Review Article

Comparative Efficacy of Oral Triclofos in Pediatric Neuroimaging and Other Procedural Sedation: A Systematic Review and Meta-analysis

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Abstract

Procedural sedation is mandatory for various diagnostic and therapeutic procedures in uncooperative or struggling children. Many drugs are advocated, but there is no consensus on drug choice, route of administration, and dose to be given. Practice varies by country, area, procedure, and clinician widely. The oral way is always preferred for its accessible acceptability, lower cost, and broader safety margin. Oral medication does not require expert handling by anesthetists, whose availability is usually complicated. Triclofos is the active metabolite of Chloral hydrate. It is used as an oral sedative and anxiolytic. Chloral hydrate and Triclofos lost their ground when they suffered a ban in the year 2000 in the United States of America. They received another setback when they were included in the World Health Organization (WHO) list of restricted pharmaceuticals in 2010. Although unmonitored drug misuse, causing severe side effects, and even death were the reasons behind the ban, different countries also stopped its monitored and supervised use. However, Triclofos remained in use in India, and no severe side effects were noted in its one-time use under medical supervision for procedural sedation in the last 20 years. Therefore, this systematic review and meta-analysis were undertaken to ascertain its safety and efficacy. The protocol was registered at PROSPERO vide no CRD42021237574. Twenty-four studies with 2337 subjects were included, comprising 18 clinical trials for safety and efficacy, while six observational studies were included for Safety only. Triclofos and oral Midazolam appeared as preferred drugs for procedural sedation without any statistically significant difference in effectiveness and safety. Triclofos was used in much higher doses in all studies, varying from 2.5 to 5 times higher than the recommended dose of 20 mg/kg in Indian books. Preservative-free intravenous midazolam preparation mixed with fruit juice was commonly used orally. No severe side effects were noted for Triclofos in any study. It was concluded that one-time use of Triclofos under medical supervision is safe and effective.

Keywords: Triclofos, Midazolam, Procedural sedation, Children, Anxiolysis

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Introduction

Procedural sedation is required in children because they may be afraid, anxious, uncooperative, or do not lie still for the successful and safe procedure completion. There is no consensus on the choice of sedating agent, medication dose, and administration route. The policy varies from country to country, area to area, institute to institute, and clinician to clinician (1). It may also differ from procedure to procedure in both diagnostic and therapeutic settings. Pediatric procedural sedation evolved mainly in the 21st century keeping pace with advancements in biomedical technology. Scope and utility of Ultrasonography (USG), Computed Tomography (CT), Magnetic Resonance Imaging (MRI), Electroencephalogram (EEG), and Brainstem evoked response audiometry (BERA) have increased tremendously together with their availability at stand-alone or district level centers in both public and private sector. It has increased the demand for safe and easy sedation for children by non-anesthetists. Indications for sedation in children are many, but the aim is always to complete the procedure quickly and successfully without any physical or emotional trauma to the child. A search for safe, effective, and painless medication acceptable to parents, children, technicians, and clinicians is ubiquitous, as there is a lack of a globally acceptable product.

Many Intravenous drugs are being used, like Ketamine, Propofol, Midazolam, Dexmedetomidine, etc., but they require expert handling. Parenteral drugs may be feasible in hospital settings. Still, parents, children, and clinicians prefer oral drugs, especially in stand-alone neuroimaging centers, small dental setups, small clinical setups, etc., as they need less specialized monitoring. They can be used on an outpatient department (OPD) basis. Available oral drugs are Promethazine, Chloral hydrate, Melatonin, Triclofos, Flunitrazepam, etc., with no clear evidence in favor of one over the other (2). Rectal and intranasal medications are also being used but are less acceptable. Chloral hydrate was censored for children with neurocognitive disability, but Triclofos remained used in many countries, including India. Kaplan et al. (3), found that Triclofos was safe in a controlled and monitored environment, even in children with neurocognitive disabilities. The two most popular and widely used drugs in India are Triclofos and Midazolam; therefore, this study was undertaken to look at the efficacy and Safety of Triclofos and how it compares with midazolam and other sedatives, especially when they are also given orally.

Triclofos is monosodium trichloroethyl phosphate. The phosphate ester of trichloroethanol is a pharmacologically active metabolite of Chloral hydrate (4). Triclofos is superior to Chloral hydrate as it has a better taste and palatability, has equivalent hypnotic potency, and does not cause gastric irritation (5). It has the most negligible side effects and anesthesia-related complications (6).

Material and Methods

A structured, systematic review of available medical literature was done in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement (7). The protocol was prepared after thoroughly studying the methods of systematic review and meta-analysis, strengthened by the Cochrane handbook and guidance from library internet sites. The protocol was registered at PROSPERO international registry site vide no CRD42021237574.

The inclusion criteria in this review were all studies involving human subjects of 0-14 years ago, published in English, where oral Triclofos was used for procedural sedation. The drug used for any other purpose were excluded from the study. The review question was**,** is oral Triclofos in any dose an effective and safe sedative drug for successful completion of neuroimaging or EEG or other similar procedures in children compared to other sedative drugs given by oral or any different route in any dose?

Search strategy

PICO model (Population, Intervention, Comparator, Outcome) was used to identify potential published studies for inclusion without any date limitation. Keywords, controlled vocabulary, subject terms, entry terms, text words, medical subject headings (MeSH), Emtree terms, synonyms considering significant headings, subheadings, supplementary concept, and explode features were used. Both simple and complex searches were done with advanced search builders. The

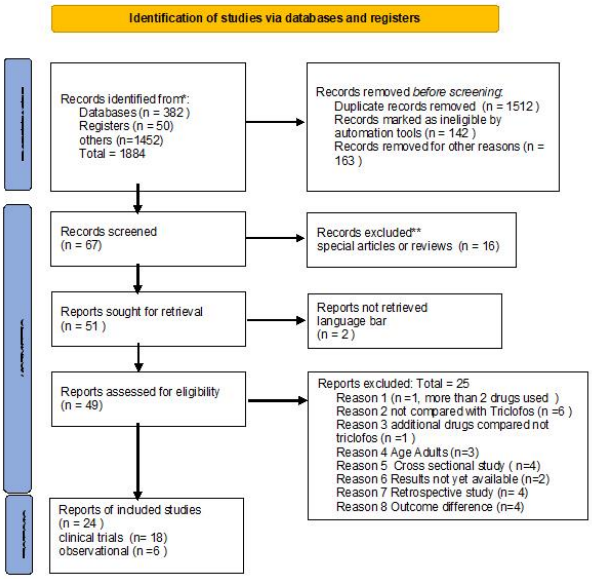

Figure 1. PRISMA 2020 flow diagram for Identification of studies in Systematic review.

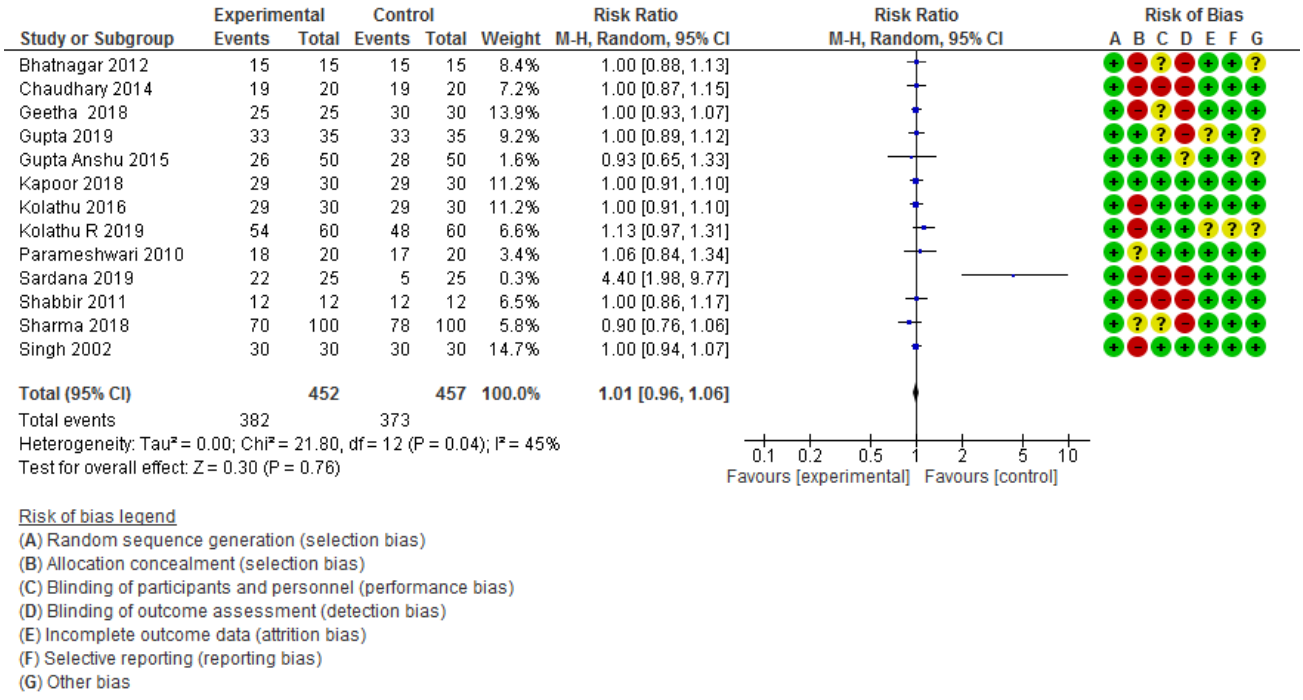

Figure 2. Meta-analysis Forest Plot for Triclofos versus Midazolam.

investigation was performed in Feb/March 2021 and rerun in August 2021. Two authors searched independently and matched their results later. Reproducibility of results was checked during the search rerun. A PICO model was prepared for PubMed search, which was tailored according to other databases being searched. The Focus area was title, abstract, and keywords. When there were zero or limited results, all fields were considered. Alerts for new information were also created wherever available.

The Major databases searched were PubMed, Embase, and Google scholar, along with citation

Table 1: Comparison between groups according to demographic data.

S.no.	Year Author Area, Country (Ref)	Study design	Total N=	Trin=	Othern=	Triclofos Dose (1st) mg/kg	Comparator Drug & Dose	Age (Year)	Sex M/F T/O	Procedure
1	2019 Gupta Bhilai, Chhattisgarh India (12)	RCT	70	35	35	75	Midazolam 0.5mg/kg oral , (I/V preparation mixed in 15 ml apple juice)	2-5	30M5F / 26M9F	Premedication
2	2018 Kapoor Udaipur, Rajasthan India (13)	RCT	60	30	30	100	Midazolam 0.5mg/kg oral (I/V preparation 1mg/ml mixed in 15 ml juice)	1-8	NA	Premedication before surgery
3	2018 Geetha Bengaluru, Karnataka India (14)	RCT	55	25	30	70	Midazolam 0.5mg/kg (5mg/ml I/V preparation so mixed in orange juice to make it 1mg/ml)	1-10	NA	Premedication
4	2019 Kolathu Kojhikode, Kerala India (15)	RCT	180	60	60 60	100	Midazolam 0.5mg/kg Oral ketamine Syp 5mg/kg Oral	1-8	46M14F/ 44M16F/ 38M22F	Minor elective procedure
5	2016 Kolathu Mallapuram, Kerala India (16)	RCT	60	30	30	100	Midazolam 0.5mg/kg oral (5mg/ml I/V preparation, mixed in orange juice to make it mg/ml)	1-8	NA	Premedication
6	2015 Gupta A New Delhi, India (17)	RCT	100	50	50	100	Midazolam 0.75mg/kg oral I/V preparation, mixed in mango juice to make it 1mg/ml)	1-5	29M21F/42M8F	CT
7	2010 Parameshwari Chennai, Tamilnadu India (18)	RCT	40	20	20	75	Midazolam 1mg/ml I/V preparation mixed in sweet clear soft drink max 15 ml	1-10	12M8F /12M8F	Premedication
8	2011 Shabbir Mangalore,Karnataka India (19)	RCT Cross over	24	12	12	70	Midazolam I/V preparation mixed with 2ml honey	3-9	NA	Dentistry
9	2014 Chaudhary New Delhi India (20)	RCT	60	20	20 20	75	Midazolam 0.5mg/kg oral I/V preparation mixed in mango juice, Hydroxyzine 0.5mg/kg	2-8	16MF4 / 16MF4 / 19MF1	Premedication
10	2012 Bhatnagar Jodhpur, Rajasthan India (21)	RCT	60	15	15 15 15	70	Midazolam 0.5mg/kg, orally I/V preparation, mixed in mango juice, Tramadol 2mg/kg orally, Zolpidem 0.4 mg/kg orally	3-9	NA	Dentistry
11	2002 Singh Lucknow, Uttar Pradesh, India (22)	RCT	90	30	30 30	70	Midazolam 0.5mg/kg orally I/V preparation, mixed in flavored sweet fruit juice Promethazine Oral Syp	3-9	NA	Dentistry
12	2018 Sharma Bangalore, Karnataka India (23)	RCT	200	100	100	50	Intranasal Midazolam 0.2mg/kg	0.25-5	60M40F/47M53F	ECHO, NCCT head, FNAC,OAE, Urinary USG CXR
13	2019 Sardanna Vadodara ,Gujrat India (24)	RCT	50	25	25	Triclofos 75 mg/kg	Syrup Midazolam 0.5mg/kg Oral	2-6	NA	Premedication
14	1990 Page Columbia USA(25)	RCT	263			Triclofos 70 mg/kg	Placebo	1-5	NA	Premedication

15	2021 Lalwani Pune, Maharashtra India (26)	RCT	228	114	114	Triclofos 50 mg/kg	Melatonin 0.3mg/kg, 3 mg or weight 10-15 kg , 6 mg > 15 kg ,(half dose repeated after 45 min if needed in both groups)	0-14	82M32F /71M43F	Electroenceph alography
16	1980 Lindgren Helsinki Finland (27)	CT	128	41	38 49	Triclofos 70 mg/kg	Diazepam 0.25 mg/kg oral flunitrazepam 0.02mg/kg oral	0-15	M31F10 M21F17 M30F19	Premedication
17	1973 Boyd London UK (28)	RCT	200	99	101	Triclofos	Diazepam	2-9 yr	NA	Premedication
18	2017 Subramanium Bengaluru ,Karnataka India (29)	RCT	60	30	30	Triclofos 70 mg/kg	40%Nitrus oxide +60% oxygen	5-10	NA	Dentistry treatment procedure
19	1991 Jackson London UK (30)	OBS	18	18	-	100 mg/kg	No comparator	<2 years	NA	PFT premedication
20	2016 Jain New Delhi India (31)	OBS	160	160	-	50 mg/kg Additional dose	No comparator	0.5-6 yr	119/41	EEG 30 min
21	2016 Kothari Thane ,Maharashtra India (32)	OBS	39	39	-	75mg/kg	No comparator	1-16 yr	20/19	Opthalmic evaluation
22	2017 Kimya Japan (33)	OBS	74	74	-	60 mg/kg, 20 mg/kg (add need)	No comparator	< 3 years	44/30	MRI
23	2021 Sethi Chandigarh India (34)	OBS	73	73	-	80 mg/kg 15mg/kg add need	No comparator	<5 years	NA	Ophthalmic evaluation, pediatr.glaucoma)
24	2015 Roy Bardhaman West Bengal India (35)	OBS	45	15	15 15	Triclofos 70 mg/kg	Intranasal Midazolam 0.5 mg/kg Per/Rectal Diazepam 0.5 mg/kg	1-6	7M8F 9M6F 8M7F	Imaging minimally invasive the procedure, Lumbar puncture, IV line

Abbreviations: Male = M, Female = F, Triclofos =Tri., Reference=Ref, RCT = Randomized Control trial, OBS = Observational study, NA = Not available

databases of Scopus and Web of Science. For clinical trials, the Cochrane central registry of controlled trials (CENTRAL) & clinical trial registry platforms, the WHO international clinical trials registry platform (ICTRP), an international standard randomized controlled trial number (ISRCTN British) registry, the united states food and drug administration (FDA), etc. were searched. Cochrane database was searched for systematic reviews also, for hand searching their bibliography. Grey literature was searched at OpenGrey. Indian studies were searched at Indian medical databases, Clinical Trials Registry India (CTRI), and the Indian Council of Medical Research (ICMR) compendium of research papers, Shodhganga and Shodhgangotri.

Data was also collected manually from the reference list of included studies and cited and cited articles. Indexes of relevant pediatric, anesthesia, and dental journals were also searched for missing studies. Grey sources were also searched at Crossref, Science Direct, and ProQuest. The search was limited to the English language only.

Identification of Included studies

The primary criteria for considering any study for further analysis was the use of Triclofos medication orally for sedating children for any procedure in one

Table 2: Summary of Outcomes (OC)

S.no.	Study	n=	OC 1 Succe dose	OC Succ lose	OC 2	OC 3 Asse time (min	C 4 uratio n sedati on min)	C 5 Ad ver se effe cts	omparato r	(=	C 1 ucces s initial ose	C 1B ucce ss on addl. dose	C 2 Fail ure	C 3 sse ss ti me mi n)	C 4 ura. . sed atio n min)	C 5 Ad ver se effe cts
1	2019 Gupta	35	33	0	2	30	NAP	0	Midazola	35	33	0	2	30	NA	0
2	2018 Kapoor	30	29	0	1	60	NAP	0	Midazola	30	29	0	1	30	NA	0
3	2018 Geetha	25	25	0	0	45	NAP	0	Midazola	30	30	0	0	35	NA	0
4	2019 Kolathu	60	54	0	6	45	NAP	0	Midazola	60	48	0	12	45	NA	0
4	2019 Kolathu	60	54	0	6	45	NAP	0	Ketamine	60	45	0	15	45	NA	2 V 2
5	2016 Kolathu	30	29	0	0	60	NAP	0	Midazola	30	29	0	0	30	NA	0
6	2015 Gupta	50	26	0	24	*38	117	0	Miadazol	50	28	12	22	*2	66	0
7	2010 Parame	20	18	0	2	90	NAP	0	Midazola	20	17	0	3	30	NA	0
8	2011 Shabbir	12	12	0	0	NA	*4.1 (m	0	Miadazol	12	12	0	0	N	*4.9	0
9	2014 Chaudh	20	19	0	1	60	NAP	*** (3R,	Midazola	20	19	0	1	60	NA	*** 3R
9	2014 Chaudh	20	19	0	1	60	NAP	*** (3R,	Hydroxyz	20	13	0	7	60	NA	3R 1D
10	2012 Bhatna	15	15	0	0	NA	*/5.0 (mean	0	Midazola	15	15	0	0	N	*/4. (me	0
10	2012 Bhatna	15	15	0	0	NA	*/5.0 (m	0	Tramadol	15	15	0	0	N	*/4. (me	
10	2012 Bhatna	15	15	0	0	NA	*/5.0 (m	0	Zolpidem	15	0	0	15	N	*/6. (me	# IR
11	2002 Singh	30	30	0	0	*35	*4.93 (m	0	Midazola	30	30	0	0	*1	*4.7 (me	0
11	2002 Singh	30	30	0	0	*35.	*4.93 (m	0	Prometha	30	30	0	0	*3	*5.2 (me	
12	2018 Sharma	100	70	30	20	*20	49	15	Midazola	100	78	22	14	*1	24	10
13	2019 Sardana	25	22	0	3	60	NAP	0	Midazola	25	5	0	20	30	NA	0
14	1990 Page	128	107	0	21	90	NAP	4 V	Placebo	135	90	0	45	90	NA	4 V

15	2021 Lalwan	114	63	41	10	45	82.39	12	Melatoni	114	61	41	12	45	80.0	5
16	1980 Lindgre	41	41	0	0	45	*4.25	0	Diazepa	38	38	0	0	45	*3.8	0
16	1980 Lindgre	41	41	0	0	45	*4.25	0	Flunitraz	49	49	0	0	45	*3.1	1 V
17	1973 Boyd	99	89	0	10	90	NAP	12 55	Diazepa	101	77	0	24	90	NA	20 53
18	2017 Subram	30	27	0	3	45	*4.80		40% oxide-	30	22	0	5	45	*4.4	1V
19	1991 Jackson	18	10	0	8	NA	NA	0	-	-	-	-	-	-	-	-
20	2016 Jain	160	149	0	11	30	90	16D 5I	-	-	-	-	-	-	-	-
21	2016 kothari	39	39	0	0	64.7	129	0	-	-	-	-	-	-	-	-
22	2017 Kimya	116	96	0	20	NA	NA	1V 4 S	-	-	-	-	-	-	-	-
23	2021 Sethi	73	49	15	9	30	NA	2S	-	-	-	-	-	-	-	-
24	Roy 2015	15	15	0	0	57.9	102.1	3V 2 R	-	-	-	-	-	-	-	-

**overall mean sedation score in dentistry during different procedures
* mean sedation time as assessed every 5 minutes without any fixed time (latency)
*** 3 R: developed restlessness, 2E: transient ventricular ectopics during anesthesia induction, V vomiting, AE headache, fatigue, irritability, vomiting, AM Abnormal movement, VB Altered blood vomiting, P Pallor, DM dry mouth, #IR irrelevant behavior, I Irritability, D dizziness, S saturation fall (SpO2<94%)
A: Agitation R: Recall NAP: Not applicable procedure, as Premedication was followed by anesthesia
*/ They used 8 points different scale for sedation rating and any score of 6 or above did not allow any possible treatment

arm of the study. If more than two sedative drugs were used in either the intervention or control arm or the drug was given as a continuous intravenous infusion, the study was excluded from the review. If more than two full doses of drugs were allowed in the study protocol, that was also excluded per the study design. Both clinical trials and prospective observational studies were included for further analysis. Case reports, case series, and cross-sectional studies were excluded from the review. Retrospective observational studies were also excluded. Clinical trials were used for further analysis of efficacy and safety both. Prospective observational studies were used only for noting adverse events/side effects.

Main outcomes

1. Achievement of adequate sedation and completion of procedure with a single dose (irrespective of dose decided in study) and sedation failure.
2. Adverse events following sedation: hypotension (25% or more significant decrease in pre-sedation arterial blood pressure), hypoxia, cyanosis, severe vomiting, severe irritability or agitation and agitational apnea, laryngospasm, bradycardia, Respiratory depression requiring assisted ventilation or oxygen saturation less than 90% were considered serious side effects or adverse events. All those events described in the study, including minor events, were considered side effects.

Additional outcomes

1. Requirement of additional dose
2. Induction time (onset latency)
3. Depth of sedation
4. Duration of sedation & Recovery time

The measure of effect

Relative risk at 95% confidence interval.

The measure of Adequate Sedation and separation (8, 9)

Level of sedation: was graded by 5-point score as 1= asleep not readily arousable, 2= asleep responds slowly

to gentle stimulation, 3= drowsy readily responds, 4= awake calm and quiet, 5= awake or agitated. Any sedation score of 1 or 2 or equivalent of that, in Ramsay sedation score or corresponding description in the study, juxtaposed to scale defined above was considered adequate sedation for uniformity of presentation of data (10).

Separation score: was assessed on the 4-point score as 1= excellent -happily separated, 2= good - separated without crying, 3= fair separated with crying, 4=poor need for restraining. Separation scores of 1 or 2 or corresponding descriptions in the study were considered adequate separation.

Overall behavior (11)**:** was assessed in dentistry procedure on the scale as 1=aborted, no treatment given, 2=Poor, treatment interrupted, or only partial treatment completed, 3=Fair, treatment interrupted but eventually, all treatment performed, 4=Good–complex but all treatment performed, 5=excellent, some limited crying or movement, 6= excellent, no crying or motion. Scores of 4 and above were considered a success and three or below a failure. The study's overall mean score was compared to compare the procedures involved**.** The separation score was considered a better indicator of ease of successful completion of the desired process than the sedation score if both were available in the study. If only the sedation score were described in the survey, comparing results would be a difficult task to assess in children because of the division of assessment into anxiolysis score, sedation score, and separation score (as three distinct entities for the entire procedure duration). Usually, children must also be separated from their parents for those procedures where sedation is required. Therefore, separation score and successful completion of the process were the primary considerations for uniformity of data presentation. Sex does not affect the pharmacokinetics of drugs under consideration; therefore, sex was omitted from the outcome analysis.

Moreover, many studies either did not describe their data sex-wise adequately or did not mention it. A separation score of 1 or 2 was considered a success and 3 or 4 a failure in the premedication group. For others, successful completion of CT /MRI/EEG, etc., with good analyzable data was considered a success. If sedation was assessed at a fixed time, that was taken for comparison. If the assessment was done every 5 minutes, sedation meantime (when the child was taken for the procedure) was considered for induction time analysis.

Data extraction and analysis

Zotero software was used for the collection and sorting of data. Endnote and Mendeley software were also used. A data dictionary was prepared, and data was extracted into Microsoft (MS) excel and MS word. A study was included after its critical appraisal and discussion among authors. Data were extracted and entered in a standard format, and pooling of data was done together for study characteristics (Table 1) and outcomes (Table 2). Data analysis was done in Cochrane RevMan 5.4 by entering relevant data for non-Cochrane review. The risk of Bias assessment was judged using the Cochrane risk of bias tool. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed for observational studies. Data were sub-grouped into clinical trials and observational studies per the study design. Size of effect and consistency of product across studies, along with the strength of evidence, were analyzed, and results were combined for meta-analysis where at least two studies were available. A random-effect model was used, and the P-value of 0.05 was considered statistically significant at a 95% confidence interval. Heterogeneity was assessed by visualizing data in a Forest plot. I^2 test statistic and Cochrane Q test were applied.

Discussion

Diagnostic and therapeutic procedures on children outside the care of an operating room setting by a pediatric anesthetist have increased tremendously without a corresponding increase in personnel and resources. Increased awareness and realization of the importance of providing sedation and anxiolysis to children have raised its demand, not only for safe and successful completion of the procedure but also for avoiding a traumatic experience for the child. Therefore, it becomes imperative that apart from traditional anesthetics, all those caring for children understand the art and science of providing them with sedation. Guidelines for monitoring and managing pediatric patients before, during, and after sedation for diagnostic and therapeutic procedures must be

followed religiously in every setting. Choice of the agent, its efficacy, and Safety in a given child, is a question that will always be needed to be answered individually, viewed, and reviewed periodically as more and more evidence emerges. This review evaluated evidence of efficacy, safety, ease, and acceptability for the drug Triclofos compared to Midazolam and other sedatives used for procedural sedation in children.

Triclofos is a phosphate ester of trichloroethanol, the pharmacologically active metabolite compound of chloral hydrate. It is a less gastric irritant and has good palatability. Chloral hydrate was synthesized by Justin Liebig in 1832 and used as a sedative-hypnotic since 1869. In 1948 Butler discovered its principal active compound, trichloroethanol. The drug was propagated as a treatment for insomnia. In the 1990's it was widely used in children for procedural sedation as an easy-to-use agent. But then its misuse by caretakers, overdosage, unnecessary dosage, and even deaths came to light. Genotoxicity and carcinogenicity were also suspected. Digestive irritation, cardiac rhythm disorders, desaturation, neuropsychiatric delusions, hallucinations, drug dependence, etc., were noticed (36-37). In and around 2000, the drug was withdrawn from the market in many countries. These side effects were mainly attributable to drug misuse and unmonitored frequent home use by parents or caretakers for other purposes. It should also be noted that procedural sedation is not equal to the treatment of insomnia. Procedural sedation is a one-time phenomenon done under medical supervision. This decade was also when other alternate agents became available for this purpose. In 2010 WHO included this drug in the list of pharmaceuticals under restrictions and availability (38). However, in India, its use under medical supervision continued for procedural sedation; surprisingly, no significant side effects were noted**.** In this review, therefore, all studies after the year 2000 are from India except one which is from Japan. India is a vast country with a share of 1.39 billion out of 7.9 billion words population as of November 2021 (39). The included studies come from different provinces and diverse geographical, genetic, and ethnic parts of the country. They, therefore, carry substantial weight for the world to know how Triclofos has been used in India. Although the well-known, Nelsons textbook of pediatrics does not even mention its name, its Indian counterpart, the IAP textbook of Pediatrics and drug formulary for children, does mention it for sedation and anxiolysis in children (40-41).

On the ease and acceptability front, the performance of Triclofos was excellent in all included studies. Administered orally, available commercially at low cost, in good palatable syrup form, which is acceptable to children, makes it suitable for use in the developing world. The most common age group for its use was 1-8 years. Neither mean age nor sex distribution was available in most studies; however, overall male preponderance was noted. Zolpidem was a total failure, whereas Hydroxyzine, Ketamine, Nitrous oxide, and Diazepam were inferior to Triclofos. Comparable results were obtained for Promethazine, Melatonin, Tramadol, and Flunitrazepam. Since only single studies with a small number of subjects were available, no further data synthesis was possible. However, Triclofos' performance was better without any significant side effects. Surprisingly all recent studies belonged to India, only making it clear that other countries are either not using Triclofos or maybe they are using Chloral hydrate (42-44).

Oral Midazolam and Triclofos had almost equal efficacy ranging between 95-100%, mainly as premedication for anxiety and separation from parents before surgery. No study used Triclofos 20 mg/kg dose as recommended in Indian textbooks and by IAP textbook. The commonly used initial dose was 70-75 mg/kg, which was 3.5 times higher, while the minimum was 50 mg/kg and the maximum 100 mg/kg, which were 2.5 to 5 times the recommended dose in books. In the future, comparative studies with different drug doses varying from 20 mg to 100 mg are required to settle the dose issue. The recommended safe dose of 20 mg/kg may be too little for achieving an adequate level of conscious sedation; currently, higher doses may be recommended under the monitoring of vitals, including oxygen saturation by pulse oximetry. Due to the Covid-19 pandemic, the public has become sensitized and familiar with pulse oximetry and oxygen saturation monitoring globally. Pulse oximeters have also become widely available at a low cost, making monitoring easy and affordable. Only in one study by

Sharma 2018, efficacy was found to be less than 70% for Triclofos and 78% for Midazolam, but then this decrease was found in both drugs; therefore, it might be related to other factors in methodology or setting or procedure. The difference between Triclofos and Midazolam was not statistically significant (P-value 0.197). Sleep deprivation of 2-4 hours was applied in some studies.

Fasting was considered necessary in some studies but was not mentioned in others. We believe that recommended guidelines for fasting should be followed in all cases. In a survey by Chandrashekhar 2018, Triclofos was instead demanded by parents in preference to total intravenous anesthesia (TIVA). This study was not included in our review because of multiple drug protocols in the comparator arm. They also reported an 80% success rate with Triclofos in a 70 mg/kg dose. They reported it as a first-line preference compared to TIVA, using a combination of midazolam, propofol, and fentanyl, with 96% success. They also considered it safe for one-time use.[45] No significant side effects were noted in both groups in all included studies, and minor side effects were also few. Details of reported incidences of minor side effects are mentioned in table 2. A fall in respiratory rate and oxygen saturation was noted in some studies, but it never went below 94%, requiring oxygen in either group.

Intravenous Midazolam was the fastest (apart from requiring an IV line). It was rarely associated with serious side effects like hypotension, hypoxia, cyanosis, severe vomiting, intractable irritability, agitation, apnea, laryngospasm, and bradycardia; so, it needs intensive care settings for its administration. We found that using preservative-free IV preparation of Midazolam orally had good efficacy and Safety in all eleven included studies. Preservative-free IV midazolam preparation is widely available and can be used orally. It can remove all pain and anxiety associated with IV cannulation with increased cost.

Conclusion

Oral Triclofos and Midazolam are potent and safe drugs with similar sedative and anxiolytic effects if given in adequate doses under medical supervision. Contrary to popular belief, Triclofos emerged as a safe drug with good efficacy and acceptability even in much higher doses. Misuse of medicine should not be the reason to ban its legitimate one-time use while following Procedural sedation and analgesia (PSA) guidelines. Thus, the value of Triclofos for procedural sedation cannot be undermined.

Another highlight of this systematic review and meta-analysis was that preservative-free IV midazolam preparation could be safely used orally with good efficacy and Safety.

Both Triclofos in dose 50 mg/kg and oral Midazolam in dose 0.5 mg/kg orally appears to be productive and safe for one-time administration for procedural sedation under medical supervision

1. This Triclofos dose is much higher than the prescribed dose of 20 mg/kg as described in the IAP drug formulary. Dose-related studies are needed in the future to settle this issue.
2. Available intravenous market preparations of Midazolam 1 mg/ml without preservatives can be conveniently given orally mixed with fruit juice or sweetened water, and problems of intravenous line insertion in children can be easily avoided.
3. No statistically significant difference was found in favor of Triclofos or Midazolam, producing adequate sedation and anxiolysis.
4. Oral Midazolam produced sedative effects earlier than Triclofos; on this count, oral Midazolam was superior to Triclofos. Practically this waiting time may not be inconvenient in most settings; once the caretaker knows how much time before the procedure, the drug needs to be given for the desired time of sedation.
5. Duration of sedation was more with Triclofos, whereas recovery was consistently faster in the Midazolam group.

In resource-poor developing countries, oral Triclofos appears to be an excellent alternative to other sedatives when before, during, and after sedation care is done by trained medical personnel and a cautious approach to misuse of the drug at home is maintained. Remember that the drug should never be allowed to be given at home.

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Conflicts of Interest

The authors declare that there are no conflicts of interest.

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