimen without dexmedetomidine or comparing multiple doses of dexmedetomidine.	"Given the limitations of the studies available in the literature, it would be advisable to conduct rigorous randomized controlled trials with larger sample sizes to assess the effects of dexmedetomidine use of in scoliosis surgery in pediatric patients."
4	Quintão et al. (2023) [4]	"Comparison of intravenous and inhalation anesthesia on postoperative behavior changes in children undergoing ambulatory endoscopic procedures: A randomized clinical trial"	Randomized Controlled Trial, Double-Blinded Level 2 evidence	157 children aged 1-12 years who underwent ambulatory endoscopic procedures were enrolled. After a peripheral line was placed, each child was allocated to sevoflurane or propofol maintenance. Emergence delirium was evaluated through the Pediatric Anesthesia Emergence Delirium scale. The child was discharged home, and behavioral changes were assessed through the Posthospitalization Behavior Questionnaire for Ambulatory Surgery on Days 1, 7, and 14.	"Post hoc analyses showed a moderate correlation between emergence delirium and negative postoperative behavior on Day 7 (r = .34; p =<.001) and an increase of 3.31 (95% CI 1.90; 4.36 p < .001) points in the mean summed score of new negative behaviors for individuals with emergence delirium. No statistically significant differences were seen between the propofol and sevoflurane groups."
5	Liew et al. (2023) [5]	"Effects of MDR1 and OPRM1 genetic polymorphisms on the pharmacodynamics of propofol-remifentanil TIVA in pediatrics"	Prospective case-control study Level 3 evidence	A total of 72 pediatric patients undergoing surgery were recruited	"A weak to no association was found between the genetic polymorphisms of MDR1 and OPRM1 and the anesthetic and adverse effects of propofol-remifentanil."

Table I. — List of included studies after initial literature search - 2.

	Author, year of publication	Title	Study Design	Study setting and Study Population	Key Findings
6	Karam et al. (2023) [6]	"Respiratory Adverse Events After LMA® Mask Removal in Children: A Randomized Trial Comparing Propofol to Sevoflurane"	prospective, randomized, double-blind clinical trial Level 2 evidence	Children aged § months to 7 years were enrolled in two different groups: the TIVA group and the sevoflurane group	"Children receiving TIVA with propofol had a significantly lower incidence (10.8.% vs 36.2%; relative risk, 0.29; 95% CI [0.14–0.64]; P = .001) and lower severity (P = .01) of respiratory adverse outcomes compared to the patients receiving inhalational anesthesia with sevoflurane. There were no statistically significant differences in secondary outcomes between the 2 groups, except for emergence agitation that occurred more frequently in patients receiving sevoflurane (P < .001).””
7	Gao et al. (2023) [7]	"Pharmacokinetics of remimazolam after intravenous infusion in anaesthetised children"	Pharmacokinetic modelling trial Level 3 evidence	24 children aged 2-6 years old, ASA status 1-2 undergoing general anesthesia with sevoflurane were enrolled. Remimazolam was administered and plasmaconcentrations of it and its metabolite were measured.	"Pharmacokinetics were best described by a three-compartment model for remimazolam and a two-compartment model for CNS7054 linked by a transit compartment. Remimazolam showed a high clearance of 15.9 (12.9, 18.2) ml kg^{-1} min^{-1} (median, Q_{25}, Q_{75}), a small central volume of distribution of 0.11 (0.08, 0.14) L kg^{-1} and a short terminal half-life of 67 (49, 85) min. The context-sensitive half-time after an infusion of 4 h was 17 (12, 21) min. The metabolite CNS7054 showed a low clearance of 0.89 (0.33, 1.40) ml kg^{-1} min^{-1}, a small central volume of distribution of 0.011 (0.005, 0.016) L kg^{-1}, and a long terminal half-life of 321 (230, 770) min."
8	Chen et al. (2023) [8]	"Application of Bispectral Index System (BIS) Monitor to Ambulatory Pediatric Dental Patients under Intravenous Deep Sedation"	Prospective case-control study Level 3 evidence	A total of 206 cases, aged 2-8 years, receiving dental procedures under deep sedation with propofol using target-controlled infusion (TCI) technique were enrolled in the study	"Although no statistical significance in the post-discharge events and total amount of propofol used was observed, a clear significance was identified in periprocedural adverse events (hypoxia, apnea, and recurrent cough, all p value < 0.05) and discharge time (63.4 ± 23.2 vs. 74.5 ± 24.0 min, p value < 0.001) between these two groups."
9	Yee et al. (2022) [9]	"Genetic polymorphisms of OPRM1 on the efficacy and safety of anesthetic and analgesic agents: a systematic review"	Systematic Review Level 2 evidence	After search, analysis and exclusion; 29 studies were selected for inclusion.	"In association with the efficacy and safety of anesthetic and analgesic agents, gene polymorphism in OPRM1 displayed a strong correlation in reduced analgesic effect and protection against adverse reactions."
10	Nevešćanin Biliškov et al (2022) [10]	"Total Intravenous Anesthesia with Ketofol versus Combination of Ketofol and Lidocaine for Short-Term Anesthesia in Pediatric Patients; Double blind, Randomized Clinical Trial of Effects on Recovery"	Randomized Clinical Trials, Double-Blinded Level 2 evidence	Two hundred children ages 1-12 years who underwent short surgical procedures were randomly allocated into two groups. One group was administered a 'ketofol' (ketamine + propofol) mixture and the other a 'lidoketofol' (lidocaine + ketamine + propofol) mixture for induction and maintenance of anesthesia.	"Extubation time showed to be considerably shorter in the lidoketofol group than in the ketofol group (120 s versus 240 s; p < 0.00001). The anesthesia duration was also significantly shorter in the lidoketofol group (35 min vs. 50 min; p < 0.00001). The lidoketofol group showed to have a lower length of stay in the post-anesthesia care unit (PACU) than the ketofol group (20 min vs. 35 min; p < 0.00001). The lidoketofol group showed lower fentanyl consumption per kg (2.1 µg per kg vs. 2.3 µg per kg; p < 0.056) and lower propofol consumption (6.6 mg per kg vs. 7.6 mg per kg; p < 0.032)."

Table I. — List of included studies after initial literature search - 3.

	Author, year of publication	Title	Study Design	Study setting and Study Population	Key Findings
11	Liu et al (2022) [11]	"Effect of bispectral index-guided total intravenous anesthesia in younger children: A prospective, randomized, controlled trial"	Randomized Controlled Trial, Single-Blinded Level 2 evidence	Patients 1-3 years scheduled for surgery under TIVA were enrolled and randomly assigned to either the BIS group or the 'standard clinical practice' group.	"There was no significant difference in time to extubation 15(10,21) vs 14 (11,20) and duration of stay in PACU 27 (20,37) vs. 29 (22,39) between the group B and group S. At the time points 30 min after the start of the operation, 60 min after the start of operation and immediately after drug withdrawal, the BIS values in group S were significantly higher than those in group B (57 ± 9, 57 ± 9, 60 ± 8 vs 52 ± 7, 54 ± 7, 57 ± 6)."
12	Chen et al. (2022) [12]	"Analysis of anesthetic effect of dexmedetomidine in femoral shaft fracture surgery"	Randomized Controlled Trial Level 3 evidence	52 patients aged 3-7 years undergoing closed reduction and intramedullary fixation of a femoral shaft fracture were divided into an experimental and a control group. The experimental group received propofol bombined with remifentanil and an infusion of dexmedetomidine. The control group received a saline infusion instead of dexmedetomidine. The mean arterial pressure (MAP) and heart rate (HR) were recorded before anesthesia induction (T0), when laryngeal mask was inserted (T1), when skin was cut (T2), when intramedullary needle was inserted (T3), and when laryngeal mask was removed (T4).	"There was no significant difference in MAP and HR between the 2 groups at T0 and T1 time points ($P > .05$). The MAP and HR of the experimental group at T2 to T4 were significantly lower than those of the control group ($P < .05$). The extubation time of the experimental group was longer than that of the control group ($P < .05$), but the Pediatric Anesthesia Emergence Delirium score and the incidence of agitation in the recovery period of the experimental group were lower than those of the control group ($P < .05$)."
13	Relland et al (2021) [13]	"Immune Function following Major Spinal Surgery and General Anesthesia"	Prospective case-control study Level 3 evidence	"Twenty-six adolescents undergoing spinal fusion were randomized to receive TIVA with propofol-remifentanil or a volatile agent-based technique with desflurane-remifentanil. Immune function measures were based on the antigen-presenting and cytokine production capacity, and relative proportions of cell populations."	"Anesthetic choice does not appear to differentially impact immune function, but exposure to anesthetics and surgical trauma results in reproducibly measurable suppression of both innate and adaptive immunity in adolescents undergoing posterior spinal fusion. The magnitude of this suppression was modest when compared with pediatric and adult patients with critical illnesses."
14	Petre et al. (2021) [14]	"Dexmedetomidine vs. total intravenous anaesthesia in paediatric emergence delirium: A network meta-analysis"	Systematic Review and Meta-Analysis Level 1 evidence	"The systematic review returned 66 eligible studies comprising 5257 patients."	"crude median emergence delirium incidences of 12.8, 9.1 and 40% in the dexmedetomidine with sevoflurane, TIVA and sevoflurane alone groups, respectively. NMA indicated that compared with TIVA, sevoflurane with adjuvant dexmedetomidine decreased the incidence of emergence delirium without statistical difference (risk ratio 0.88, 95% CrI 0.61 to 1.20, low quality of evidence), but resulted in a higher incidence of PONV (risk ratio: 2.3, 95% CrI 1.1 to 5.6, low quality of evidence)."
15	Grabowski et al. (2021) [15]	"The effects of early anesthesia on neurodevelopment: A systematic review"	Systematic review and meta-analysis Level 1 evidence	"In total, 493 titles were initially identified, with 56 articles selected for full analysis and 44 included for review."	"There is no conclusive evidence that a single short anesthetic in infancy has a detectable neurodevelopmental effect. Data do not support waiting until later in childhood to perform general anesthesia for single short procedures."

Table I. — List of included studies after initial literature search - 4.

	Author, year of publication	Title	Study Design	Study setting and Study Population	Key Findings
16	West et al. (2020) [16]	"Reducing preoperative anxiety with Child Life preparation prior to intravenous induction of anesthesia: A randomized controlled trial"	Randomized Controlled Trial Level 2 evidence	Children aged 3-10 years, with no known preexisting anxiety and no preoperative anxiolytics, undergoing elective day surgery lasting ≤ 2 hours, were enrolled. The child was randomly assigned to intervention (minimum 15 minutes Child Life preparation) or control (standard practice without Child Life preparation).	"Operating room anxiety was higher than baseline in 16/31 (52%) children in the control group and 6/28 (21%) in the Child Life preparation group. ANCOVA revealed a significant effect of baseline mYPAS-SF anxiety and group on operating room anxiety ($F = 10.31$, $P < .001$, adjusted $R(2) = .24$); individual parameter estimates indicated that Child Life preparation reduced operating room anxiety by 13.8 (95% CI 4.4-23.1) points compared to control, $P = .005$."
17	Weng et al. (2020) [17]	"Comparison of Cardioprotective Effects of Propofol versus Sevoflurane in Pediatric Living Donor Liver Transplantation"	Randomized Controlled Trial Level 3 evidence	120 children who underwent living donor liver transplantation were randomly and equally divided into a sevoflurane group and a propofol group.	"There was no statistically significant difference in the characteristics of children in the 2 groups. Compared with T0, the levels of IL-6 and TNF-alpha at T1, T2, and T3 were higher, while the HMGB1 at T2 and T3 were higher ($P<0.05$). A similar trend for IL-6, TNF-alpha, and HMGB1 at different time points in the 2 groups was observed. Compared with T0, the cTnI and CK-MB at T2 and T3 were significantly higher ($P<0.05$), but there was no significant difference at different time points in the 2 groups. For the adverse events, there was no significant difference between the 2 groups."
18	Sheikhzade et al. (2020) [18]	"A Comparison of the Sevoflurane and Total Intravenous Anesthesia on the Quality of Recovery in 2 to 10-Year-Old Children"	Randomized Controlled Trial Level 3 evidence	Eighty children, aged 2 to 10 years old undergoing outpatient surgery, were randomly divided into two groups (40 patients each). One group received TIVA with propofol and remifentanil, the other received maintenance anesthesia with sevoflurane.	"Patients did not differ significantly in terms of demographic characteristics. The incidence of postoperative agitation was 62% higher in the sevoflurane group than the TIVA group (5%, P < 0.001). The highest percentage of pain was obtained as 52.5% in the sevoflurane group. Postoperative nausea and vomiting did not differ significantly among groups, and there was a significant decrease in the heart rate of the subjects in the T group as one of the hemodynamic variables ($P = 0.01$)."
19	Porter et al. (2020) [19]	"Respiratory and hemodynamic perioperative adverse events in intravenous versus inhalational induction in pediatric anesthesia: A systematic review and meta-analysis"	Systematic review and meta-analysis Level 1 evidence	"Of the 1602 applicable publications, four were included in the final review."	"Data were heterogenous, and pooled estimates may not be reliable. The present systematic review and meta-analysis revealed no significant difference in the occurrence of perioperative respiratory adverse events between inhalation and intravenous induction. More respiratory adverse events during and after inhalation induction were found, in particular in children with multiple risk factors for respiratory adverse events. This did not reach significance."

Table I. — List of included studies after initial literature search - 5.

	Author, year of publication	Title	Study Design	Study setting and Study Population	Key Findings
20	Peker et al. (2020) [20]	"Effects of intravenous and mask induction on post-operative emergence delirium in pediatric patients undergoing tonsillectomy with or without adenoidectomy"	Randomized Controlled Trial, single-blinded Level 3 evidence	"Sixty-seven children (aged 3-12 years) were randomly assigned to receive either mask induction (group M) or intravenous induction (group IV)."	"PAED scores were significantly higher in group M at 5 min (group M = 12.2 ± 4.215, group IV = 9.1 ± 4.0; mean difference = 3.094, 95% CI [1.108; 5.081]; P = 0.003), at 15 min (group M = 8.0 ± 2.6, group IV = 5.1 ± 2.3; mean difference = 2.942, 95% CI [1.586-4.301]; P < 0.001), and at 30 min (group M = 5.1 ± 2.8, group IV = 2.5 ± 1.8; mean difference = 2.620, 95% CI [1.457; 3.783]; P < 0.001) than in group IV. The FLACC scale scores were similar between the two groups."
21	Pavlovic et al. (2020) [21]	"The Effect of UGT1A9, CYP2B6 and CYP2C9 Genes Polymorphism on Propofol Pharmacokinetics in Children"	Case-control study Level 3 evidence	"94 children, ASA I-II status, 1 to 17 years of age, who undergone standard anesthetic protocol for TIVA, which implied the continuous use of propofol. Before the administration of propofol, venous blood was sampled to determine the presence of genetic variations in UGT1A9, CYP2B6 and CYP2C9 gene using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP)."	"UGT1A9 genotype is an independent predictor of the propofol concentration in children immediately after the end of the continuous infusion and 10 mins afterwards. In the carriers of the polymorphic UGT1A9 C allele, the propofol distribution constant was higher. The carriers of the polymorphic CYP2B6 T allele received a significantly lower overall and initial dose of propofol. Unlike polymorphism of the UGT1A9 gene, the tested CYP2C9 and CYP2B6 gene polymorphisms are not independent predictors of the pharmacokinetics of propofol."
22	Omara et al. (2019) [22]	"Recovery with Propofol Anesthesia in Children Undergoing Cleft Palate Repair Compared with Sevoflurane Anesthesia"	Randomized Controlled Trial Level 3 evidence	Eighty infants, aged from six months to one year, scheduled for cleft palate repair surgery, were randomly divided into two groups (40 patients each). One group received TIVA with propofol, the other group inhalational anesthesia with sevoflurane.	"The quality of emergence was assessed by modified Hannallah score, there was a significant decrease in the number of patients developed agitation after propofol TIVA in comparison to sevoflurane anesthesia ($P < 0.001$) with a significant decrease in the number of patients developed postoperative laryngeal spasm ($P < 0.047$). On the other hand, a significantly prolonged time of extubation was observed in the propofol TIVA group ($P < 0.001$)."
23	Ballard et al. (2019) [23]	"Efficacy of the Buzzy Device for Pain Management During Needle-related Procedures: A Systematic Review and Meta-Analysis"	Systematic Review and meta-analysis Level 1 evidence	"A total of 9 studies involving 1138 participants aged between 3 and 18 years old were included in the systematic review and 7 were suitable for meta-analysis."	"The meta-analysis compared the Buzzy device with a no-treatment comparator and the effect of the device was significant in reducing self-report procedural pain (standardized mean difference [SMD]: -1.11; 95% confidence interval [CI]: -1.52 to -0.70; P<0.0001), parent-reported procedural pain (SMD: -0.94; 95% CI: -1.62 to -0.27; P=0.006), observer-report procedural pain (SMD: -1.19; 95% CI: -1.90 to -0.47; P=0.001), observer-reported procedural anxiety (SMD -1.37; 95% CI: -1.77 to -0.96; P<0.00001), and parent-reported procedural anxiety (SMD -1.36; 95% CI: -2.11 to -0.61; P=0.0004). There was no significant difference for the success of the procedure at first attempt and the occurrence of adverse events."

Table I. — List of included studies after initial literature search - 6.

	Author, year of publication	Title	Study Design	Study setting and Study Population	Key Findings
24	Schraag et al. (2018) [24]	"Propofol vs. inhalational agents to maintain general anaesthesia in ambulatory and in-patient surgery: a systematic review and meta-analysis"	Systematic review and meta-analysis Level 1 evidence	"The search of three databases resulted in 11,391 records, one further RCT was identified by checking manually the reference list of included papers. After exclusion of duplicates, 6688 records were screened based on title or abstract, whereof 5854 were excluded. After the detailed review of 834 full-text articles, we found that 86 did not report any outcome of interest, in 224 trials the intervention was not in accordance with the inclusion criteria, 9 did not fulfil the population criteria, 41 were not RCTs or had an unclear design, 29 reported in a non-selected language, for 157 no full text was available, and 59 were duplicates. Finally, 229 RCTs were included in the qualitative synthesis and primary meta-analysis (Fig. 1). These studies account for a total of 20,991 patients."	"The risk for PONV was lower with propofol than with inhalational agents (relative risk (RR) 0.61 [0.53, 0.69], $p < 0.00001$). Additionally, pain score after extubation and time in the post-operative anaesthesia care unit (PACU) were reduced with propofol (mean difference (MD) −0.51 [−0.81, −0.20], $p = 0.001$; MD −2.91 min [−5.47, −0.35], $p = 0.03$). In turn, time to respiratory recovery and tracheal extubation were longer with propofol than with inhalational agents (MD 0.82 min [0.20, 1.45], $p = 0.01$; MD 0.70 min [0.03, 1.38], $p = 0.04$, respectively). Notably, patient satisfaction, as reported by the number of satisfied patients and scores, was higher with propofol (RR 1.06 [1.01, 1.10], $p = 0.02$; MD 0.13 [0.00, 0.26], $p = 0.05$). Secondary analyses supported the primary results."
25	Scheiermann et al. (2018) [25]	"Intravenous versus inhalational anesthesia for pediatric inpatient surgery - A systematic review and meta-analysis"	Systematic Review and meta-analysis Level 1 evidence	"In total, nine RCTs (762 children) were analyzed."	"Regarding primary endpoints, the use of propofol during strabismus surgery significantly increased the relative risk (RR) of oculocardiac reflex (RR 4.96, 95% confidence interval [CI]: 3.13-7.87, $p < 0.00001$; two studies, 257 children). PONV was significantly less frequent after general anesthesia with intravenous than with volatile anesthetic agents (RR 0.68, 95% CI: 0.48-0.98, $p = 0.04$; five studies, 563 children). We did not find identify any further difference with regards to the predefined primary or secondary endpoints due to clinical or statistical heterogeneity."

Table I. — List of included studies after initial literature search - 7.

	Author, year of publication	Title	Study Design	Study setting and Study Population	Key Findings
26	Li et al. (2018) [26]	"Effects of different doses of intranasal dexmedetomidine on preoperative sedation and postoperative agitation in pediatric with total intravenous anesthesia undergoing adenoidectomy with or without tonsillectomy"	Randomized Controlled Trial, Double-Blinded Level 2 evidence	Three groups, each containing thirty pediatric patients undergoing adenoidectomy were randomly divided, receiving respectively 1μg/kg (D1), 2μg/kg (D2) or normal saline (S) intranasally as a pre-operative sedative.	"The proportions of satisfactory sedation in the D1, D2, and S groups were 63.3%, 76.7%, and 0%, respectively. There was a statistically significant difference between D1 and S groups (P=.000) and D2 versus S groups (P=.000), while there was no statistically significant difference between D1 and D2 groups (P=.399). As for scale on the behavior of separation from parents, there was a statistically significant difference between D1 and S groups (P=.009) and D2 versus S groups (P=.009), whereas there was no significant difference between D1 and D2 groups (P=1). The incidence of postoperative agitation in the D1, D2, and S groups was 43.3%, 30.0%, and 63.3%, respectively, and there was a statistical difference between D2 and S groups (P=.010). There was a significant difference in the Pediatric Anesthesia Emergence Delirium (PAED) scale between D2 and S groups (P=.029). The Children's Hospital of Eastern Ontario Pain Scale (CHEOPS) in the D2 group was significantly lower than the S group (P=.013).The intranasal dexmedetomidine of 1 or 2μgkg 25 to 40 minute before induction of anesthesia both could deliver effective preoperative sedation, reducing the children's distress of separation from parents."
27	Schaefer et al. (2017) [27]	"Total intravenous anesthesia vs single pharmacological prophylaxis to prevent postoperative vomiting in children: A systematic review and meta-analysis"	Systematic review and meta-analysis Level 1 evidence	"patients <18 years of age undergoing general anesthesia were included, with one group receiving propofol-based total intravenous anesthesia and another group receiving inhalational anesthesia with single pharmacological prophylaxis. Primary outcome was the overall incidence for postoperative vomiting. Secondary outcomes included early and late postoperative vomiting, the need for postoperative antiemetic medication, time to first oral intake, duration of stay in the postanesthesia care unit, and any adverse events defined as such by the respective authors… Four randomized controlled trials including 558 children were included in the final analysis. All patients underwent strabismus surgery."	""Total intravenous anesthesia and single pharmacological prophylaxis were equally effective in preventing overall postoperative vomiting (RR 0.99 [95% CI 0.77; 1.27]; 4 trials), as well as vomiting in the early (1.48 [0.78; 2.83]; 4 trials) and late (0.89 [0.56;1.42]; 2 trials) postoperative period. There was no difference in the need for postoperative antiemetic medication. Although patients resumed drinking and eating significantly earlier following total intravenous anesthesia (MD -1.40 hours [-2.01; -0.80], P < .001), the duration of PACU stay did not differ between groups. The incidence of intraoperative oculocardiac reflex was the only reported adverse event, which was more likely to occur after total intravenous anesthesia (1.86 [1.01; 3.41])."

Table I. — List of included studies after initial literature search - 8.

	Author, year of publication	Title	Study Design	Study setting and Study Population	Key Findings
28	Qiao et al. (2017) [28]	"Pediatric premedication: a double-blind randomized trial of dexmedetomidine or ketamine alone versus a combination of dexmedetomidine and ketamine"	Randomized Controlled Trial, Double-Blinded Level 2 evidence	"A total of 135 children, aged 2-5 years and American Society of Anesthesiologists status I-II, scheduled for eye surgery were randomly allocated to receive intranasal dexmedetomidine 2.5 μg/kg (group D), oral ketamine 3 mg/kg and intranasal dexmedetomidine 2 μg/kg (group DK), or oral ketamine 6 mg/kg (group K) 30 min before surgery."	"The rate of successful venous cannulation was 47% with dexmedetomidine alone, 68% with ketamine alone, and 80% with combined premedication (P=0.006). The rate of satisfactory separation from parents was not different among groups. The incidence of adverse events was higher in group K compared with the other two groups (postoperative vomiting, P=0.0041; respiratory-related complications during the perioperative period, P=0.0032; and postoperative psychological/psychiatric adverse events, P=0.0152)."
29	Lang et al. (2017) [29]	"Efficacy of lidocaine on preventing incidence and severity of pain associated with propofol using in pediatric patients: A PRISMA-compliant meta-analysis of randomized controlled trials"	Systematic review and meta-analysis Level 1 evidence	"All randomized controlled trials that using lidocaine for propofol injection pain in children were enrolled. The primary outcome included the incidence of injection pain and the incidence of propofol injection pain in different degrees. The data were combined to calculate the relative ratio and relevant 95% confidence interval. A meta-analysis was performed following the guidelines of the Cochrane Reviewer's Handbook and the PRISMA statement."	"Data from the included 11 studies indicated that the incidence of injection pain was lower in lidocaine group than the incidence in saline control group and in propofol lipuro (medium- and long-chain triglycerides) group (pain occurrence: 22.1% in lidocaine vs 66.8% in saline, RR with 95% 0.34 [0.26, 0.43], I=38%; 30.5% in lidocaine vs 46.9% in propofol lipuro, RR with 95% 0.68 [0.46, 1.00], I=9%). There was no difference between lidocaine and ketamine/alfentanil both in reducing pain occurrence and in reducing pain severity (pain occurrence: 29.7% in lidocaine vs 25.8% in ketamine, RR with 95% 1.47 [0.16, 13.43], I=94%; 31.0% in lidocaine vs 30.7% in alfentanil, RR with 95% 1.01 [0.69, 1.46], I=11%). And the reported side effects revealed that the safety of lidocaine in pediatric patients was acceptable."
30	Impellizzeri et al. (2017) [30]	"Premedication with melatonin vs midazolam: efficacy on anxiety and compliance in paediatric surgical patients"	Randomized Clinical Trial Level 3 evidence	"The primary outcome of this randomized clinical trial was to evaluate the effectiveness of oral melatonin premedication, in comparison to midazolam, in reducing preoperative anxiety in children undergoing elective surgery. As secondary outcome, compliance to intravenous induction anaesthesia was assessed. There were 80 children undergoing surgery randomly assigned, 40 per group, to receive oral midazolam (0.5 mg/kg, max 20 mg) or oral melatonin (0.5 mg/kg, max 20 mg)."	"Children premedicated with melatonin and midazolam did not show significant differences in preoperative anxiety levels, either in the preoperative room or during anaesthesia induction. Moreover, compliance during anaesthesia induction was similar in both groups."

Table I. — List of included studies after initial literature search - 9.

	Author, year of publication	Title	Study Design	Study setting and Study Population	Key Findings
31	Stipic et al. (2015) [31]	"Are postoperative behavioural changes after adenotonsillectomy in children influenced by the type of anaesthesia?: A randomised clinical study"	Randomized controlled trial Level 3 evidence	""Sixty-four children (aged 6 to 12 years, ASA 1 to 2) undergoing adenotonsillectomy assigned into one of two groups: sevoflurane (S) (n=32) or total intravenous anaesthesia (TIVA) (n=32)"	"The prevalence of at least one NPOBC (negative postoperative behavioural changes) after surgery ranged from a maximum of 80% [95% confidence interval (CI) 71 to 90%] on POD 1 to a minimum of 43% (95% CI 31 to 56%) 6 months after surgery. Absolute risk reduction for at least one NPOBC in the TIVA group compared with the S group increased from 0.24 on POD 1 to 0.55 6 months after surgery. The number of NPOBCs was also lower in the TIVA group [median 5, interquartile range (IQR) 2 to 10] than in the S group (median 22, IQR 10 to 32) (P<0.001). The overall number of NPOBCs within PHBQ subscales was significantly lower in the TIVA group than in the S group. The largest difference in the number of NPOBCs between groups was observed for the separation anxiety subscale (mean 5, 95% CI 1 to 9; P<0.001) followed by the general anxiety subscale (mean 4, 95% CI 3 to 5; P<0.001) and apathy/withdrawal subscale (mean 3, 95% CI 1 to 5; P<0.001)."
32	Orliaguet et al. (2015) [32]	"Feasibility of closed-loop titration of propofol and remifentanil guided by the bispectral monitor in pediatric and adolescent patients: a prospective randomized study"	Randomized controlled trial, single-blinded	"Twenty-three patients (12 [10 to 14] yr) were assigned to the auto group and 19 (14 [7 to 14] yr) to the manual group. The closed-loop controller was able to provide induction and maintenance for all patients."	"The percentage of time with BIS40-60 was greater in the auto group (87% [75 to 96] vs. 72% [48 to 79]; P = 0.002), with a decrease in the percentage of BIS<40 (7% [2 to 17] vs. 21% [11 to 38]; P = 0.002). Propofol (2.4 [1.9 to 3.3] vs. 1.7 [1.2 to 2.8] mg/kg) and remifentanil (2.3 [2.0 to 3.0] vs. 2.5 [1.2 to 4.3] µg/kg) consumptions were similar in auto versus manual groups during induction, respectively. During maintenance, propofol consumption (8.2 [6.0 to 10.2] vs. 7.9 [7.2 to 9.1] mg kg h; P = 0.89) was similar between the two groups, but remifentanil consumption was greater in the auto group (0.39 [0.22 to 0.60] vs. 0.22 [0.17 to 0.32] µg kg min; P = 0.003). Perioperative adverse events and length of stay in the postanesthesia care unit were similar."
33	Costi et al. (2015) [33]	"Transition to propofol after sevoflurane anesthesia to prevent emergence agitation: a randomized controlled trial"	Randomized Controlled Trial	"230 children aged 1-12 years, undergoing magnetic resonance imaging (MRI) scans under sevoflurane anesthesia were randomized to receive either propofol 3 mg · kg(-1) over 3 min (propofol group), or no propofol (control group), at the end of sevoflurane anesthesia."	"The incidence of EA was lower in the propofol group on both PAED (29% vs 7%; relative risk = 0.25; 95% confidence interval 0.12-0.52; P < 0.001) and Watcha (39% vs 15%; relative risk = 0.37; 95% confidence interval 0.22-0.62; P < 0.001) scales. Duration and severity of EA were also reduced in the propofol group. Preplanned subgroup analyses for midazolam premedication, preexisting cognitive or behavioral disturbance, and age group did not alter our findings. Emergence time and time in PACU were both increased by a mean of 8 min in the propofol group (P < 0.001) with no difference in time to discharge home."

Table I. — List of included studies after initial literature search - 10.

	Author, year of publication	Title	Study Design	Study setting and Study Population	Key Findings
34	Ortiz et al. (2014) [34]	"Intravenous versus inhalational anaesthesia for paediatric outpatient surgery"	Systematic Review and meta-analysis Level 1 evidence	16 trials that included 900 children were included in the systematic review and meta-analysis.	"The authors found that when compared to inhaled anaesthesia with sevoflurane, intravenous anaesthesia with propofol may reduce the risk of PONV and the risk of behavioural problems with no difference in the time to recovery from anaesthesia and discharge from hospital in children having day surgery. The effect on complications was imprecise. The studies that compared other anaesthetic agents involved different types of surgical procedures, different procedure durations and drugs, making it difficult to sum the results."

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fluent legibility and to provide depth, further database searches for articles containing key-words relevant to the initially selected articles were performed when necessary, in order to expand on the subject matter. One article was included based on a recommendation after peer-review.

Results

Summary of established evidence

TIVA has been proven safe as compared to IHA[18] (see Table II - Advantages and disadvantages of TIVA in the pediatric population). A 2014 Cochrane review comparing IHA versus TIVA for pediatric outpatient surgery found that there may be a reduced risk of post-operative nausea and vomiting (PONV) with propofol TIVA, found no difference in time to recovery and was unable to make conclusions on incidence of complications due to low quality and heterogeneous trials[19]. A large 2018 systematic review and meta-analysis including both pediatric and adult data that compared IHA with TIVA showed a statistically significant lower incidence of PONV, lower post-operative pain scores, longer time to respiratory recovery, longer time to extubation and higher patient satisfaction when using TIVA[4]. A 2018 systematic review undertaken in a pediatric population shows increased relative risk of triggering the oculocardiac reflex during strabismus surgery and a lower incidence of PONV when using a TIVA technique compared to inhalational anesthesia[20]. Primary motivations for adoption of TIVA technique– according to an international survey of anesthesiologists with specific expertise or interest[9] – are: positive impact of TIVA on patient experience, especially in pediatrics; benefit to procedural outcome; impact on the environment; effect on patient physiology such as hemodynamic and airway control and the positive effect on PONV. Another survey conducted in 2019, which was a follow-up survey among pediatric anesthesia practitioners in the UK and Ireland found that the use of TIVA had doubled in the past ten years, though IHA remained more prevalent[21]. Commonly used agents for TIVA include propofol, remifentanil, alfentanil, ketamine, midazolam and dexmedetomidine[22]. Delivery of anesthetic agents during TIVA can be achieved either through a manual infusion regimen or through TCI (target controlled infusion)[23,24]. TCI uses algorithms based on PK/PD models to make real-time calculations which determine infusion rates of IV anesthetics. In this way a user-defined target effect-site concentration based on the PK/PD model can be achieved. Several different TCI algorithms based on PK/PD models exist. Some of these algorithms are pre-programmed into commercially available infusion pumps and are widely used[24]. A review by Vandemoortele et al. contains a summary of commercially used TCI models for different anesthetic medications and the age ranges of the original study populations for each model[25]. PK/PD models based on adult parameters tend to over-predict plasma-concentrations for children. This can be explained through variation in size,

Table II. — Advantages and disadvantages of TIVA in the pediatric population[1,2].

Advantages	Disadvantages
- Rapid induction of anesthesia, independent from alveolar ventilation - Reduced incidence of emergence delirium, 'smooth recovery' - Increased patient and parental satisfaction in the post-operative period - Reduced incidence of post-operative nausea and vomiting - Favorable profile of propofol for neuro-anesthesia and ear-nose-throat surgery - Preferred method in patients with malignant hyperthermia or neuromuscular disease - Preferred method when using evoked potential monitoring e.g. scoliosis surgery - Reliable delivery of anesthetic in shared airway surgery - No release of greenhouse gases into the atmosphere - Reduced exposure to volatile anesthetics for healthcare staff - Avoidance of face mask in awake fearful children	- Pain on injection of IV agents (specifically propofol) - Heterogeneity in algorithms for target controlled infusion - Faults in administration of the IV agent (improper infusion line management), risk of awareness - Variability in PK/PD per individual patient - Inadequate methods / patient variability for depth of anesthesia monitoring - No real-time measurements nor available proxies of anesthetic concentration in plasma - Closed-loop administration of TIVA inferior to that of inhaled anesthetics - Propofol infusion syndrome - Administration of lipid load when using propofol - Risk of bacterial contamination when using propofol - Long context-sensitive half-life in prolonged procedures for obese patients when using propofol - Increased use of single-use plastic packaging

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tissue ratios and organ function, maturation of enzyme pathways and genetic polymorphisms[26]. There remains a paucity in available validated models for use in the pediatric population, though this may change in the coming years[22].

Despite advances, gaps in applicability of different PK/PD models exist for different population groups, therefore caution is warranted when using one model for different patients. Rather than creating PK/PD models specific to children there is also increasing interest in creating 'general purpose' models applicable to patients from all ages and body compositions. This would reduce the risk of invalid model selection by the user of the TCI pump[25]. Administration of TIVA with automated pumps can happen in either an open-loop or closed-loop fashion. Closed-loop systems make use of a feedback loop that automatically influences the anesthetic infusion, thus making the infusion a function of the feedback output[27]. This feedback could be based off of e.g. bispectral index (BIS), hemodynamic parameters or nociception monitoring[28,29]. Measured exhaled propofol is theoretically very interesting for closed-loop systems, but has many practical hurdles[30]. Current practice of TIVA still mostly uses open-loop systems where there is no feedback mechanism. Though there have been feasibility trials with positive conclusions, the technology has not yet been widely adopted[27,29]. Thus the practicing anesthesiologist must use their knowledge and experience in order to maintain an appropriate anesthetic and avoid awareness and other adverse effects.

For safe practice of TIVA, joint guidelines were published by the Association of Anaesthetists and the Society for Intravenous Anaesthesia (United Kingdom) in 2018[31].

Several reviews and opinions were published in the early 2010's detailing circumstances and remaining challenges for TIVA practice in pediatric anesthesia[5,12,32]. In the next segment of this manuscript an update on research in the last ten years will be provided.

Recent evidence

Intravenous induction of anesthesia

The term 'TIVA' implies that 100% of given anesthetics are intravenous. This is not always accurate in pediatric anesthesia as regularly a child will be induced using inhaled anesthetics, before placing an IV cannula and switching over to intravenous maintenance. There have been reports of awareness after switching from gas induction to a propofol maintenance infusion. Using only a fixed infusion rate may not be adequate because steady-state concentrations of propofol will not be established before 3 to 4 elimination half-lives. If a loading dose is not given or is delayed, chances of awareness increase[33]. In guidelines for TIVA practice in the adult patient, when using TCI, it is recommended that to set an initial propofol target of 4 μg.ml−1 and to decrease the target after the pump indicates that a 2–3 mg/kg bolus has been delivered[31]. A reduced bolus dose of 1 mg/kg followed by propofol infusion according to McFarlans regime[34] appears sufficient children 1-8 years old[35].

A systematic review published in 2020 looked into respiratory and hemodynamic adverse events during either IV or inhalational induction of anesthesia. They concluded a lack of available data to draw conclusions. Future large trials looking into the subject matter were advised[36]. An RCT conducted in children undergoing tonsillectomy with or without adenoidectomy found that mask induction was associated with significantly higher emergence delirium (ED) scores than IV induction[37].

An alternative technique is sometimes also used: sevoflurane induction and maintenance, switching to propofol at the end of the case, in order to reduce PONV and ED. This strategy has been shown to decrease ED, and cause slightly longer emergence- and recovery time, with no difference in time to discharge home[38,39].

A complete TIVA technique requires placing an IV catheter without use of inhaled anesthesia. Creating optimal circumstances for placing an IV line in a child can be a challenge. It requires a holistic approach to the child and coordinated action of the team[40]. Predictors for success according to a prospective audit included: older age of the child and child behavior at first encounter. Qualitative data also suggested positive effects from distraction, preparing family for IV induction, parental presence, effective use of local analgesic cream, individualizing approach and the anesthesiologists efficiency[41]. Pre-operative preparation sessions and virtual reality can also be useful nonpharmacological adjuncts when placing an IV catheter[42,43]. Pharmacological strategies include premedication and topical skin anesthesia.

Premedication with a sedative/anxiolytic

Oral midazolam has long been the gold standard pre-operative sedative for children. Some mixed evidence regarding negative effect of prolonged benzodiazepine use on neurodevelopmental changes as well as known side-effects prompt the search for better alternatives[44,45]. Fentanyl

lollipops are well tolerated by children and show comparable anxiolysis to midazolam, but are burdened by opioid induced respiratory depression and increased nausea and vomiting. Alfa-2 agonists also perform well anxiolytically and can reduce ED, but have been associated with increased incidence of bradycardia, hyper- and hypotension. Ketamine has desirable sedative, anxiolytic and analgesic effects; but increased nausea and vomiting, hallucinations and increased ED make it less attractive[44].

Li et al. performed an RCT showing intranasal dexmedetomidine of 1-2 µg/kg 25 to 40 minutes before induction of anesthesia to provide satisfactory sedation in 63.3% to 76.7% of cases. A dose of 2 µg/kg also showed significantly lower ED as compared to the control group that received normal saline intranasally[46].

Another trial compared intranasal dexmedetomidine, oral ketamine combined with intranasal dexmedetomidine and only oral ketamine. At trial dosages, using only oral ketamine resulted in more adverse events such as PONV, respiratory events and agitation. The combination of dexmedetomidine and ketamine had the highest successful venous cannulation rate[47]. Impellizzeri et al. studied melatonin as a preoperative anxiolytic compared to midazolam and found no significant differences in anxiety levels pre-operatively nor during induction of anesthesia between the two groups[48]. In contrast, a more recent 2024 publication by Bolt et al. reported a clinically relevant inferiority of melatonin as compared to midazolam in reducing pre-operative anxiety for elective surgery under general anesthesia in their MAGIC trial[49].

Topical skin anesthesia for IV access

Available products for topical anesthesia of the skin include EMLA ('eutectic mixture of local anesthetics' an emulsion preparation with equal quantities lidocaine and prilocaine) and Rapydan® (a patch containing lidocaine and tetracaine). They have similar efficiency profiles, with Rapydan® showing a faster onset of effect, requiring 30-60 minutes of application, while EMLA is preferably applied >60 minutes[50].

As a nonpharmacological method, numbing of skin right before a procedure using rapid cooling has seen increased use in the last ten years. A systematic review and analysis into effectiveness of the Buzzy device – which combines cold and vibration for needle-related pain in children- showed significant reduction in self-, parent-, and observer reported pain. Though unfortunately comparative effect is uncertain due to heterogeneity and low quality of studies[51]. The Coolsense® pain numbing applicator is a device that was originally developed for use in cosmetic procedures that uses the cryoanalgesia principle. A 2017 clinical audit in 100 pediatric patients using Coolsense as analgesia for IV cannulation showed it to be possibly effective with few complications[52]. Thind et al. published a randomized crossover trial in 64 healthy adult volunteers, finding reduced pain scores and a higher subjective preference for EMLA over Coolsense[53]. In 2024 Xess et al. published their RCT comparing the efficacy of EMLA vs. CoolSense in 140 ASA 1-2 children, reporting a reduced pain score as well as reduced anxiety scores when using CoolSense. Similar devices and cooling sprays (vapocoolants) have been studied versus placebo in the past with mixed results[51,54].

Reducing propofol injection pain

A 2017 systematic review and meta-analysis reported that lidocaine effectively reduces pain on injection of propofol when compared to normal saline in a pediatric population. Ketamine or alfentanil can also be used for pain relief, though lidocaine has a superior safety profile[55].

Drug development and PK/PD modeling

Drug development and anesthesia-induced neurotoxicity

There are many IV anesthetic agents. Not all of them are suited for TIVA. Propofol appears to have the most favorable pharmacological profile of currently available anesthetics for TIVA[56]. Remifentanil, midazolam, dexmedetomidine and (es)ketamine are also frequently used. New compounds are always under development. A 2022 review gives a broad scope of compounds that are in the pipeline such as remimazolam, fospropofol, ciprofol, phaxan, … [22] These have yet to gain widespread use in adults, with more delay expected until they are trialed in the pediatric population. Concerns of anesthesia-induced neurotoxicity, which have shown lasting behavioral impairment in animal models, complicates researching new compounds in a pediatric population[57]. Retrospective studies in humans have shown some association between repeated exposure to general anesthesia as an infant and neurological or behavioral problems later in childhood. Though these studies are not free of confounding factors[15]. One systematic review concluded that there is no conclusive evidence for deleterious effects of a single short anesthetic in infancy on neurodevelopment[14]. There has also been interest in dexmedetomidine as a potential neuroprotective agent[58].

Remimazolam as a short-acting compound may find increased application in TIVA because of its

pharmacological profile[59]. A 2023 pharmacokinetic study in 24 children aged 2-6 years old reported that remimazolam was characterized by a high clearance and short context-sensitive half-time. When normalized to weight, pharmacokinetic properties were similar to those reported for adults[60].

PK/PD models for propofol TCI

The Marsh, Paedfusor and Kataria models for propofol TCI in children over 2 years old have been commercially available for a while and are clinically valid with their own strengths and pitfalls[61-64]. A 2011 study by Sepúlveda et al. found that 6 different propofol PK/PD models could perform well in children aged 3 – 26 months old[65]. With recent interest in 'general purpose' PK/PD models, Eleveld and colleagues have published models for propofol and remifentanil based on data from subjects aged 0-85 years old[66,67]. One validation study for the Eleveld propofol model suggests adequate accuracy for clinical use in children and adults. However more work needs to be done to fully validate the model 13. Forays have also been made into integrative PK/PD models that combine propofol and remifentanil administration and their impact on BIS monitoring as shown by Fuentes et al.[68]

A PK/PD model for dexmedetomidine TCI

In 2015 the Hannivoort three-compartment allometric model was published after research on 18 healthy adult volunteers[69]. In 2020 Morse et al. published their PK/PD 'universal' PK/PD model which was developed using pooled data from pediatric and adult subjects[70]. Subsequently there was some discussion over appropriate loading dose of dexmedetomidine in order to prevent adverse hemodynamic consequences[71,72]. Morse and colleagues later also published an overview of pharmacokinetic concepts for use of dexmedetomidine TCI in children[73]. For now, prospective clinical trials validating these models are lacking.

PK/PD modeling in obese children

Childhood obesity is increasing globally, as reported by the World Health Organization ("While just 2% of children and adolescents aged 5–19 were obese in 1990 (31 million young people), by 2022, 8% of children and adolescents were living with obesity (160 million young people))"[74]. Fat mass has an influence on both volume and clearance of administered drugs. Whether to use actual body weight, ideal body weight or lean body weight for calculation of drug doses matters. The use of allometric size scaling is better, though this requires quite a bit of arithmetic. The use of TCI pumps, provided the practitioners have a solid understanding of the PK/PD within programs, enables easier and superior dosing in the obese child[26,75].

PK/PD modeling in low cardiac output states

Allegaert et al. performed a computer-simulated PK/PD study using the Simcyp® PBPK simulator platform with a previously validated PK/PD model[76] in order to investigate propofol clearance under low cardiac output states in different age groups. Hepatic and renal extraction ratios in normal circumstances increase from neonate to adult. In low cardiac output states, the relative change in clearance increased with age, with the lowest impact on neonates. With cardiac output reduced by half, a propofol dose reduction of 15% appeared warranted in neonates, infants and children; while in adolescents and adults a dose reduction of 25% would seem optimal[77].

Decrement time in TCI models

A 2023 study from Birmingham Children's Hospital investigated calculated decrement time in their TCI pumps for propofol anesthesia. They aimed to compare the decrement time (which is a predicted time for the effect-site propofol concentration to fall to a certain value, here 1,5 µg/mL) with recovery time which was defined by eye-opening of the patient. The recovery time was longer by 5 minutes than decrement time for nearly half their subjects, showing marked discrepancy between decrement time and recovery time. The decrement time shown on the pump ought to be used with caution when predicting recovery time[78]. Use of adjuvant drugs, a child's clinical status and genotype are factors that could delay recovery times past decrement times[79].

Electro-encephalogram and emergence delirium

EEG monitoring in the pediatric patient

Non-invasive EEG neuromonitoring has shown clinical benefits in ensuring adequate sedation and analgesia for a range of adult patients and surgery settings[80-82]. Implementation of EEG monitoring in the pediatric population is still lagging behind. In recent years, larger multichannel EEG studies on the developing brain under anesthesia are being undertaken[83-85]. Especially for small infants, the EEG appears to have some fundamental differences that require separate calibration of monitors[83,86]. Available EEG monitors meant for use during anesthesia - such as BISmonitor (Medtronic), SedLine (Masimo), Narcotrend

compact M (MonitorTechnik) and EntropyModule (GE Healthcare)[87] - have been used clinically to monitor children, though they were developed with algorithms verified in adult populations. The exact way the processed EEG is derived from the manufacturers proprietary algorithm also remains unclear. The manufacturers provide the caveat of not being safe for use in infants (1-12 months) and neonates (< 1 month). There is a paucity in large studies that analyze correlations between application of EEG-based monitors and clinical post-anesthesia outcomes, preventing any firm conclusions on benefit of their use[88]. Though small studies are being undertaken: these two trials investigated use of Narcotrend and BIS guided propofol sedation for endoscopy and dental procedures, indicating faster recovery and fewer episodes of oversedation[89,90]. Another study concluded that BIS guided propofol-remifentanil TIVA showed no shorter extubation times nor reduced stay in the post-anesthesia care unit (PACU) when compared to their standard of care[91].

A 2019 RCT showed marked difference between BIS and EEG monitoring in 5-18 year olds during anesthesia with propofol or sevoflurane. Their results showed that under propofol, BIS showed a linear decline and EEG slowed down as propofol concentrations rose. Sevoflurane on the other hand showed a decrease in BIS from 0% to 4% end-tidal sevoflurane, with a paradoxical rise from 4% to 5% expired concentration. Propofol appeared to be associated with more delta waves and burst suppression periods[92].

A 2018 survey among members of the European Society for Paediatric Anaesthesiology revealed that EEG monitoring was mainly used during TIVA in children over 4 years old with the specific aim of avoiding awareness[93,94].

Emergence delirium and postoperative behavioral changes

Emergence delirium after anesthesia is well recognized[95]. There is evidence that TIVA using propofol lowers the incidence of ED, provides a smooth recovery period and increases parental/guardian satisfaction[5,19,96,97]. Quintão et al. performed an RCT in an age group of 1-12 years old that underwent ambulatory endoscopic procedures, comparing sevoflurane IHA and propofol TIVA. Their results weren't able to show a significant difference in behavioral changes between the two groups, but did show that children who do experience ED may show a greater incidence of late negative postoperative behavior changes[98].

A systematic review by Petre et al. compared how TIVA versus sevoflurane combined with use of dexmedetomidine affected ED in children. They concluded that when compared to TIVA alone, sevoflurane combined with dexmedetomidine lowered the incidence of ED with no statistically significant difference to the TIVA group, with the latter resulting in a higher incidence of PONV. The quality of evidence for this conclusion however was low[99].

Electro-encephalogram and emergence delirium

TIVA when using motor- and somatosensory evoked potentials (MEPs and SSEPs)

Use of anesthetic agents has an impact on reliability of MEPs and SSEPs, which are used for intraoperative neurophysiological monitoring[100]. Anesthetic agents act on the monitoring pathways by either directly inhibiting synaptic pathways or by indirectly changing the balance between excitatory and inhibitory influences[101]. Because of its favorable profile, propofol-based TIVA anesthesia has become the preferred technique for procedures requiring cortical SSEP or MEP monitoring in adult patients[100]. A review of literature undertaken by Nakahari et al. concluded that for neonates and infants, the optimal combination and dose of anesthetics for intraoperative neurophysiological monitoring has yet to be elucidated. The authors hypothesize that with increasing knowledge in PK/PD modeling, more specific target concentration dosing will be possible in future, allowing for more directed studies to investigate optimal anesthetic strategies[102].

This type of monitoring is frequently used during corrective scoliosis surgery in the pediatric patient. Abdelaal et al. performed a systematic review to evaluate the impact of dexmedetomidine use on MEP/SSEP monitoring. They found few articles that also showed low quality of evidence, prompting the medical community to conduct more rigorous studies on the subject[103].

TIVA and the laryngeal mask airway (LMA)

Karam et al. performed an RCT comparing adverse respiratory events during LMA removal in pediatric patients aged 6 months to 7 years when using either TIVA with propofol or sevoflurane IHA. Their results showed a protective effect of propofol induction and maintenance on respiratory events in healthy children who have minimal risk factors for perioperative respiratory complications[104].

TIVA in the patient with neuromuscular disease

A 2022 consensus statement from an expert panel delegated by the European Neuromuscular Centre stated with a level of evidence 2+ that prolonged use of volatile anesthetics should be avoided

where possible. They also state however that TIVA and IHA have both been used effectively in this population and choice of method should be individualized for each case[105].

TIVA in shared airway surgery

The complex field of shared airway surgery has clearly benefitted from TIVA. For example: use of high frequency jet ventilation is not feasible using inhaled anesthetics. Also, prolonged airway surgery in the adequately sedated and spontaneously breathing patient with a 'tubeless' surgical field is made possible by TIVA[106]. There are specific advantages to both inhalational anesthetics and intravenous anesthetics in airway surgery. For a more in-depth comparison the author recommends the cited expert pro-con discussion published in Pediatric Anesthesia in 2019[6].

TIVA in orthopedic surgery

Chen et al. performed an RCT comparing the addition of dexmedetomidine to a propofol-remifentanil regime in pediatric patients 3-7 years old undergoing femoral shaft reduction and fixation. They noted significantly lower mean arterial pressures toward the end of the procedure, longer extubation times and lower incidence of ED in the dexmedetomidine group[107].

TIVA in strabismus surgery

One systematic review which only included children undergoing strabismus surgery found that TIVA alone as compared to IHA with single pharmacological prophylaxis showed a similar incidence of PONV. Patients who received TIVA did start eating and drinking significantly earlier. Incidence of intraoperative oculocardiac reflex was more likely when using TIVA[108].

Environmental and economic impact

A 2021 survey among pediatric anesthesiologists in the United Kingdom's National Health Service reported one third of practitioners using TIVA for environmental reasons and because of personal preference. Main barriers to using TIVA were lack of proper equipment and awareness monitoring, lack of familiarity with the technique and concerns over efficiency in a high turnover operating theatre schedule[109].

In an effort to reduce greenhouse gas emissions (up to 5% of carbon equivalent emissions in anesthesia care) Nickel et al. make an argument for reducing use of IHA and provide recommendations to save anesthetic gas waste through minimal fresh gas flows and a rational approach to mask induction[16].

A model analysis by Kampmeier et al. concluded that maintenance of general anesthesia with propofol was cost-saving compared to IHA in the United States. They stated that lower PONV rate and shorter stay in the post-anesthesia care unit offset any increased costs associated with TIVA[8].

Various

Genetic polymorphisms

With the human genome at our disposal with increasing ease, genetic factors that affect anesthesia care will enter the spotlight more in future[110]. For example: polymorphism of the micro-opioid receptor gene (OPRM1 118>G) has been reported to influence fentanyl-induced analgesia[111]. A 2023 systematic review on this gene reported a strong correlation between reduced analgesic effect and protection against adverse reactions to use of anesthetic and analgesic agents in the presence of OPRM1 polymorphism[112]. A case-control study investigating differences between clinical data of pediatric patients undergoing propofol-remifentanil TIVA with and without genetic polymorphisms in MDR1 and OPRM1 genes, was not able to show any significant difference in outcomes[113].

Genotypes influencing propofol metabolism might also explain interindividual responses to propofol dosing. One study denoted polymorphism of the gene UGT1A9 to be an independent predictor of plasma propofol concentration after ceasing propofol infusion in children[114].

TIVA and immune function in the surgical patient

The impact that anesthetic drugs have on our immune system has a theoretical potential to guide our clinical decision making, as impaired immune function due to stress may influence clinical outcomes[115]. Anesthetic medications can have anti- and pro inflammatory effects[116]. Surgery can inhibit immune defenses and promote development of metastases and infection. Particularly cancer surgeries and surgeries that carry a high physical stress burden are of interest. In light of this, a 2019 meta-analysis investigated recurrence-free survival in adults after cancer surgery for a variety of cancers, suggesting that propofol TIVA may have a beneficial influence. Though there were inherent limitations in the included studies[117].

One study from Relland et al. investigated immune function in adolescents undergoing major spinal surgery with either IHA or TIVA, finding no significant difference between groups in the immediate post-operative period[118].

Mixtures of intravenous anesthetics

Anesthesiologists appear to have a desire to combine different anesthetics and analgesics into

one single mixture that is easy to administer and would provide superior anesthesia care. This becomes apparent when regarding the history of 'ketofol'[119]. In 2022 an RCT investigated the use of 'ketofol' versus 'lidoketofol' for short surgical procedures in children and found that recovery was superior when using this admixture of lidocaine, ketamine and propofol in their study group 120. Small studies investigating ketofol mixtures appear every now and then[121-124].

TIVA using a mixture of propofol and remifentanil in the same syringe has seen use by pediatric anesthesiologists, prompting debate about safety and accurate dosing when using this technique[125,126].

Discussion

TIVA is a safe and effective way of providing anesthesia care for pediatric patients. Advantages over IHA include reduced risk of PONV, reduced risk of ED, higher patient and guardian satisfaction and reduced impact on the environment. Disadvantages include possible longer extubation times, absence of measurable plasma or effect site concentrations[4,18-20].

IV induction of anesthesia can be a hurdle for implementation of a complete TIVA anesthetic. Various pharmacological and non-pharmacological adjuncts can facilitate placement of an IV catheter without use of inhaled anesthetics: concerning premedication with a sedative, intranasal dexmedetomidine is proven effective[46], with an added positive effect on post-operative ED. Trials with ketamine and melatonin show mixed results[47-49]. Concerning IV placement, one trial showed promising results using the Coolsense device for cryoanalgesia for IV placement[127]. If this can be reproduced, this technology may see more widespread use after mixed evidence for cryoanalgesia using vapocoolants in the past.

The practice of inhalational induction followed by switching to propofol maintenance is also used for facilitation of IV placement, risk of awareness when using this technique can be reduced with a small loading dose of propofol[35].

Propofol, often combined with remifentanil, is the most used drug for TIVA. It has a good profile and has seen extensive clinical use[56]. Dexmedetomidine has been gaining popularity in the past ten years128. Remimazolam is a more recent and promising new molecule, of which clinical trials in the pediatric population are still lacking[59]. Any new agents for use in the pediatric population will need well-designed preclinical studies to ascertain the absence of neurotoxic potential[15,57].

Drug dosing in TIVA can be achieved through manual infusion regimens or TCI using either open- or closed-loop systems. PK/PD models for TCI use in children are available for propofol and remifentanil. Research is being done for pediatric models for dexmedetomidine[70,73]. A propofol model for 27 weeks post menstrual age (PMA) up to 88 years (the Eleveld model) is being used increasingly[13]. While a 'general purpose' PK/PD model is intuitively attractive, some would suggest the use of the most appropriate available model for a child, adult or obese person. The pump might select the best one depending on covariates the user has put in. This way of working would also accommodate for future models for specific subgroups, while we keep working toward the holy grail of 'one model that fits all'[129]. Further research on different variables that influence PK/PD such as fat mass or (epi)genetics may also impact TCI algorithms in the future[75]. Effect of low cardiac output states on clearance has also been investigated in a PK/PD model 77. This could steer us toward more optimal closed-loop TCI systems when coupled with cardiac output measurements.

The EEG monitor can be a powerful tool for the anesthesiologist to help guide anesthetic and analgesic dosing. Based on evidence in the adult population[82], expert experience[94] and physiologic hypotheses[58], increasingly anesthesiologists see benefit in its use in the pediatric population. This benefit seems more advantageous in the context of TIVA, where PK/PD modeling is still evolving and depth of anesthesia monitoring by proxy of expired anesthetic is not (yet?) possible[30]. Treatment algorithms and robust evidence for clinical benefit of the intra-operative EEG are lacking , especially for infants and neonates[87]. Our knowledge of the EEG under anesthesia for this age group is evolving however, and this may lead to new algorithms with clinical applicability. Since the best alternative for processed EEG is relying on experience and clinical surrogate parameters for depth of anesthesia, the technology is seeing more use in pediatric practice: Jones Oguh et al. reported on a quality improvement project in their academic pediatric hospital with the goal to increase use of EEG guided propofol-based TIVA[130,131]. After specific measures were implemented and several cycles of project evaluation and adjustment, they increased use of EEG guided TIVA from 5% to 75% over 18 months and sustaining the level at 72% nine months later.

TIVA can have advantages and disadvantages for specific surgical settings. Whether it is the preferred method when using MEP and SSEP monitoring in children is unclear, further research is needed[102].

What is abundantly clear is that TIVA - when used instead of IHA - is less taxing for the environment, with reduced equivalent emissions[16]. It also appears to be cost-effective[8].

A few genetic polymorphisms that influence metabolism of anesthetic drugs have been identified[112-114]. Their role in the future of anesthesia and personalized medicine could be promising. A patients genetics could become a reason to choose or avoid TIVA. The role surgery and anesthesia play in immune function and its impact on outcomes is also a topic of interest. Some weak evidence points to a positive effect on cancer outcomes when using TIVA in adults[117]. These types of studies are rare in pediatric populations. New insights may provide more arguments for or against TIVA, depending on the patients illness and type of surgery.

Conclusion

TIVA as a technique is already well-established. There is continuing research on many different facets of its application that is changing the way we practice its use.

The following are avenues for future research based on this manuscript:

- reproducing the promising results of cryoanalgesia for venipuncture in children
- long-term prospective trials elucidating neurotoxic effects of anesthetic exposure in children
- prospective trials investigating and validating use of EEG monitoring during TIVA in children
- creating and validating new PK/PD models for different drugs and covariates
- improving and commercializing closed-loop anesthetic TCI systems
- optimizing sedation and anesthesia regimens for specific subpopulations and surgeries
- research on epigenetic factors and impact of anesthesia and surgery on immune function
- researching the impact of anesthetic drugs on neurophysiologic monitoring in children
- finding genes that impact anesthesia care and then ways to use that knowledge to personalize anesthesia management
- finding ways to minimize the impact of anesthesia care on the environment

This review has provided a broad overview on recent research in the field of TIVA in pediatric practice: avenues for future research were presented.

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